SIXTH
EDITION

COMPREHENSIVE CLINICAL NEPHROLOGY

John **Feehally**
Jürgen **Floege**
Marcello **Tonelli**
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2015v1.0

Comprehensive Clinical Nephrology

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Edinburgh London New York Oxford Philadelphia St Louis Sydney 2019

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First edition 2000
Second edition 2003
Third edition 2007
Fourth edition 2010
Fifth edition 2015

Cover Image
Three dimensional reconstruction of mouse glomeruli in which podocyte nuclei are labelled in green. The vasculature was labelled in red using CD31 antibody. Image was provided by Dr. Victor Puelles and Prof. Marcus Moeller from RWTH Aachen University Clinic, Dep. of Nephrology and Clinical Immunology, Aachen, Germany.

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ISBN: 978-0-323-47909-7
E-ISBN: 978-0-323-54719-2

Content Strategist: Nancy Anastasi Duffy
Content Development Specialist: Joanne Scott
Project Manager: Anne Collett, Andrew Riley
Design: Patrick Ferguson
Illustration Manager: Nichole Beard
Marketing Manager: Michele Milano

Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

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PREFACE

In the sixth edition of *Comprehensive Clinical Nephrology,* we continue to offer a text for fellows, practicing nephrologists, and internists that covers all aspects of the clinical work of the nephrologist, including fluids and electrolytes, hypertension, diabetes, dialysis, and transplantation. We recognize that this single volume does not compete with multivolume or highly referenced online texts, and it remains our goal to provide "comprehensive" coverage of clinical nephrology yet also ensure that inquiring nephrologists can find the key scientific issues and pathophysiology that underlie their clinical work.

All chapters have been extensively revised and updated in response to the advice and comments that we have received from many readers and colleagues. These revisions include latest developments, such as new insights into complement mediated glomerular diseases, and the latest data on epidemiology and consequences of acute kidney injury and renal replacement therapy. Also included is a chapter on the emerging problem of endemic nephropathies in low and middle income countries. This edition retains the consistent design of the algorithms, which are a popular feature of the book, to emphasize different aspects of the information provided: yellow boxes for general information, blue boxes for necessary investigations, and green boxes for therapeutic interventions. By popular demand we continue to offer readers access to the images from the book. We are pleased to see them used in lectures and seminars in many parts of the world.

This is the third edition that features access to a companion Expert Consult website, with fully searchable text, a downloadable image library, and links to PubMed. New to this edition is an online question bank with more than 400 multiple-choice questions.

And finally, we welcome a new co-editor, Marcello Tonelli, who will bring great epidemiological expertise (and significantly lower the average age of the editors).

John Feehally
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To our colleagues and collaborators, as well as others, whose research continues to light the way

To our wives and families, who have once again endured the preparation of this sixth edition with unfailing patience and support

To our patients with renal disease, for whom it is a privilege to care

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1

Renal Anatomy

Wilhelm Kriz, Marlies Elger

The complex structure of the mammalian kidney is best understood in the unipapillary form that is common to all small species. Fig. 1.1 is a schematic coronal section through a unipapillary kidney, with a cortex enclosing a pyramid-shaped medulla, the tip (papilla) of which protrudes into the renal pelvis. The medulla is divided into an outer and an inner medulla; the outer medulla is further subdivided into an outer and an inner stripe.

STRUCTURE OF THE KIDNEY

The specific components of the kidney are the nephrons, the collecting ducts (CDs), and a unique microvasculature.[1] The multipapillary kidney of humans contains approximately 1 million nephrons, although this number varies considerably. The number of nephrons is already established during prenatal development; after birth, new nephrons cannot be developed and a lost nephron cannot be replaced.

Nephrons

A nephron consists of a renal corpuscle *(glomerulus)* connected to a complicated and twisted tubule that finally drains into a CD (Fig. 1.2 and Table 1.1). Three types of nephron can be distinguished by the location of renal corpuscles within the cortex: superficial, midcortical, and juxtamedullary nephrons. The tubular part of the nephron consists of a proximal tubule and a distal tubule connected by a loop of Henle[2] (see later discussion). There are two types of nephrons: those with long loops of Henle and those with short loops. Short loops turn back in the outer medulla or even in the cortex (cortical loops). Long loops turn back at successive levels of the inner medulla.

Collecting Ducts

A CD is formed in the renal cortex when several nephrons join. A connecting tubule (CNT) is interposed between a nephron and a cortical CD. Cortical CDs descend within the medullary rays of the cortex. Then they traverse the outer medulla as unbranched tubes. On entering the inner medulla, they fuse successively and open finally as papillary ducts into the renal pelvis (see Fig. 1.2 and Table 1.1).

Microvasculature

The microvascular pattern of the kidney is similarly organized in mammalian species[1,3] (Fig. 1.3; see also Fig. 1.1). The renal artery, after entering the renal sinus, finally divides into the interlobar arteries, which extend toward the cortex in the space between the wall of the pelvis (or calyx) and the adjacent cortical tissue. At the junction between cortex and medulla, the interlobar arteries divide and pass over into the arcuate arteries, which also branch. The arcuate arteries give rise to the cortical radial arteries (interlobular arteries), which ascend radially through the cortex. No arteries penetrate the medulla.

Afferent arterioles supply the glomerular tufts and generally arise from cortical radial arteries. As a result, the blood supply of the peritubular capillaries of the cortex and the medulla is exclusively *postglomerular.*

Glomeruli are drained by efferent arterioles. Two basic types of efferent arterioles can be distinguished: cortical and juxtamedullary. *Cortical* efferent arterioles, which derive from superficial and midcortical glomeruli, supply the capillary plexus of the cortex. The efferent arterioles of *juxtamedullary* glomeruli represent the supplying vessels of the renal medulla. Within the outer stripe of the medulla, these vessels divide into the *descending* vasa recta and then penetrate the inner stripe in cone-shaped vascular bundles. At intervals, individual vessels leave the bundles to supply the capillary plexus at the adjacent medullary level.

Ascending vasa recta drain the renal medulla. In the inner medulla, the vasa recta arise at every level, ascending as unbranched vessels, and traverse the inner stripe within the vascular bundles. The ascending vasa recta that drain the inner stripe may join the vascular bundles or may ascend directly to the outer stripe between the bundles. All the ascending vasa recta traverse the outer stripe as individual wavy vessels with wide lumina interspersed among the tubules. Because true capillaries derived from direct branches of efferent arterioles are relatively scarce, the ascending vasa recta form the capillary plexus of the outer stripe. The ascending vasa recta empty into arcuate veins.

The vascular bundles represent a countercurrent exchanger between the blood entering and that leaving the medulla. In addition, the organization of the vascular bundles results in a separation of the blood flow to the inner stripe from that to the inner medulla. Descending vasa recta supplying the inner medulla traverse the inner stripe within the vascular bundles. Therefore blood flowing to the inner medulla has not been exposed previously to tubules of the inner or outer stripe. All ascending vasa recta originating from the inner medulla traverse the inner stripe within the vascular bundles. Thus blood that has perfused tubules of the inner medulla does not subsequently perfuse tubules of

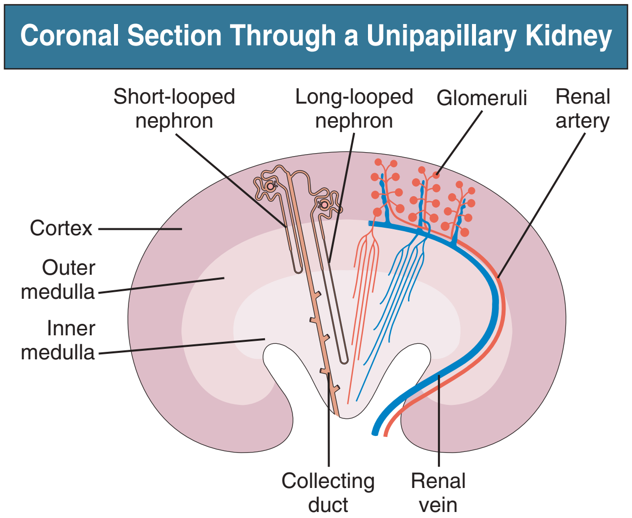


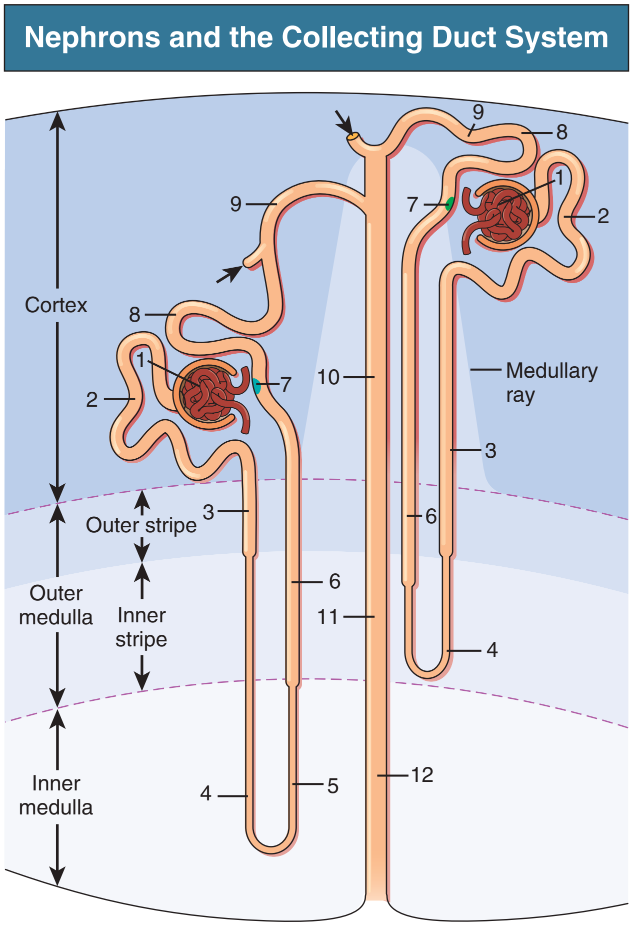
Fig. 1.1 Coronal section through a unipapillary kidney.

TABLE 1.1 Subdivisions of the Nephron and Collecting Duct System

Section	Subsections
Nephron	
Renal corpuscle	*Glomerulus:* term used most frequently to refer to entire renal corpuscle
	Bowman capsule
Proximal tubule	Convoluted part
	Straight part (pars recta), or thick descending limb of Henle loop
Intermediate tubule	Descending part, or thin descending limb of Henle loop
	Ascending part, or thin ascending limb of Henle loop
Distal tubule	Straight part, or thick ascending limb of Henle loop: subdivided into medullary and cortical parts; the cortical part contains the macula densa in its terminal portion
	Convoluted part
Collecting Duct System	
Connecting tubule	Includes the arcades in most species
Collecting duct	Cortical collecting duct
	Outer medullary collecting duct: subdivided into an outer stripe and an inner stripe portion
	Inner medullary collecting duct: subdivided into basal, middle, and papillary portions

the inner stripe. However, the blood returning from either the inner medulla or the inner stripe afterward does perfuse the tubules of the outer stripe.

The intrarenal veins accompany the arteries. Central to the renal drainage of the kidney are the arcuate veins, which, in contrast to arcuate arteries, do form real anastomosing arches at the corticomedullary border.



1. Renal corpuscle
2. Proximal convoluted tubule
3. Proximal straight tubule
4. Descending thin limb
5. Ascending thin limb
6. Distal straight tubule (thick ascending limb)
7. Macula densa
8. Distal convoluted tubule
9. Connecting tubule
10. Cortical collecting duct
11. Outer medullary collecting duct
12. Inner medullary collecting duct

Fig. 1.2 Nephrons and the collecting duct system. Shown are short-looped and long-looped nephrons, together with a collecting duct (not drawn to scale). *Arrows* denote confluence of further nephrons.

The intrarenal arteries and the afferent and efferent glomerular arterioles are accompanied by sympathetic nerve fibers and terminal axons representing the efferent nerves of the kidney.[1] Tubules have direct contact to terminal axons only when the tubules are located around the arteries or the arterioles. Tubular innervation consists of "occasional fibers adjacent to perivascular tubules."[4] The density of nerve contacts to convoluted proximal tubules is low; contacts to straight proximal tubules, thick ascending limbs of Henle loops, and CDs have never been encountered. Afferent nerves of the kidney are believed to be sparse.[5]

Glomerulus (Renal Corpuscle)

The glomerulus comprises a tuft of specialized capillaries attached to the mesangium, both of which are enclosed in a pouch-like extension of the tubule that represents the Bowman capsule (Figs. 1.4 and 1.5). The capillaries together with the mesangium are covered by epithelial cells (podocytes) forming the visceral epithelium of the Bowman capsule. At the vascular pole, this is reflected to become the parietal epithelium of the Bowman capsule. At the interface between the glomerular capillaries and the mesangium on one side and the podocyte layer on the

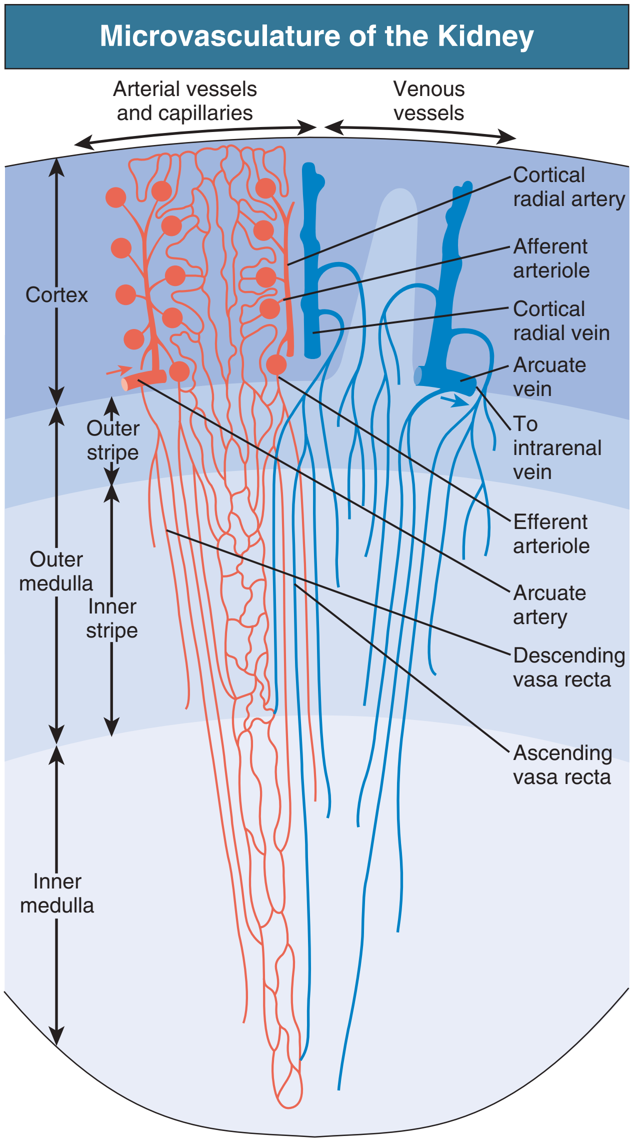
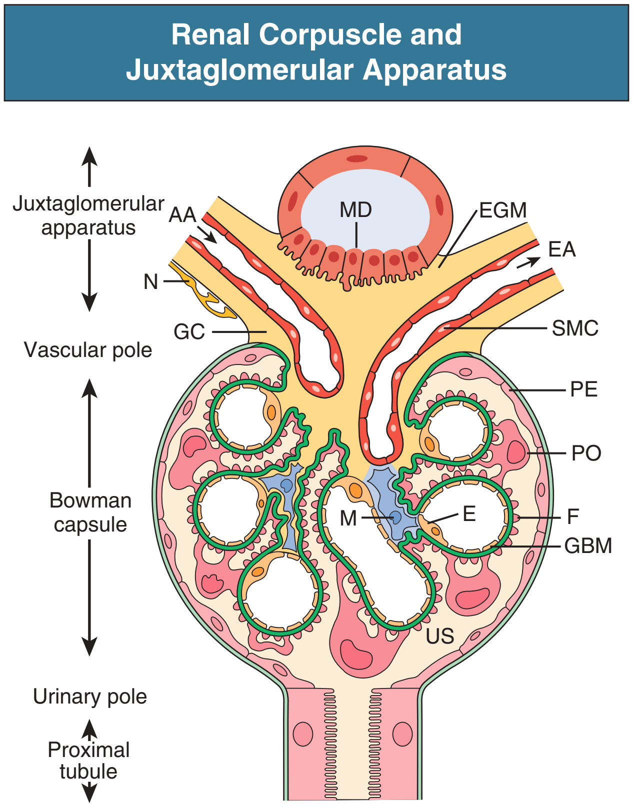

Microvasculature of the Kidney
Arterial vessels and capillaries
Venous vessels
Cortex
Outer stripe
Outer medulla
Inner stripe
Inner medulla
Cortical radial artery
Afferent arteriole
Cortical radial vein
Arcuate vein
To intrarenal vein
Efferent arteriole
Arcuate artery
Descending vasa recta
Ascending vasa recta

Fig. 1.3 **Microvasculature of the Kidney.** Afferent arterioles supply the glomeruli, and efferent arterioles leave the glomeruli and divide into the descending vasa recta, which together with the ascending vasa recta form the vascular bundles of the renal medulla. The vasa recta ascending from the inner medulla all traverse the inner stripe within the vascular bundles, whereas most of the vasa recta from the inner stripe of the outer medulla ascend outside the bundles. Both types traverse the outer stripe as wide, tortuous channels.


Renal Corpuscle and Juxtaglomerular Apparatus
Juxtaglomerular apparatus
AA
MD
EGM
EA
N
GC
SMC
Vascular pole
PE
PO
Bowman capsule
M
E
F
GBM
US
Urinary pole
Proximal tubule

AA	Afferent arteriole	PE	Parietal epithelium
MD	Macula densa	PO	Podocyte
EGM	Extraglomerular mesangium	M	Mesangium
EA	Efferent arteriole	E	Endothelium
N	Sympathetic nerve terminals	F	Foot process
GC	Granular cells	GBM	Glomerular basement membrane
SMC	Vascular smooth muscle cells	US	Urinary space

Fig. 1.4 **Glomerulus and juxtaglomerular apparatus.** (Modified with permission from reference 1.)

other side, the glomerular basement membrane (GBM) is developed. The space between both layers of the Bowman capsule represents the urinary space, which at the urinary pole continues as the tubule lumen.

On entering the tuft, the afferent arteriole immediately divides into several primary capillary branches, each of which gives rise to an anastomosing capillary network representing a glomerular lobule. In contrast, the efferent arteriole is already established inside the tuft by confluence of capillaries from each lobule.[6] Thus the efferent arteriole has a significant intraglomerular segment located within the glomerular stalk.

Glomerular capillaries are a unique type of blood vessel composed of nothing but an endothelial tube (Figs. 1.6 and 1.7). A small stripe of the outer aspect of this tube directly abuts the mesangium; the major part bulges toward the urinary space and is covered by the GBM and the podocyte layer. This peripheral portion of the capillary wall represents the filtration area.

Glomerular Basement Membrane

The GBM serves as the skeleton of the glomerular tuft. This membrane is a complexly folded sack with an opening at the glomerular hilum (see Fig. 1.4). The outer aspect of this GBM sack is completely covered with podocytes. The interior of the sack is filled with the capillaries and the mesangium. As a result, on its inner aspect, the GBM is in contact with either capillaries or the mesangium. At any transition between these two locations, the GBM changes from a convex pericapillary to a concave perimesangial course; the turning points are called *mesangial angles.* In electron micrographs of traditionally fixed tissue, the GBM appears as a trilaminar structure, with a lamina densa bounded by two less dense layers, the lamina rara interna and lamina rara externa (see Fig. 1.7). Studies with freeze techniques reveal only one thick, dense layer directly attached to the bases of the epithelium and endothelium.[7]

The major components of the GBM include type IV collagen, laminin, and heparan sulfate proteoglycans, as in basement membranes at other sites. However, the GBM has several unique properties, notably a distinct spectrum of type IV collagen and laminin isoforms. The mature GBM consists of type IV collagen made of $\alpha3$, $\alpha4$, and $\alpha5$ chains and laminin 11, made of $\alpha5$, $\beta2$, and $\gamma1$ chains.[8] Type IV collagen is the antigenic target in Goodpasture disease (see Chapter 16), and mutations in the

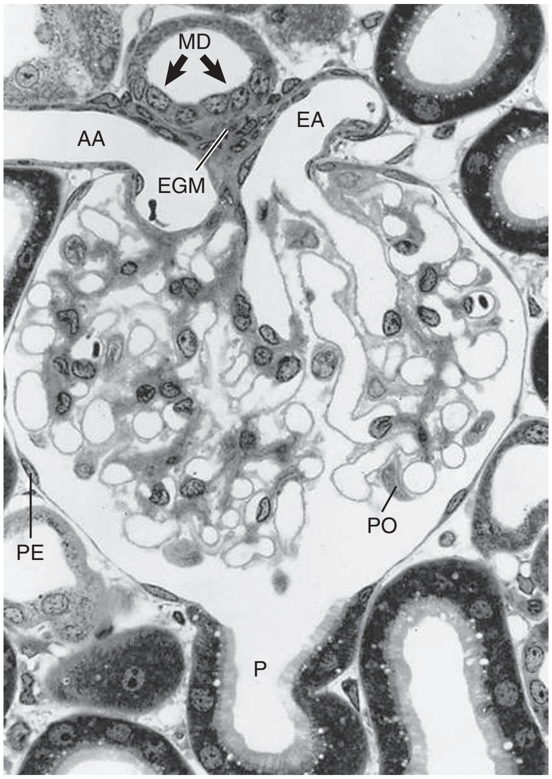


Fig. 1.5 **Longitudinal section through a glomerulus (rat).** At the vascular pole, the afferent arteriole *(AA),* the efferent arteriole *(EA),* the extraglomerular mesangium *(EGM),* and the macula densa *(MD)* are seen; *PO,* podocyte. At the urinary pole, the parietal epithelium *(PE)* transforms into the proximal tubule *(P).* (Light microscopy; magnification ×390.)

genes of the α3, α4, and α5 chains are responsible for Alport syndrome (see Chapter 46).

Current models depict the basic structure of the GBM as a three-dimensional network of type IV collagen.[7] The type IV collagen monomer consists of a triple helix that is 400 nm in length, with a large, noncollagenous globular domain at its C-terminal end called NC1. At the N terminus, the helix possesses a triple helical rod 60 nm long: the 7S domain. Interactions between the 7S domains of two triple helices or the NC1 domains of four triple helices allow type IV collagen monomers to form dimers and tetramers. In addition, triple helical strands interconnect by lateral associations through binding of NC1 domains to sites along the collagenous region. This network is complemented by an interconnected network of laminin 11, resulting in a flexible, nonfibrillar polygonal assembly that provides mechanical strength and elasticity to the basement membrane and serves as a scaffold for alignment of other matrix components.[9,10]

The electronegative charge of the GBM mainly results from the presence of polyanionic proteoglycans. The major proteoglycans of the GBM are heparan sulfate proteoglycans, including perlecan and agrin. Proteoglycan molecules aggregate to form a meshwork that is kept well hydrated by water molecules trapped in the interstices of the matrix.

Mesangium

Three major cell types occur within the glomerular tuft, all of which are in close contact with the GBM: mesangial cells, endothelial cells, and podocytes. The mesangial/endothelial/podocyte cell ratio is 2 : 3 : 1 in the rat. The mesangial cells and mesangial matrix establish the glomerular mesangium.

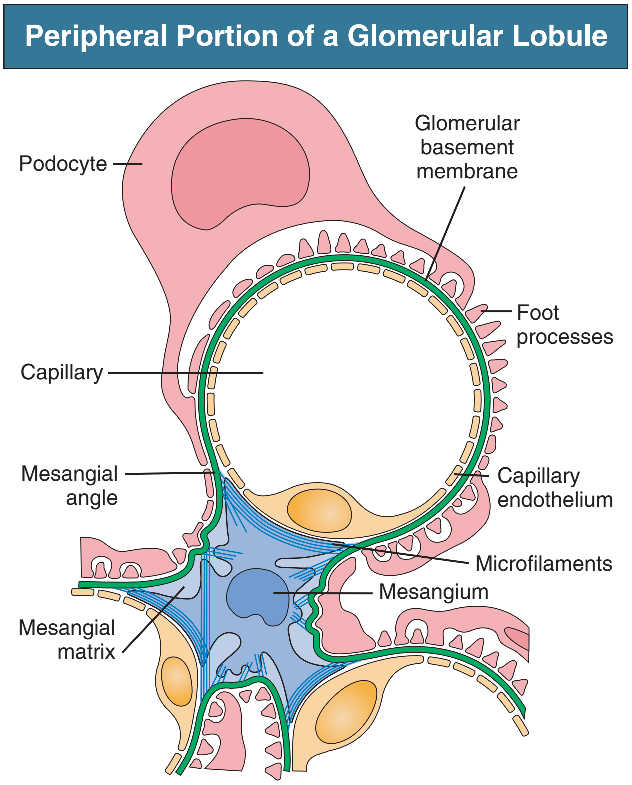


Fig. 1.6 **Peripheral portion of a glomerular lobule.** This part shows a capillary, the axial position of the mesangium, and the visceral epithelium (podocytes). At the capillary-mesangial interface, the capillary endothelium directly abuts the mesangium.

Mesangial cells. Mesangial cells are irregular in shape, with many processes extending from the cell body toward the GBM (see Figs. 1.6 and 1.7). In these processes, dense assemblies of microfilaments are found, containing α-smooth muscle actin, myosin, and α-actinin.[11]

The processes are attached to the GBM directly or through the interposition of microfibrils The GBM represents the effector structure of mesangial contractility. Mesangial cell–GBM connections are found throughout the mesangium-GBM interface but are especially prominent at the turning points of the GBM infoldings (mesangial angles). The folding pattern of the GBM is permanently challenged by the expansile forces of the high intraglomerular perfusion pressure. Centripetal mesangial cell contraction balances the expansile forces. Thus the folding pattern of the GBM, including the complex convolutions of glomerular capillaries, are maintained by mesangial cells.

Mesangial cells possess a great variety of receptors, including those for angiotensin II (Ang II), vasopressin, atrial natriuretic factor, prostaglandins, transforming growth factor β (TGF-β), and other growth factors (platelet-derived growth factor [PDGF], epidermal growth factor [EGF], connective tissue growth factor [CTGF]).[12]

Mesangial matrix. The mesangial matrix fills the highly irregular spaces between the mesangial cells and the perimesangial GBM, anchoring the mesangial cells to the GBM.[6] Many common extracellular matrix proteins have been demonstrated within the mesangial matrix, including collagen types IV, V, and VI and microfibrillar protein components such as fibrillin and the 31-kilodalton microfibril-associated glycoprotein. The matrix also contains several glycoproteins, most abundantly fibronectin.

Endothelium

Glomerular endothelial cells consist of cell bodies and peripherally located, attenuated, and highly fenestrated cytoplasmic sheets (see Figs.

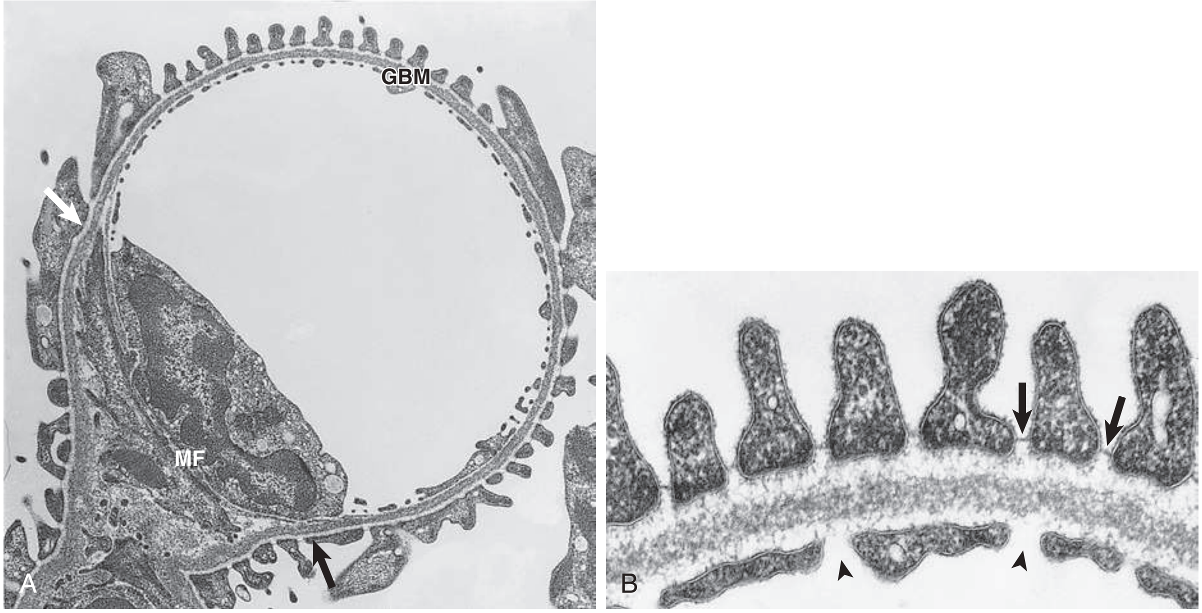


Fig. 1.7 Glomerular capillary. (A)The layer of interdigitating podocyte processes and the glomerular basement membrane *(GBM)* do not completely encircle the capillary. At the mesangial angles *(arrows)*, both deviate from a pericapillary course and cover the mesangium. Mesangial cell processes containing dense bundles of microfilaments *(MF)*, interconnect the GBM, and bridge the distance between the two mesangial angles. (B) Filtration barrier. The peripheral part of the glomerular capillary wall comprises the endothelium with open pores *(arrowheads)*, the GBM, and the interdigitating foot processes (FPs). The GBM shows a lamina densa bounded by the lamina rara interna and externa. The FPs are separated by filtration slits bridged by thin diaphragms *(arrows)*. (Transmission electron microscopy [TEM]; magnification: **A,** [×8770]; **B,** [×50,440].)

1.6 and 1.7). Glomerular endothelial pores lack diaphragms, which are encountered only in the endothelium of the final tributaries to the efferent arteriole.[6] The round to oval pores have a diameter of 50 to 100 nm. A negatively charged layer of membrane-bound and loosely attached molecules (glycocalyx) covers the entire luminal surface, including, as sieve plugs, the endothelial pores.[13] Endothelial cells are active participants in processes controlling coagulation and inflammation. Endothelial cells have receptors for vascular endothelial growth factor (VEGF), angiopoietins, and TGFβ-1, among others. They synthesize and release PDGF-B, endothelin-1, and endothelium-derived relaxing factor (EDRF), among others.[14]

Visceral Epithelium (Podocytes)

The visceral epithelium of the Bowman capsule comprises highly differentiated cells, the podocytes (Fig. 1.8; see also Fig. 1.6). Differentiated podocytes are unable to replicate; therefore lost podocytes cannot be replaced in the adult. All efforts of the last decade to find progenitor cells that might migrate into the tuft and replace lost podocytes have failed.

Podocytes have a voluminous cell body that floats within the urinary space, separated from the GBM by a subpodocyte space.[15] The cell bodies give rise to primary processes that fall apart into foot processes (FPs) that fix the cells to the capillaries, i.e. to the GBM. Sporadic FPs also may arise directly from the cell body. The FPs of neighboring podocytes regularly interdigitate with each other, leaving meandering slits (filtration slits) between them that are bridged by a complex extracellular structure, the *slit diaphragm* (SD) that may be seen as a modified adherens junction (Fig. 1.9; see also Figs. 1.6 to 1.8). Traditional scanning electron micrograph (SEM) pictures (see Fig.1.8A) do not convey the correct pattern of how FPs interdigitate and adhere to the GBM. As seen by block-face SEM (see Fig. 1.8B), individual FPs may terminate with a final branching and primary processes fall off into basal ridges that actually are also FPs.[16] Thus the interdigitating FP pattern as it adheres to the GBM is completely homogeneous, forming a uniform cover of interdigitating filopodia.

In contrast to the cell body, which harbors a prominent endoplasmic reticulum and Golgi system and has well-developed endocytotic and autophagic machinery, the cell processes apart from endocytotic elements contain only a few organelles. A sophisticated cytoskeleton accounts for the complex shape of the cells. In the cell body and the primary processes, microtubules and intermediate filaments (vimentin, desmin) dominate. Within the FPs, microfilaments (β-actin) form prominent U-shaped bundles arranged in the longitudinal axis of two successive FPs in an overlapping pattern. Above, the bends of these bundles are linked to the microtubules of the primary processes; peripherally, these bundles terminate in the dense cytoplasm associated with the sole plates, being part of the anchoring system of the FPs to the GBM (see later discussion). In addition, FPs have well developed sub-plasmalemmal actin network that has intimate contact to the anchor line of the SD and diffusely to the actin bundles. Multiple actin-associated proteins, including α-actinin-4 and synaptopodin myosin (myo-1e), among many others, establish the specific cytoskeleton in podocytes.[19]

The luminal membrane contains a great variety of receptors (see later discussion), and together with the luminal surface of the SD it is covered by a thick surface coat that is rich in sialoglycoproteins, including podocalyxin and podoendin, accounting for the high negative surface charge of the podocytes.

The abluminal cell membrane comprises a narrow band of lateral cell membrane extending from the SD to the GBM and, most important, the soles of the FPs abutting to the GBM. A complex anchoring system connects the cytoskeleton of the FPs to the GBM. Two systems are known: (1) α3β1 integrin dimers interconnect the cytoplasmic focal adhesion proteins vinculin, paxillin, and talin with the α3, α4, and α5

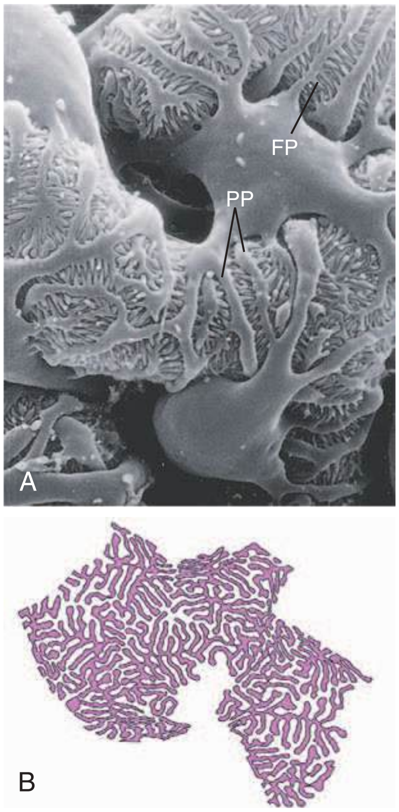


Fig. 1.8 **Branching pattern of podocyte foot processes (rat).** (A) Scanning electron micrograph (SEM) showing the urinary side of the podocyte cover of a glomerular capillary consisting of cell bodies, large primary processes *(PP)* and interdigitating foot processes *(FP)* separated by the filtration slits. (B) Drawing of the basal aspect of the FP-branching pattern as seen by block-face SEM. A fully homogeneous branching pattern of FPs attaches to the glomerular basement membrane (GBM) that may be compared with a pattern of interdigitating filopodia connected by adherens junctions. The high degree of branching (not seen from the luminal aspect) provides a high degree of adaptability to area changes of the underlying GBM. (**B,** From reference 45, with permission.)

chains of type IV collagen and laminin 521; and (2) β-α-dystroglycans interconnect the cytoplasmic adapter protein utrophin with agrin and laminin α5 chains in the GBM.[9]

The junctional connection of podocyte FPs by the SD bridging the filtration slits is complex and unique. The filtration slits have a constant width of approximately 30 to 40 nm: thus the SD has to connect the FPs over a considerable distance. By transmission electron microscopy (TEM), in routinely glutaraldehyde-fixed material, the SD shows up as a single dark line in cross sections and in an en-face view as a homogenous network of fibrillar structures interconnecting both membranes. Combined tannic acid and glutaraldehyde–fixed tissue reveals, in en-face view, a zipper-like structure with a row of pores approximately 14 × 2 nm on either side of a central bar. The transmembrane proteins that establish the slit diaphragm (SD) and its connection to the actin cytoskeleton of the FPs include nephrin, P-cadherin, FAT1, NEPH 1-3, podocin, and CD2AP, among others[20] (see Fig. 1.9).

Podocytes contain a great variety of surface receptors and ion channels, many of which accumulate close to the SD; the schematic in Fig. 1.9 shows some of them. They include receptors for cyclic guanosine monophosphate (cGMP) signaling, stimulated by natriuretic peptides (atrial natriuretic peptide [ANP], brain natriuretic peptide [BNP], and C-type natriuretic peptide [CNP]) and nitric oxide; receptors for cyclic adenosine monophosphate (cAMP) signaling stimulated by prostaglandin E_2 (PGE_2), dopamine, VEGF, isoproterenol, parathyroid hormone (PTH), PTH-related peptide; and receptors for Ca^{2+} signaling stimulated by numerous ligands, including angiotensin II, acetylcholine, PGF2, arginine vasopressin (AVP), adenosine triphosphate (ATP), endothelin, and histamine.[20] Among the transient receptor potential (TRP) cation channels, TRPC5 and TRPC6 have received much attention.[21-23] The major target of this signaling orchestra is the cytoskeleton (see later discussion). Other receptors, such as for TGF-β, fibroblast growth factor (FGF-2), and other cytokines/chemokines, have been shown to be involved in synthesis functions (GBM components) or in development of podocyte diseases.[20] Megalin is a multiligand endocytotic receptor and the major antigen of Heymann nephritis in the rat,[24] but is not present in humans.[12] On the other hand, podocytes, by paracrine and autocrine signaling, regulate the interplay with endothelial and mesangial cells; during development they are responsible for building a glomerulus. VEGF, angiopoietins, and PDGF, among others, are of crucial importance for the homeostatic maintenance of the tuft.[25]

Function and Maintenance of the Filtration Barrier

Most glomerular diseases start in the glomerulus, beginning with the breakdown of the filtration barrier. It is commonly accepted that the physical forces associated with filtration represent crucial challenges that account for the break down; they comprise filtration pressure and filtrate flow.

Filtration pressure and expansion. Traditionally, the high transmural hydrostatic pressure gradients necessary for filtration have been considered the main challenge to the filtration barrier. Podocyte FPs were considered a kind of pericyte process counteracting variations and derailments in perfusion pressures. This view has been challenged since we learned that the major way podocytes are lost (under any circumstances) is by detachment from the GBM as viable cells. It seems self-contradictory that FPs, which need their cytoskeleton to continually adapt their pattern of attachment to the GBM (see later discussion), would simultaneously function as contractile pericyte-like processes, counteracting the expansion of the GBM by increasing their tone. Consequently, it may be concluded that the principal burden for counteracting transmural pressure gradients (i.e., for developing wall tension) falls instead on the GBM.[26]

As described earlier, the GBM is an elastic membrane that expands or shrinks in surface area with increasing or decreasing transmural hydrostatic pressure, respectively. Its expansion decreases with increasing pressure and is limited.

Expansion of the GBM affords the immediate coordinated increase in the cover by interdigitated FPs; thus the FPs and the SD have to increase correspondingly (and vice versa when pressure decreases). The ability for such acute adaptions has been previously shown in the isolated perfused kidney. It is suggested that the changes in FP length occur by actin polymerization/depolymerization and the changes in SD length by coordinated exocytotic and endocytotic processes of SD components.[26,27]

An orchestrated connection between the mobility of the actin cytoskeleton and the dynamics of the SD has been uncovered in great depth by innumerable studies during the past two decades.[28,29]

Filtrate flow and shear stress. The flow of the filtrate through the filtration barrier represents by far the highest extravascular fluid flow in the body. It consists of the outflow from glomerular capillaries, through the GBM, and into the Bowman space. This latter step creates a problem: in contrast to the exit of filtrate from capillaries, where flow presses the endothelium against the basement membrane, its entry into the Bowman space tends to separate the podocytes from

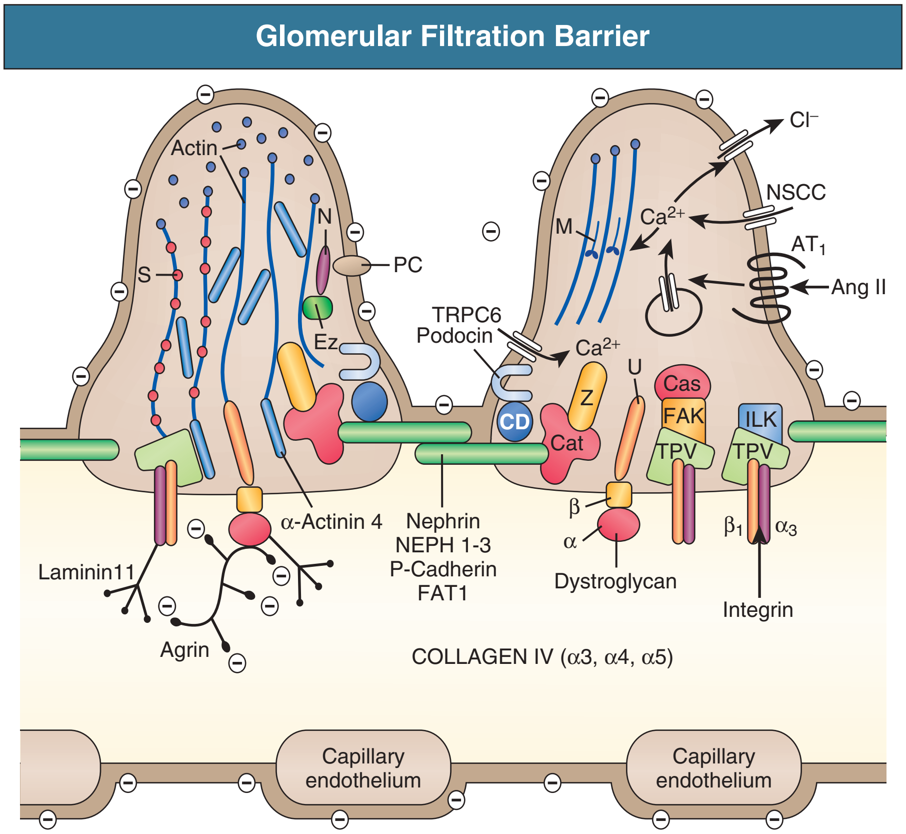


Fig. 1.9 Glomerular filtration barrier. Two podocyte foot processes (FPs) bridged by the slit membrane (SM), the glomerular basement membrane (GBM) and the porous capillary endothelium, are shown. The surfaces of podocytes and of the endothelium are covered by a negatively charged glycocalyx containing the sialoprotein podocalyxin *(PC).* The GBM is mainly composed of type IV collagen (α3, α4, and α5), laminin 11 (α5, β2, and γ1 chains), and the heparan sulfate proteoglycan agrin. The SM represents a porous proteinaceous membrane composed of (as far as is known) nephrin, NEPH 1-3, P-cadherin, and FAT1. The actin-based cytoskeleton of the FPs connects to both the GBM and the SM. Regarding the connections to the GBM, β1α3 integrin dimers specifically interconnect the talin, paxillin, vinculin *(TPV)* complex to laminin 11; the β- and α-dystroglycans interconnect utrophin to agrin. The SM proteins are joined to the cytoskeleton by various adapter proteins, including podocin, Zonula Occludens protein 1 (ZO-1; Z), CD2-associated protein *(CD),* and catenins *(Cat).* Among the nonselective cation channels *(NSCC),* TRPC6 associates with podocin (and nephrin, not shown) at the SM. Only the angiotensin II *(Ang II)* type 1 receptor *(AT_1)* is shown as an example of the many surface receptors. *Cas,* p130Cas; *Ez,* ezrin; *FAK,* focal adhesion kinase; *ILK,* integrin-linked kinase; *M,* myosin; *N,* Na$^+$-H$^+$ exchanger regulatory factor (NHERF2); *S,* synaptopodin. (Modified from reference 17.)

the GBM. The insight that the major way of losing podocytes in disease is by detachment has brought the shear stress created by the filtrate flow into discussion.

The strength of the shear stress depends on the flow rate and the geometry of the channel; the narrower the channel or the higher the flow velocity, the higher is the shear stress. In rats the filtrate flow amounts to 30 nl/min, creating a shear stress to the FPs within the filtration slit as high as 8 Pa.[30] Much lower values of shear stress to the podocyte cell bodies may lead to detachment when podocytes come to lie within the urinary orifice.[27] Moreover, a high sensitivity of podocytes to shear stress has been shown in cell culture studies.

This led to a new view of the relevance of the SM (in addition to its barrier function; see later discussion). Shear stress tends to lead to deformations of the lateral walls of FPs, and thus widens the slit. The interconnection of both opposite FPs by the SD at the narrowest site of the slit is ideally positioned to counteract these destabilizing forces. The SD uses the shear stress against one side of the slit to balance the shear stress against the opposite side. This means that during filtrate flow the SD is permanently under tension that counteracts the shear stress to both sides of the slit.[27]

Barrier function. Filtrate flow through the barrier occurs along an extracellular route, including the endothelial pores, GBM, and SD (see Figs. 1.7 and 1.9). The barrier shows a high permeability for water, small solutes, and ions, whereas the barrier is fairly tight for macromolecules, selective for size, shape, and charge.[20] The charge selectivity of the barrier results from the dense accumulation of negatively charged molecules throughout the entire depth of the filtration barrier, most importantly the surface coat of endothelial cells, and from the high content of negatively charged heparan sulfate proteoglycans in the GBM. Most plasma proteins, including albumin, are negatively charged, and thus their repulsion is dominantly charge dependent.

The size/shape selectivity seems to be established by the SD.[13] Uncharged macromolecules up to an effective radius of 1.8 nm pass freely through the filter. Larger components are increasingly restricted (indicated by their fractional clearances, which progressively decrease) and are totally restricted at effective radii of more than 4 nm. Plasma albumin has an effective radius of 3.6 nm; without the repulsion from the negative charge, plasma albumin would pass through the filter in considerable amounts.

Studies by the group of Marcus Moeller proposed an electrophoretic mechanism for the repulsion and exclusion of plasma proteins from the glomerular filter.[31,32] According to their hypothesis, the flow of the filtrate through the charged filter creates a streaming potential. This electrical field is negatively charged on the urinary side of the glomerular filter compared with the capillary side by approximately –0.05 mV/10 mm Hg filtration pressure. Thus the negatively charged molecules (albumin) that approach the filter will be exposed to an electrophoretic force that drives them back toward the capillary lumen. The charm of this hypothesis consists of being independent of any structural pore preventing their passage. The barrier actually consists of a strictly filtration-dependent potential difference; without sufficient convective flow of filtrate, the barrier will become permeable.[31,32]

Pathology. The hypothesis that the mechanical interconnection of the FPs by the SD is the most vulnerable structure to the physical challenges of filtration is supported by the pathologic changes. The loss of the SD connection between adjacent FPs represents the earliest failure that starts the detachment of podocytes.[27]

This can be interpreted as the loss of local control of filtrate flow. Unchanneled filtrate flow through such leaks will exert unbalanced shear stress to the FPs, initiating locally the detachment of FPs. Repair of such leaks seems impossible in the face of ongoing filtrate flow, accounting for the observation that the damage will proceed.

Taken together, the layer of interdigitating FPs interconnected by the SD regulates the entry of the filtrate flow into the Bowman space by channeling the flow through the filtration slits. The geometry of the slits is maintained against the shear forces to both opposite FPs through the interconnection of opposing FPs by the SD. Loss of the junctional connection is detrimental because it opens leaks for uncontrolled filtrate flow with the tendency to increase the leaks.[33]

Parietal Epithelium

The parietal epithelium of the Bowman capsule consists of squamous epithelial cells resting on a basement membrane (see Figs. 1.4 and 1.5). The flat cells are filled with bundles of actin filaments running in all directions. In contrast to the GBM, the parietal basement membrane comprises several proteoglycan-dense layers that, in addition to type IV, contain type XIV collagen. The predominant proteoglycan of the parietal basement membrane is a chondroitin sulfate proteoglycan.[34]

Renal Tubule

The renal tubule is subdivided into several distinct segments: a proximal tubule (convoluted and straight portions), an intermediate tubule, a distal tubule (straight and convoluted portion), a CNT, and the CD (see Figs. 1.1 and 1.3).[1,2,34] The loop of Henle comprises the straight part of the proximal tubule (representing the thick descending limb), the thin descending and the thin ascending limbs (both thin limbs together represent the intermediate tubule), and the thick ascending limb (representing the straight portion of the distal tubule), which includes the macula densa. The CNT connects the nephron to the CD system.

The renal tubules are outlined by an epithelium that comprises a single layer of cells anchored to a basement membrane. The epithelial cells have multiple transport functions and show numerous structural adaptations to their special roles. They are connected apically by a junctional complex consisting of a tight junction (zonula occludens), an adherens junction, and, at some sites, a desmosome. As a result of this organization, two different pathways through the epithelium exist (Fig. 1.10): a transcellular pathway, including the transport across the luminal and basolateral cell membrane and through the cytoplasm and a paracellular pathway through the junctional complex and the lateral intercellular spaces. The functional characteristics of paracellular transport are determined by the tight junction, which differs markedly in its elaboration in the various tubular segments. The transcellular transport is determined by the specific channels, carriers, and transporters included in the apical and basolateral cell membranes. The various nephron segments differ markedly in function, distribution of transport proteins, and responsiveness to hormones and drugs such as diuretics. The cell surface area of the plasmalemmal compartments carrying the transport systems is extensively enlarged in many tubule cells, that is, by microvilli at the luminal membrane domain, by lamellar folds of the basolateral membrane interdigitating with those of the neighboring cells (interdigitations), or by lamellar folds of the basal cell membrane invaginating into its own cells (invaginations).

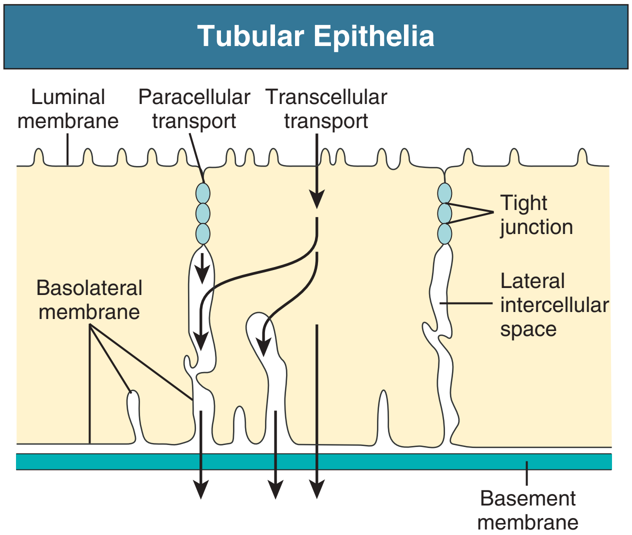


Fig. 1.10 **Tubular epithelia.** Transport across the epithelium may follow two routes: transcellular, across luminal and basolateral membranes, and paracellular, through the tight junction and intercellular spaces.

Proximal Tubule

The proximal tubule reabsorbs the bulk of filtered water and solutes (Fig. 1.11). The proximal tubule is generally subdivided into three segments (known as S_1, S_2, and S_3) that differ considerably in cellular organization and, consequently, also in function.[35] Generally, the proximal tubule has a prominent brush border and e xtensive interdigitation by basolateral cell processes. This lateral cell interdigitation extends up to the leaky tight junction, thus increasing the tight junctional belt in length and providing a greatly increased passage for the passive transport of ions. Proximal tubule cells have large prominent mitochondria intimately associated with the basolateral cell membrane where the Na^+,K^+–adenosine triphosphatase (Na^+,K^+-ATPase) is located; this machinery is the molecular mechanism initiating numerous secondary transcellular transport processes. The luminal transporter for Na^+ reabsorption specific for the proximal tubule is the Na^+-H^+ exchanger (NHE3) located in the plasma membrane of the apical microvilli and accounts for reabsorption of most of the filtered sodium. Further, sodium-coupled transporters in the microvillous membrane are the sodium-glucose cotransporters SGLT2 and SGLT1 and several sodium-phosphate cotransporters. The abundance of channel protein aquaporin 1 in the apical microvillous membrane and the basolateral cell membrane accounts for the high hydraulic permeability for water of this epithelium. An apical tubulovesicular compartment is part of the prominent

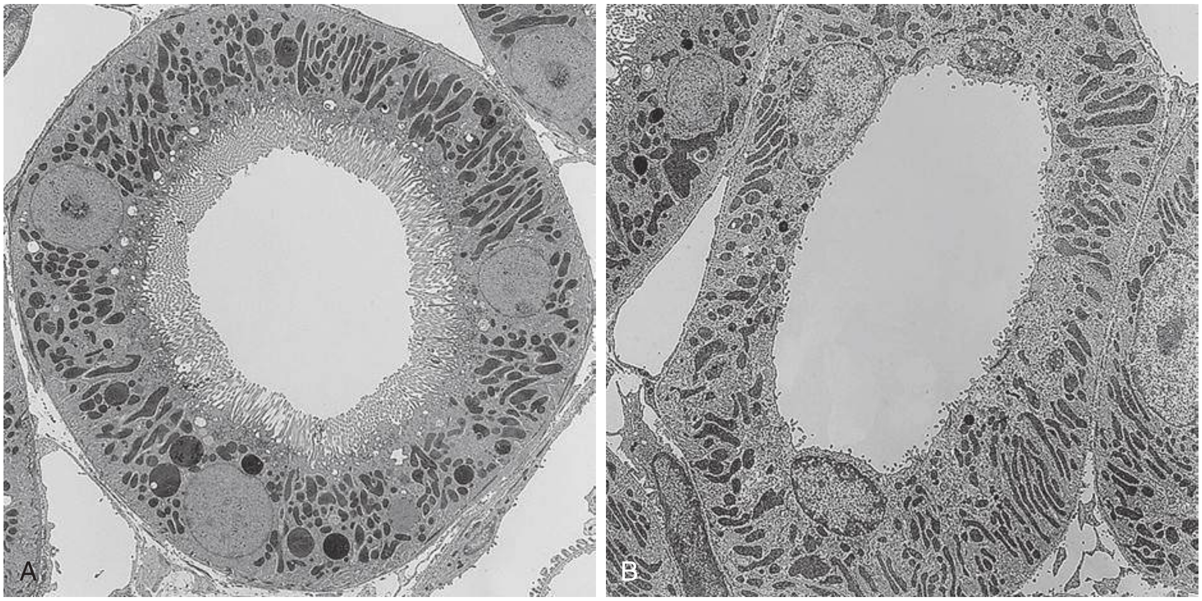


Fig. 1.11 Tubules of the renal cortex. (A) Proximal convoluted tubule is equipped with a brush border and a prominent vacuolar apparatus in the apical cytoplasm. The rest of the cytoplasm is occupied by a basal labyrinth consisting of large mitochondria associated with basolateral cell membranes. (B) Distal convoluted tubule also has interdigitated basolateral cell membranes intimately associated with large mitochondria. In contrast to the proximal tubule, however, the apical surface is amplified only by some stubby microvilli. (TEM; **A,** ×1530; **B,** ×1830.)

endosomal-lysosomal system and is responsible for the reabsorption of macromolecules (polypeptides and proteins such as albumin) that have passed the glomerular filter. The proximal tubule segment S_3, including portions of S_2, in addition, are engaged in many secretory processes of toxic substances and drugs via organic anion transporters and anorganic cation transporters. Proximal tubule cells are electrically coupled by gap junctions.

Intermediate Tubule

The intermediate tubule comprises the thin portion of the loop of Henle displaying a flat epithelium and consists of a thin descending and (only in long loops) a thin ascending limb (Fig. 1.12; see also Fig. 1.2). The thin descending limb, like the proximal tubule, is highly permeable for water (the channels are of aquaporin 1), whereas, beginning at the turning point, the thin ascending limb is impermeable to water. The latter has a highly interdigitated epithelium also along the tight junction, which is highly permeable to ions.

Distal Straight Tubule (Thick Ascending Limb of the Loop of Henle)

The thick ascending limb of the loop of Henle is often called the diluting segment. It is water impermeable but reabsorbs considerable amounts of sodium and chloride, resulting in the separation of salt from water. The salt is trapped in the medulla (see Fig. 1.12), whereas the water is carried away into the cortex, where it may return into the systemic circulation. The specific transporter for Na^+ reabsorption in this segment is the $Na^{2+}K^{2+}2Cl^-$ symporter (NKCC2), which is specifically inhibited by loop diuretics such as furosemide. This transporter is inserted in the luminal membrane, which is amplified by only solitary microvilli. The tight junctions of the thick ascending limb are elongated by lateral interdigitation of the cells. They have a comparatively low overall permeability; however, they contain the protein Claudin 16 for paracellular reabsorption of divalent ions, notably of magnesium. The cells are heavily interdigitated by basolateral cell processes, associated with large mitochondria supplying the energy for the transepithelial transport. The cells synthesize a specific protein, the Tamm-Horsfall protein, and release it into the tubular lumen. This protein is thought to be important for preventing the formation of kidney stones. A short distance before the transition to the distal convoluted tubule, the thick ascending limb contains the macula densa, which adheres to the glomerulus of the same nephron (see Juxtaglomerular Apparatus).

Distal Convoluted Tubule

The epithelium exhibits the most extensive basolateral interdigitation of the cells and the greatest numerical density of mitochondria compared with all other nephron portions (see Fig. 1.11). Apically, the cells are equipped with numerous solitary microvilli. The specific Na^+ transporter of the distal convoluted tubule is the luminal $Na^{2+}Cl^-$ cotransport system (NCC), which can be inhibited by the thiazide diuretics. Magnesium is reabsorbed via the transient receptor potential channel melastatin subtype 6 (TRPM6) in the luminal membrane and, along the paracellular route, through the tight junctional proteins Claudin 16 and 19.

COLLECTING DUCT SYSTEM

The CD system (see Fig. 1.2) includes the CNT and the cortical and medullary CDs. The embryologic origin of the CNT, which is interposed between the distal convoluted tubule and the CD, is unclear in whether it derives from the nephron anlage or the ureteral bud. Two nephrons may join at the level of the CNT, forming an arcade. Two types of cell establish the CNT: the CNT cell, which is specific to the CNT, and the intercalated (IC) cell, which is also present in varying amounts in the distal convoluted tubule and in the CD. The CNT cells are similar to the CD cells in cellular organization. Both cell types share sensitivity

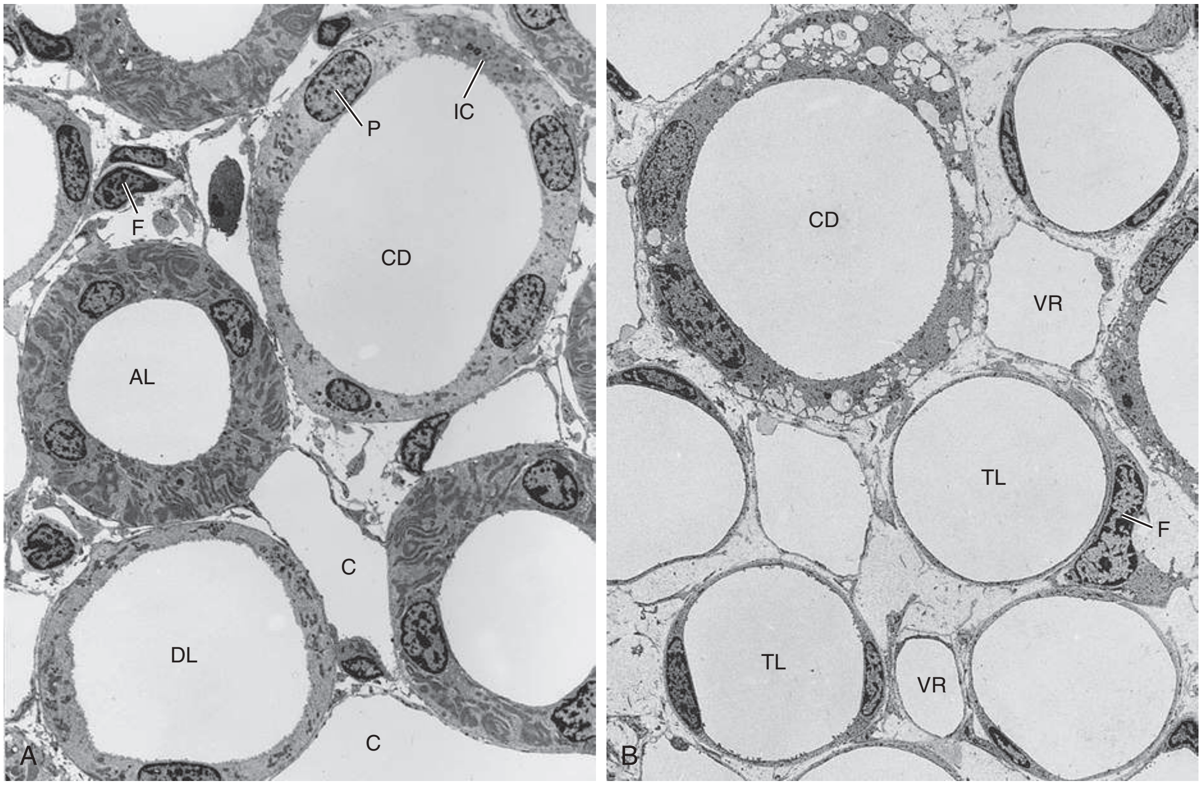


Fig. 1.12 **Tubules in the medulla.** (A) Cross section through the inner stripe of the outer medulla shows a descending thin limb of a long Henle loop *(DL),* the medullary thick ascending limbs of Henle *(AL),* and a collecting duct *(CD)* with principal *(P)* cells and intercalated *(IC)* cells. *C,* Peritubular capillaries; *F,* fibroblast. (B) In the inner medulla cross section, thin descending and ascending limbs *(TL),* a collecting duct *(CD),* and vasa recta *(VR)* are seen. (TEM; **A,** ×990; **B,** ×1120.)

to vasopressin (antidiuretic hormone [ADH]; see later discussion). The amiloride-sensitive epithelial sodium channel (ENaC) and the epithelial calcium channel (TRPV5) are located in the apical membrane beginning in the distal convoluted tubule and extending into the CNT.

Collecting Ducts

The CDs (see Fig. 1.12) may be subdivided into cortical and medullary ducts, and the medullary ducts into an outer and inner portion; the transitions are gradual. Like the CNT, the CDs are lined by two types of cell: CD cells (principal cells) and IC cells. The IC cells decrease in number as the CD descends into the medulla and are absent from the inner medullary CDs.

The CD cells (Fig. 1.13A) increase in size toward the tip of the papilla. The basal cell membrane amplifies by lamellar invaginations into the cell (basal infoldings). The tight junctions have a large apicobasal depth, and the apical cell surface has a prominent glycocalyx. Along the entire CD, these cells contain an apical shuttle system for aquaporin 2 under the control of vasopressin, providing the potential to switch the water permeability of the CDs from zero to very low levels to permeable.[36] A luminal amiloride-sensitive Na^+ channel is involved in the responsiveness of cortical CDs to aldosterone. The terminal portions of the CD in the inner medulla express the urea transport system UTB1, which, in an antidiuretic hormone (ADH)-dependent fashion, accounts for the recycling of urea, a process that is crucial in the urine-concentrating mechanism.[37,38]

The second cell type, the IC cell (see Fig. 1.13B), is present in both the CNT and the CD. There are at least two types of IC cells, designated A and B cells, distinguished on the basis of structural, immunocytochemical, and functional characteristics. Type A cells have been defined as expressing an H^+-ATPase at their luminal membrane; they secrete protons. Type B cells express H^+-ATPase at their basolateral membrane; they secrete bicarbonate ions and reabsorb protons.[38]

With these different cell types, the CDs are the final regulators of fluid and electrolyte balance, playing important roles in the handling of Na^+, Cl^-, and K^+ and in acid-base homeostasis. The responsiveness of the CDs to vasopressin enables an organism to live in arid conditions, allowing production of concentrated urine and, if necessary, dilute urine.

JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus comprises the macula densa, the extraglomerular mesangium, the terminal portion of the afferent arteriole with its renin-producing granular cells (also often termed *juxtaglomerular cells*), and the beginning portions of the efferent arteriole (see Fig. 1.4).

The macula densa is a plaque of specialized cells in the wall of the thick ascending limb of Henle at the site where the limb attaches to the extraglomerular mesangium of the parent glomerulus (Fig. 1.14A; see also Fig. 1.5). The most obvious structural feature is the narrowly packed cells with large nuclei, which account for the name macula *densa.* The cells are anchored to a basement membrane, which blends with the matrix of the extraglomerular mesangium. The cells are joined by tight junctions with very low permeability and have prominent lateral

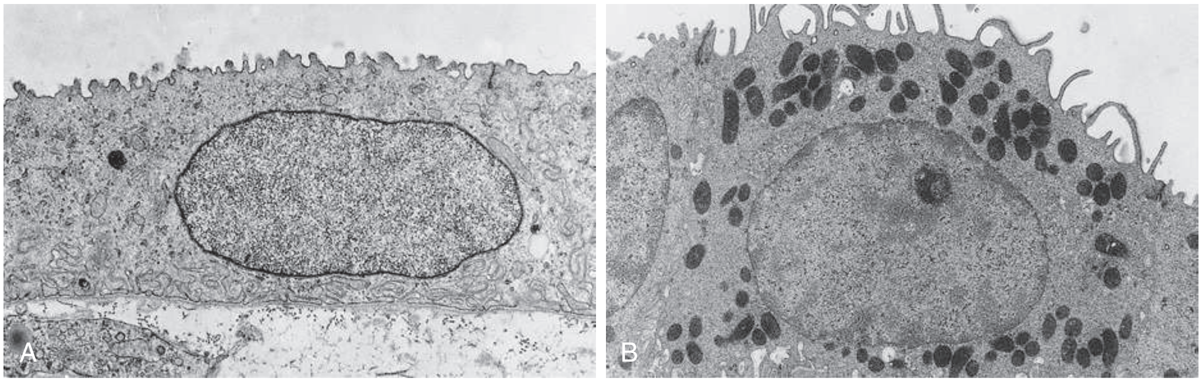


Fig. 1.13 **Collecting duct cells.** (A) Principal cell (CD cell) of a medullary collecting duct. The apical cell membrane bears some stubby microvilli covered by a prominent glycocalyx; the basal cell membrane forms invaginations. Note the deep tight junction. (B) Intercalated cells, type A. Note the dark cytoplasm *(dark cells)* with many mitochondria and apical microfolds; the basal membrane forms invaginations. (TEM; **A,** ×8720; B, ×6970.)

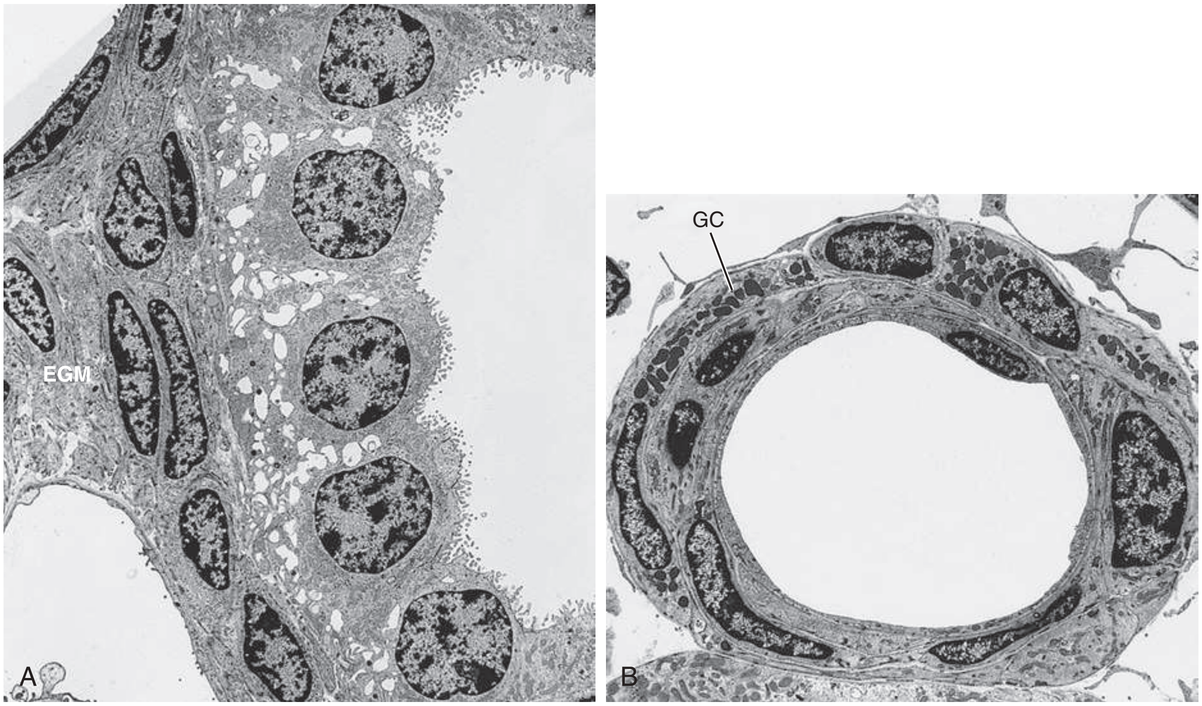


Fig. 1.14 **Juxtaglomerular apparatus.** (A) Macula densa of a thick ascending limb of Henle. The cells have prominent nuclei and lateral intercellular spaces. Basally, they attach to the extraglomerular mesangium *(EGM).* (B) Afferent arteriole near the vascular pole. Several smooth muscle cells are replaced by granular cells *(GC)* containing accumulations of renin granules. (TEM; **A,** ×1730; **B,** ×1310.)

intercellular spaces. The width of these spaces varies under different functional conditions.[1] The most conspicuous immunocytochemical difference between macula densa cells and other epithelial cells of the nephron is the high content of neuronal nitric oxide synthase and cyclooxygenase-2 in macula densa cells.[39,40]

The basal aspect of the macula densa is firmly attached to the extraglomerular mesangium, a solid complex of cells and matrix penetrated by neither blood vessels nor lymphatic capillaries. As with the mesangial cells proper, extraglomerular mesangial cells are heavily branched. Their processes are interconnected by gap junctions, contain prominent bundles of microfilaments, and are connected to the basement membrane of the Bowman capsule and the walls of both glomerular arterioles. As a whole, the extraglomerular mesangium interconnects all structures of the glomerular entrance.[6]

The granular cells are assembled in clusters within the terminal portion of the afferent glomerular arteriole (see Fig. 1.14B), replacing ordinary smooth muscle cells. *Granular* refers to the specific cytoplasmic granules in which renin, the major secretion product of these cells, is stored. Granular cells are the main site of the body where renin is secreted. Renin release occurs by exocytosis into the surrounding interstitium. Granular cells are connected to extraglomerular mesangial cells, adjacent smooth muscle cells, and endothelial cells by gap junctions and are densely innervated by sympathetic nerve terminals. Granular cells are modified smooth muscle cells; under conditions requiring enhanced renin synthesis (e.g., volume depletion, renal artery stenosis), additional smooth muscle cells of the afferent arteriole may transform into granular cells.

RENAL INTERSTITIUM

The interstitium of the kidney is comparatively sparse. Its fractional volume in the cortex ranges from 5% to 7%, with a tendency to increase with age. Renal interstitium increases across the medulla from cortex to papilla. In the outer stripe, it is 3% to 4%, the lowest value of all kidney zones; this is interpreted as forming a barrier to prevent loss of solutes from a hyperosmolar medulla into the cortex. Renal interstitium is 10% in the inner stripe and up to about 30% in the inner medulla. The cellular constituents of the interstitium include resident fibroblasts, which establish the scaffold frame for renal corpuscles, tubules, and blood vessels, as well as varying numbers of migrating cells of the immune system, especially dendritic cells. The space between the cells is filled with extracellular matrix, that is, ground substance (proteoglycans, glycoproteins), fibrils, and interstitial fluid.[41]

Morphologically, fibroblasts are the central cells in the renal interstitium. Fibroblasts are interconnected by specialized contacts and adhere by specific attachments to the basement membranes surrounding the tubules, renal corpuscles, capillaries, and lymphatics.

Renal fibroblasts are difficult to distinguish from interstitial dendritic cells on a morphologic basis, because both may show a stellate cellular shape and both display substantial amounts of mitochondria and endoplasmic reticulum. However, renal fibroblasts may be easily distinguished by immunocytochemical techniques. Dendritic cells constitutively express the major histocompatibility complex class II antigen and may express antigens such as CD11c. Dendritic cells may have an important role in maintaining peripheral tolerance in the kidney (Fig. 1.15).[42] In contrast, fibroblasts in the renal cortex (not in the medulla) contain the enzyme ecto-5′-nucleotidase (5′-NT). A subset of 5′-NT–positive fibroblasts of the renal cortex synthesizes epoetin.[43] Under normal conditions, these fibroblasts are exclusively found within the juxtamedullary portions of the cortical labyrinth. When there is an increasing demand for epoetin, the synthesizing cells extend to more superficial portions of the cortical labyrinth.[44]

Fibroblasts within the medulla, especially within the inner medulla, have a particular phenotype known as *lipid-laden interstitial cells.* The cells are oriented strictly perpendicularly toward the longitudinal axis of the tubules and vessels (running all in parallel) and contain conspicuous lipid droplets. These fibroblasts of the inner medulla produce large amounts of glycosaminoglycans and, possibly related to the lipid droplets, vasoactive lipids, in particular PGE_2.[42]

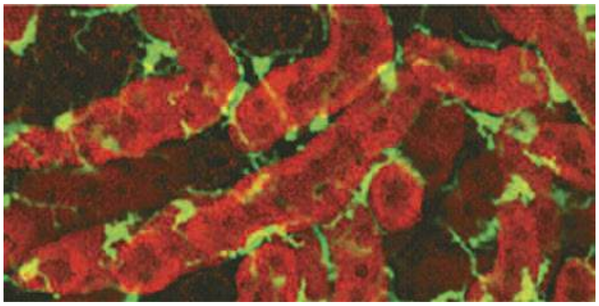


Fig. 1.15 **Renal dendritic cells.** Dendritic cells ($CX_3CR_1^+$ cells, *green*) surrounding tubular segments in the medulla of mice (three-dimensional reconstruction). (Reprinted with permission from reference 18.)

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SELF-ASSESSMENT QUESTIONS

1. Podocytes:
   - **A.** Are unable to replicate
   - **B.** Are connected by gap junctions
   - **C.** Have a positively charged glycocalyx
   - **D.** Are connected to the GBM by hemidesmosomes
   - **E.** Are in direct contact with mesangial cells
2. The glomerular basement membrane:
   - **A.** Consists of α1 and α2 chains of type IV collagen
   - **B.** Is produced mainly by the endothelium of glomerular capillaries
   - **C.** Transforms at the urinary pole of a glomerulus into the basement membrane of the parietal epithelium
   - **D.** Has a thickness of roughly 300 μm in humans
   - **E.** Serves as the effector structure of mesangial cell contraction
3. The slit membrane has a width of roughly:
   - **A.** 30 nm
   - **B.** 100 nm
   - **C.** 300 nm
   - **D.** 1 μm
   - **E.** 3 μm
4. Macula densa cells:
   - **A.** Are a cell plaque within the distal convoluted tubule
   - **B.** Are connected to the extraglomerular mesangial cells by gap junctions
   - **C.** Are densely innervated by sympathetic nerve terminals
   - **D.** Contain nitric oxide synthase
   - **E.** Produce renin

2

Renal Physiology

Matthew A. Bailey, Robert J. Unwin

GLOMERULAR STRUCTURE AND ULTRASTRUCTURE

Urine formation begins with the production of an ultrafiltrate of plasma. Chapter 1 describes glomerular anatomy and ultrastructure in detail, and the present discussion provides only the essentials for an understanding how the ultrafiltrate is formed. The pathway for ultrafiltration of plasma from the glomerulus to the Bowman space consists of the fenestrated capillary endothelium, the capillary basement membrane, and the visceral epithelial cell layer (podocytes) of the Bowman capsule; the podocytes have large cell bodies and make contact with the basement membrane only by cytoplasmic foot processes. Mesangial cells, which fill the spaces between capillaries, have contractile properties and can alter the capillary surface area available for filtration.

Filtration is determined principally by the molecular size and shape of the filtered solute and to a lesser extent by its charge. The size cut-off is not absolute, with resistance to filtration beginning at an effective molecular radius of just under 2 nm, whereas substances with an effective radius of around 4 nm or greater are not filtered at all. The fenestrations between capillary endothelial cells have a diameter of 50 to 100 nm. The podocyte foot processes have gaps—filtration slits—with a diameter of 30 to 40 nm. The filtration slits are bridged by the slit diaphragms (SDs), which are themselves penetrated by small pores. The SDs likely constitute the main filtration barrier, although the endothelium (by preventing the passage of blood cells) and the basement membrane also contribute.[1] Furthermore, the podocytes and endothelial cells are covered by a glycocalyx composed of negatively charged glycoproteins, glycosaminoglycans, and proteoglycans, and the basement membrane is rich in heparan sulfate proteoglycans. This accumulation of fixed negative charges restricts filtration of large negatively charged ions, mainly proteins (Fig. 2.1). Thus, with an effective radius of 3.6 nm (35 Å), albumin is normally almost completely excluded from filtration. If these fixed negative charges are lost, as in some forms of early or mild glomerular disease (e.g., minimal change disease), albumin filterability increases and proteinuria results. However, it has been proposed that albumin is normally filtered and then almost completely reabsorbed along the proximal tubule; this remains controversial. Proximal tubular cells can take up albumin, and genetic engineering experiments in mice have identified two proteins in the apical membrane—megalin and cubilin—as essential components of this uptake pathway.[2] However, deletion of this tubular transport system increases albumin excretion only approximately sixfold, suggesting that glomerular filtration is normally low and is still the major determinant of urinary albumin excretion. Nonetheless, recent studies suggest that the filtration-to-reabsorption relationship is dynamic and physiologically regulated.[3] The relationship is changed in diseases such as diabetic nephropathy, contributing to overall albuminuria.[4]

The glomerular barrier is usually considered to be a passive unidirectional filter, but this is not the case. Filtration pressure generates a potential difference across the filtration barrier, and although its magnitude is small, this potential difference may help in clearing the filter continuously by driving negatively charged proteins such as albumin out of the SD and back into the blood.[5]

GLOMERULAR FILTRATION RATE

At the level of the single glomerulus, the driving force for glomerular filtration (the *net ultrafiltration pressure*) is determined by the sum of the hydrostatic and oncotic (colloid osmotic) pressure gradients from plasma to the Bowman space. The single-nephron glomerular filtration rate (SNGFR) is determined by the product of the net ultrafiltration pressure and the *ultrafiltration coefficient;* the latter being a composite of the surface area available for filtration and the hydraulic conductivity of the glomerular membranes. Thus the SNGFR is calculated as:

$$K_f[(P_{gc} - P_{bs}) - (\pi_{gc} - \pi_{bs})]$$

where K_f is the ultrafiltration coefficient, P_{gc} is the glomerular capillary hydrostatic pressure (~45 mm Hg), P_{bs} is the Bowman space hydrostatic pressure (~10 mm Hg), π_{gc} is the glomerular capillary oncotic pressure (~25 mm Hg), and π_{bs} is the Bowman space oncotic pressure (0 mm Hg).

Net ultrafiltration pressure is approximately 10 mm Hg at the afferent end of the capillary tuft. As filtration of plasma from blood proceeds along the glomerular capillaries, proteins are concentrated and the glomerular capillary oncotic pressure (π_{gc}) increases. Theoretically, toward the efferent end of a glomerular capillary, π_{gc} may equal the net hydrostatic pressure gradient, at which point ultrafiltration pressure would fall to zero: *filtration equilibrium* in the human kidney is approached, but rarely (if ever) achieved (Fig. 2.2).

The (total) glomerular filtration rate (GFR) is the sum of the SNGFRs of the functioning nephrons in each kidney. The normal range for GFR is wide, but is typically cited at about 120 ml/min per 1.73 m^2 surface area. GFR can be measured with renal clearance techniques. The renal clearance of any substance not metabolized by the kidneys is the volume of plasma required to provide that amount of the substance excreted in the urine per unit time. This is a virtual volume that can be expressed mathematically as follows:

$$C_y = U_y/P_y \times V$$

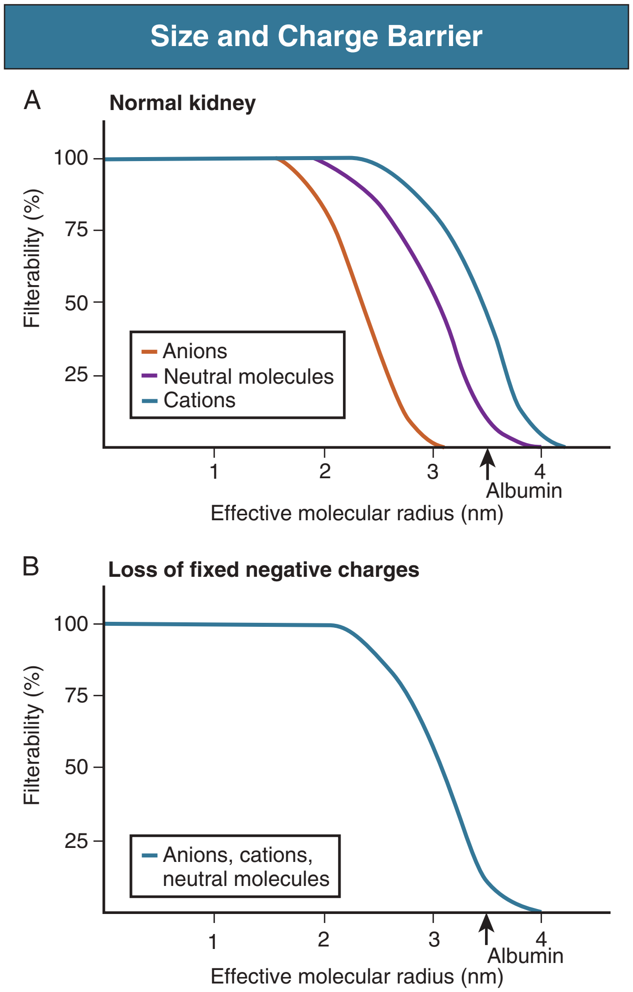

Fig. 2.1 Effects of size and electrical charge on filterability. (A) Normal kidney. (B) Loss of fixed negative charges. Filterability of 100% indicates the substance is freely filtered; that is, its concentration in the Bowman space equals that in glomerular capillary plasma. For molecules and small ions (e.g., Na^+, Cl^-), charge has no effect on filterability; but for ions whose effective molecular radius exceeds 1.6 nm, anions are filtered less easily than neutral molecules or cations. Thus insignificant amounts of albumin (anion) are normally filtered. If the fixed negative charges of the glomerular basement membranes are lost, as in early minimal change nephropathy, charge no longer influences filterability; consequently, significant albumin filtration occurs.

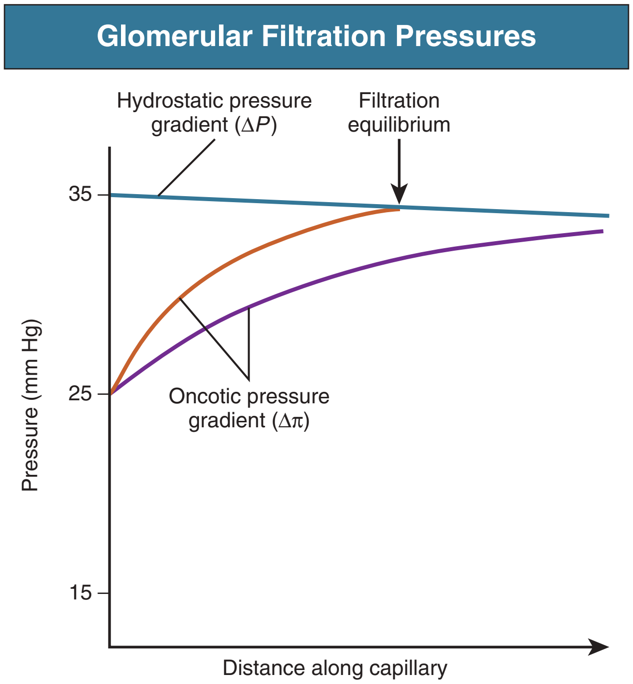

Fig. 2.2 Glomerular filtration pressures along a glomerular capillary. The hydrostatic pressure gradient ($\Delta P = P_{gc} - P_{bs}$) is relatively constant along the length of a capillary, whereas the opposing oncotic pressure gradient ($\Delta\pi = \pi_{gc}$) increases as protein-free fluid is filtered, thereby reducing net ultrafiltration pressure. Two curves are shown: one in which filtration equilibrium is reached and one in which it is merely approached.

where C_y is the renal clearance of y; U_y and P_y are the concentrations of y in the urine and plasma, respectively, and V is the urine flow rate. If a substance is freely filtered by the glomerulus and is not reabsorbed or secreted by the tubule, its renal clearance equals the GFR; that is, renal clearance measures the volume of plasma filtered through the glomeruli per unit time. The various methods for measuring GFR and their pitfalls are discussed in Chapter 3.

MEASUREMENT OF RENAL PLASMA FLOW

The use of the clearance technique and the availability of substances that undergo both glomerular filtration and almost complete (or *effective*) tubular secretion have made it possible to measure renal plasma flow (RPF; typically ~650 ml/min). Para-aminohippuric acid (PAH, hippurate) is an organic acid filtered by the glomerulus and actively secreted by the proximal tubule through organic anion transporters in the cell membranes. The amount of PAH found in the urine is the sum of that filtered plus that secreted. PAH clearance is measured using intravenous (IV) infusion to achieve a steady-state plasma concentration of PAH. When the plasma concentration is less than 10 mg/dl, PAH clearance is a robust marker of *effective* RPF, because under this concentration threshold most of the PAH reaching the peritubular capillaries is cleared by tubular secretion. Little PAH appears in renal venous plasma, and the amount found in the final urine approximates that delivered to the kidneys in the plasma. Therefore:

$$\mathrm{RPF} \times \mathrm{P_{PAH}} = \mathrm{U_{PAH}} \times \mathrm{V}$$
$$\text{or } \mathrm{RPF} = (\mathrm{U_{PAH}} \times \mathrm{V})/\mathrm{P_{PAH}} = \text{PAH clearance}$$

where U_{PAH} and P_{PAH} are the concentrations of PAH in the urine and plasma, respectively, and V is the urine flow rate. Renal blood flow (RBF) can be calculated as follows:

$$\mathrm{RBF} = [\mathrm{RPF}/(100 - \text{Hematocrit})] \times 100$$

Typically, RBF is approximately 1200 ml/min.

The most important limitation of this method is the renal extraction of PAH, which is always less than 100%. At high plasma concentrations, greater than 10 mg/dl, the organic anion transport (OAT) proteins that mediate PAH secretion become saturated, the fractional tubular secretion of PAH declines, and considerable amounts of PAH appear in the renal veins. When this occurs, PAH clearance significantly underestimates RPF. In patients with liver or renal failure, the production of toxins and weak organic acids can interfere with PAH secretion or cause tubular damage, leading to inhibition of PAH transport. Certain drugs, such as probenecid, are organic acids and compete with PAH for tubular

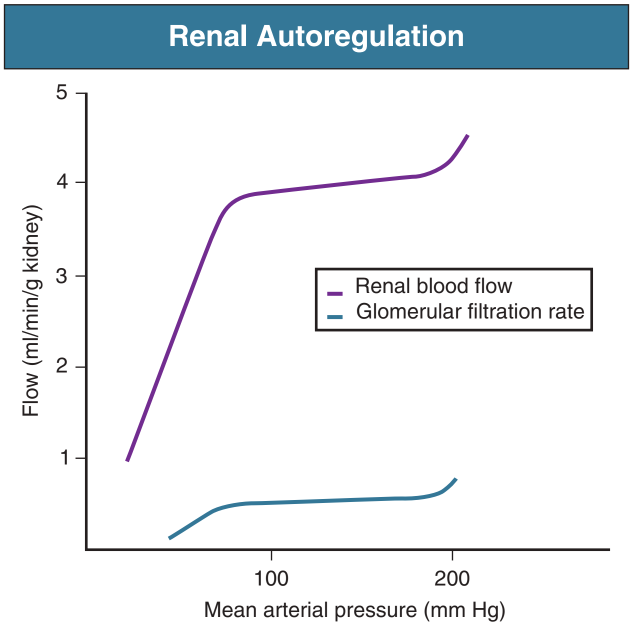

Fig. 2.3 Renal autoregulation of renal blood flow and glomerular filtration rate. If mean arterial blood pressure is in the range of 80 to 180 mm Hg, fluctuations in blood pressure have only marginal effects on renal blood flow and glomerular filtration rate. This is an intrinsic mechanism and can be modulated or overridden by extrinsic factors.

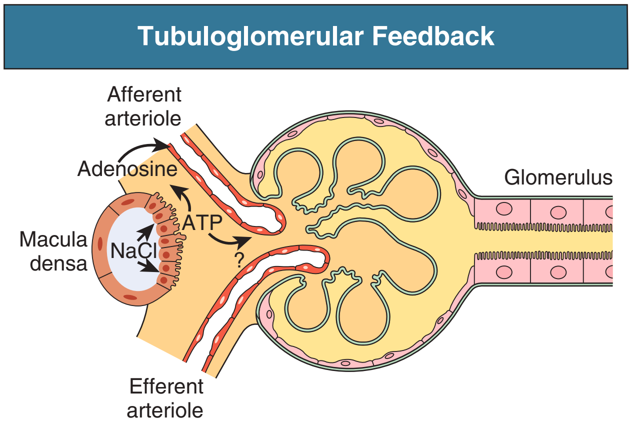

Fig. 2.4 Tubuloglomerular feedback. Changes in the delivery of NaCl to the macula densa region of the thick ascending limb of the Henle loop cause changes in the afferent arteriolar caliber. The response is mediated by adenosine triphosphate (ATP), either directly or after metabolism to adenosine, and modulated by other locally produced agents such as angiotensin II and nitric oxide. Increased macula densa NaCl delivery results in afferent arteriolar constriction, thereby reducing GFR.

secretion, thereby reducing PAH clearance. Moreover, the expression of the OAT proteins is hormonally regulated, influencing the extraction efficiency of PAH.

In a variety of patient settings, the secretion of PAH can be influenced by the abundance/pharmacokinetics of the OAT pathway, and PAH clearance can be independent of true RPF. Given that PAH clearance is invasive (requiring intravenous infusion) and expensive and has the potential to be nonquantitative, alternative nonoptical imaging approaches, such as Doppler ultrasound and arterial spin labeling magnetic resonance imaging, are being refined to measure RBF.[6]

AUTOREGULATION OF RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Although acute physiologic variations in arterial blood pressure cause corresponding changes in RBF and GFR, these are usually short-lived, because compensatory (autoregulation) mechanisms return both RBF and GFR toward normal within seconds[7] (Fig. 2.3). Autoregulation is achieved primarily at the level of the afferent arterioles and is believed to result from a combination of the following two mechanisms:

Myogenic reflex. Increased renal perfusion pressure stretches arteries and afferent arterioles, depolarizing smooth muscle cells to promote constriction of the vessel wall.

Tubuloglomerular feedback (TGF). Increased renal perfusion pressure will increase delivery of sodium chloride (NaCl) to the nephron's macula densa region, a specialized plaque of cells at the distal end of the ascending limb of Henle. Increased delivery is sensed by the macula densa, promoting vasoconstriction of the afferent arteriole supplying the same nephron's glomerulus.

These mechanisms are tonically active and dynamic. In combination, they act to restore both RBF and P_{gc} toward normal, reversing the initial change in GFR. The TGF system is possible because of the juxtaglomerular apparatus (see Chapter 1), which consists of the macula densa region of each nephron, the adjacent glomerulus, and afferent and efferent arterioles (Fig. 2.4). Both myogenic and TGF mechanisms are dependent on extracellular adenosine triphosphate (ATP) signaling. ATP is released from cells during vascular stretch and can promote vasoconstriction via P2Y6 purinoceptors.[8] ATP is also the primary mediator of TGF. Increased NaCl delivery to the macula densa leads to increased NaCl uptake by these cells through a furosemide-sensitive $Na^+,K^+,2Cl^-$ cotransporter, triggering ATP release into the surrounding extracellular space.[9] ATP can have a direct vasoconstrictor effect on the afferent arteriole, activating $P2X_1$ purinoceptors to depolarize the smooth muscle cells. However, because the macula densa is anatomically separated from the afferent arteriole by the extraglomerular mesangium, the final signal for TGF is likely to be adenosine, rather than ATP, acting on afferent arteriolar A_1 receptors to cause vasoconstriction.[9] The sensitivity of TGF is modulated by locally produced angiotensin II (Ang II), nitric oxide (NO), and certain eicosanoids (see later discussion).

The TGF regulation of GFR may be more complex than usually described, with evidence for regulatory cross-talk between the distal nephron and vasculature sites beyond the macula densa,[10] as well as for synchronization of blood flow across networks of nephrons in response to changes in sodium delivery.[11]

Despite renal autoregulation, several extrinsic factors (neural and humoral) can alter renal hemodynamics. Independent or unequal changes in the resistance of afferent and efferent glomerular arterioles, together with alterations in K_f (thought to result largely from mesangial cell contraction/relaxation), can result in disproportionate, or even contrasting, changes in RBF and GFR. In addition, changes in regional vascular resistance can alter the distribution of blood flow within the kidney. For example, medullary vasoconstriction may affect whole-kidney blood flow, because blood can be diverted through the cortex; nevertheless, this renders the medulla hypoxic and vulnerable to ischemic injury.[12] Fig. 2.5 indicates how changes in afferent and efferent arteriolar resistance can affect net ultrafiltration. Table 2.1 lists some of the vasoactive factors that can alter renal hemodynamics (see Integrated Control of Renal Function). In addition, damage to the renal afferent arteriole, as in patients with hypertension and progressive kidney disease, also may interfere with renal autoregulatory mechanisms.

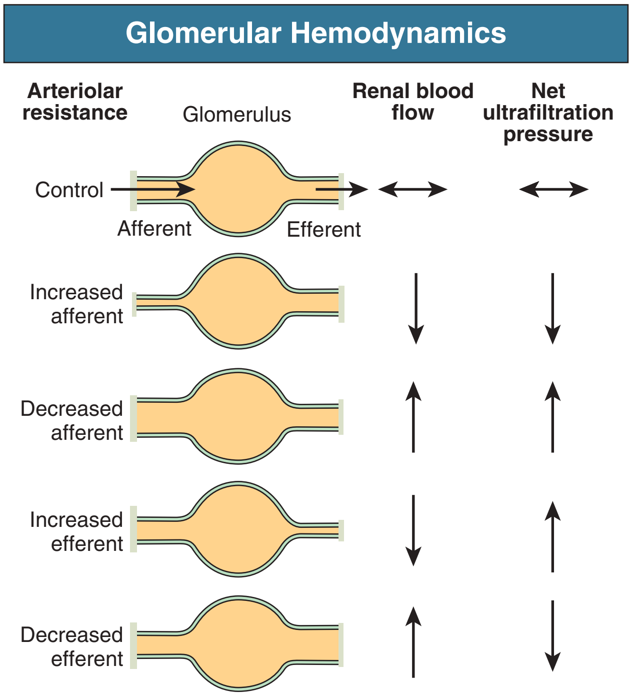

Fig. 2.5 **Glomerular hemodynamics.** Changes in afferent or efferent arteriolar resistance will alter renal blood flow and (usually) net ultrafiltration pressure. However, the effect on ultrafiltration pressure depends on the relative changes in afferent and efferent arteriolar resistance. The overall effect on glomerular filtration rate will depend not only on renal blood flow and net ultrafiltration pressure but also on the ultrafiltration coefficient (K_f; see Table 2.1).

TUBULAR TRANSPORT

Vectorial transport is net movement of substances from tubular fluid to blood (reabsorption) or vice versa (secretion). The cell membrane facing the tubular fluid (*luminal* or *apical*) must have different properties than the membrane facing the blood (*peritubular* or *basolateral*). Such epithelia are said to be "polarized," thus allowing the net movement of substances across the cell (transcellular route). The *tight junction*, which is a contact point close to the apical side of adjacent cells, limits water and solute movement between cells (paracellular route).

Solute transport across cell membranes uses either passive or active mechanisms.

Passive Transport

Simple diffusion always occurs down an electrochemical gradient, which is a composite of the concentration and electrical gradients (electrochemical gradient). With an undissociated molecule, only the concentration gradient is relevant; for a charged ion the electrical gradient also must be considered. Simple diffusion does not require a direct energy source, although active transport is usually necessary to establish the initial concentration and electrical gradients.

Facilitated diffusion (coupled or carrier-mediated diffusion) depends on an interaction of the molecule or ion with a specific membrane carrier protein that facilitates its passage across the cell membrane's lipid bilayer. In almost all cases of carrier-mediated transport in the kidney, two or more ions or molecules share the carrier: one moiety moves down its electrochemical gradient, and the other(s) moves against the gradient and is transported "uphill."

Diffusion through a membrane channel (or pore) formed by specific integral membrane proteins is also a form of facilitated diffusion, because it allows charged, polar, and lipophobic molecules to pass through the membrane at a high rate.

TABLE 2.1 Physiologic and Pharmacologic Influences on Glomerular Hemodynamics

	ARTERIOLAR RESISTANCE					
	Afferent	Efferent	Renal Blood Flow	Net Ultrafiltration Pressure	K^f	GFR
Renal sympathetic nerves	↑↑	↑	↓	↓	↓	↓
Epinephrine	↑	↑	↓	→	?	↓
Adenosine	↑	→	↓	↓	?	↓
Cyclosporine	↑	→	↓	↓	?	↓
NSAIDs	↑↑	↑	↓	↓	?	↓
Angiotensin II	↑	↑↑	↓	↑	↓	↓→
Endothelin-1	↑	↑↑	↓	↑	↓	↓
High-protein diet	↓	→	↑	↑	→	↑
Nitric oxide	↓	↓	↑	?	↑	↑ (?)
ANP (high dose)	↓	→	↑	↑	↑	↑
PGE_2/PGI_2	↓	↓ (?)	↑	↑	?	↑
Calcium channel blockers	↓	→	↑	↑	?	↑
ACE inhibitors, ARBs	↓	↓↓	↑	↓	↑	?*

Note: The overall effect on glomerular filtration rate (GFR) will depend on renal blood flow, net ultrafiltration pressure, and the ultrafiltration coefficient (K_f), which is controlled by mesangial cell contraction and relaxation. The effects shown are those seen when the agents are applied (or inhibited) in isolation; the actual changes that occur are dose dependent and are modulated by other agents.

*In clinical practice, GFR is usually either decreased or unaffected.

ACE, Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *ANP,* atrial natriuretic peptide; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PGE_2/PGI_2,* prostaglandins E_2 and I_2.

Active Transport

Ion movement directly against an electrochemical gradient (uphill) requires a source of energy and is known as active transport. In cells, this energy is derived from ATP production and its hydrolysis. The most important active cell transport mechanism is the sodium pump, which extrudes sodium ions (Na^+) from inside the cell in exchange for potassium ions (K^+) from outside the cell. In the kidney, this process is confined to the basolateral membrane. The "Na pump" derives energy from the enzymatic hydrolysis of ATP and is more correctly named Na^+,K^+-ATPase. It exchanges $3Na^+$ for $2K^+$ and is electrogenic, because it extrudes a net positive charge from the cell; Na^+,K^+-ATPase is an example of a *primary* active transport mechanism. Other well-defined primary active transport processes in the kidney are the proton-secreting H^+-ATPase, important in hydrogen ion secretion in the distal nephron, and the Ca^{2+}-ATPase, partly responsible for calcium reabsorption.

Activity of the basolateral Na^+,K^+-ATPase underpins the operation of all the passive transport processes outlined earlier. It ensures that the intracellular Na^+ concentration is kept low (10 to 20 mmol/l) and the K^+ concentration high (~150 mmol/l), compared with their extracellular concentrations (~140 and 4 mmol/l, respectively). The *pump-leak* model of sodium transport uses the electrochemical gradient established and maintained by the Na pump to allow "leak" of Na^+ into the cell through a variety of membrane transport proteins. These can be Na^+ channels (in the distal nephron) or specific membrane carrier proteins that couple Na^+ entry to the influx (*symport* or *cotransport*) or efflux (*antiport* or *counter-transport*) of other molecules or ions. In various parts of the nephron, glucose, phosphate, amino acids, K^+, and chloride ions (Cl^-) can all be cotransported with Na^+; moreover, H^{2+} and Ca^{2+} can be counter-transported against Na^+ entry. In each case, the non-Na molecule or ion is transported against its electrochemical gradient, using energy derived from the "downhill" movement of Na^+. Their ultimate dependence on the Na^+,K^+-ATPase makes them *secondary* active transporters.

TRANSPORT IN SPECIFIC NEPHRON SEGMENTS

Among people with normal GFR, approximately 180 liters of plasma (largely protein-free) is filtered each day, necessitating massive reabsorption by the whole nephron. Fig. 2.6 shows the major transport mechanisms operating along the nephron (except the loop of Henle, which is dealt with separately).

Proximal Tubule

The proximal tubule is adapted for bulk reabsorption of the glomerular filtrate. The epithelial cells have microvilli (brush border) on their apical surface that provide a large absorptive area, and the basolateral membrane has folds, also increasing its surface area. The cells are rich in mitochondria, and these are concentrated at the basolateral membrane to supply the Na^+,K^+-ATPase with ATP. Proximal tubule transport is heavily reliant on oxidative phosphorylation (aerobic metabolism) and is susceptible to hypoxia and mitochondrial dysfunction. Drugs that are toxic to mitochondria (e.g., tenofovir) can cause Fanconi syndrome. Future mitochondrial protection strategies may be useful in the management of patients with some forms of acute kidney injury.[13]

The proximal convoluted tubule (PCT, *pars convoluta*) makes up the first two thirds of the proximal tubule, and the final third is the proximal straight tubule *(pars recta)*. The proximal tubular epithelium is subdivided into three segments based on subtle structural and functional differences: S_1 is the initial short segment of the PCT; S_2, the remainder of the PCT and the cortical segment of the pars recta; and S_3, the medullary segment of the pars recta.

The NHE3 isoform of the Na^+-H^+ exchanger (antiporter) is the main route of Na^+ entry into proximal tubular cells. A battery of specialized transporters is also expressed in the apical membrane coupling Na^+ entry to other solutes. Thus the proximal tubule accounts for the bulk of Na^+, K^+, Cl^-, and bicarbonate (HCO_3^-) reabsorption and the almost complete reabsorption of amino acids and low-molecular-weight proteins (e.g., retinol binding protein, α- and β-microglobulin) that have passed the filtration barrier. The proximal tubule reabsorbs almost all the filtered glucose via the SGLT2 isoform of the sodium-glucose cotransporter. In contrast to SGLT1, which is also expressed in the small intestine, SGLT2 is exclusive to the kidney and is expressed predominantly in the brush border of S_1 and S_2. SGLT2 inhibitors (gliflozins) induce glycosuria and polyuria and can lower blood glucose levels and blood pressure in diabetes; in animal models they have been shown to reduce diabetes-associated glomerular hyperfiltration by inhibiting TGF and can reduce albuminuria in diabetic kidney disease. These compounds are now an important new class of antidiabetic drug mainly used to treat type 2 diabetes.

Most other filtered solutes are also reabsorbed to some extent in the proximal tubule (e.g., ~60% of calcium, 80% of phosphate, 50% of urea). Constitutive expression of aquaporin 1 (AQP1) water channels in both membranes confers a large hydraulic permeability to cells. Furthermore, the protein junctional complexes (such as Claudin 1 and Zonula Occludens 1) that connect proximal tubular cells are "leaky," facilitating the reabsorption of large amounts of sodium, potassium, and water. Overall, the substantial hydraulic permeability requires only a very small osmotic driving force (<5 mOsm/kg/H_2O) and the osmolality of the tubular fluid changes little along the proximal tubule—"isosmotic" reabsorption.

In the final section of the proximal tubule (late S_2 and S_3), there is efficient secretion of weak organic acids and bases, including most diuretics, PAH (see Measurement of Renal Blood Flow), nonsteroidal antiinflammatory drugs (NSAIDs), antiretroviral drugs, and some antibiotics. The molecular machinery for secretion is complex, mediated by 13 members of the SLC22 family of transport proteins. This comprises OATs and organic cation transporters (OCTs) that operate as facilitated transporters or exchangers.[14]

Loop of Henle

The loop of Henle is defined anatomically as comprising the pars recta of the proximal tubule (thick descending limb), the thin descending and ascending limbs (thin ascending limbs are present only in long-looped nephrons), the thick ascending limb, and the macula densa. In addition to its role in further reabsorption of solutes (Na^+, Cl^-, K^+, Ca^{2+}, Mg^{2+}), the loop of Henle is responsible for the kidney's ability to generate a concentrated or dilute urine, which is described in detail later. The thick limb of Henle also produces the Tamm-Horsfall protein, also known as *uromodulin,* normally the most abundant protein in urine. Mutations in the encoding gene, *UMOD,* cause rare autosomal dominant renal diseases with medullary cyst formation, hyperuricemia, and progressive loss of renal function. Common gain-of-function polymorphisms are associated with an increased risk for hypertension and chronic kidney disease. The physiologic role of uromodulin is not fully understood, but studies in mice suggest that it activates $Na^+,K^+,2Cl^-$ cotransport to promote sodium reabsorption in the thick limb of Henle. Uromodulin also may be a constitutive inhibitor of calcium stone formation and protect the kidney from ascending urinary infections.[15]

Distal Nephron

The distal tubule comprises three segments: the distal convoluted tubule (DCT), in which thiazide-sensitive NaCl reabsorption via an apical NaCl cotransporter (NCC)[16] occurs; the connecting tubule (CNT),

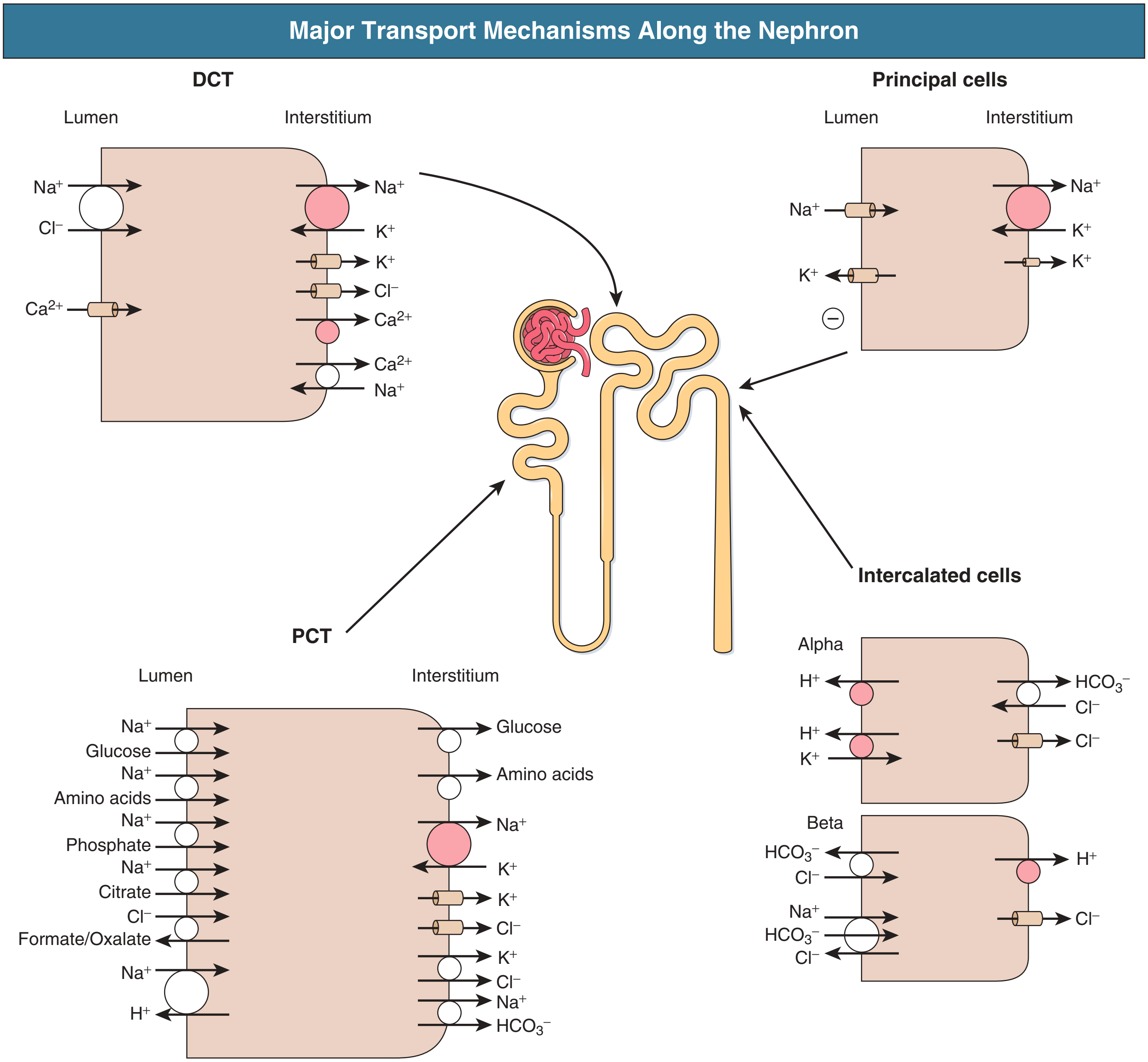
Major Transport Mechanisms Along the Nephron
DCT
Lumen
Interstitium
Na+
Cl−
Ca2+
Na+
K+
K+
Cl−
Ca2+
Ca2+
Na+
Principal cells
Lumen
Interstitium
Na+
K+
Na+
K+
K+
Intercalated cells
Alpha
H+
H+
K+
HCO3−
Cl−
Cl−
Beta
HCO3−
Cl−
Na+
HCO3−
Cl−
H+
Cl−
PCT
Lumen
Interstitium
Na+
Glucose
Na+
Amino acids
Na+
Phosphate
Na+
Citrate
Cl−
Formate/Oxalate
Na+
H+
Glucose
Amino acids
Na+
K+
K+
Cl−
K+
Cl−
Na+
HCO3−

Fig. 2.6 **Major transport mechanisms along the nephron.** Major transport proteins for solutes in the apical and basolateral membranes of tubular cells in specific regions of the nephron. Stoichiometry is not indicated; it is not 1 : 1 in all cases. *Red circles* represent primary active transport; *white circles* represent carrier-mediated transport (secondary active); *cylinders* represent ion channels. In the proximal convoluted tubule *(PCT),* Na^+ enters the cell through an Na^+-H^+ exchanger and a series of cotransporters. In the distal convoluted tubule *(DCT),* Na^+ enters the cell through the thiazide-sensitive Na^+-Cl^- cotransporter. In the principal cells of the cortical collecting duct, Na^+ enters through the epithelial sodium channel (ENaC). In all cases, Na^+ is extruded from the cells through the basolateral Na^+,K^+-ATPase. Transporters in the thick ascending limb of Henle are dealt with separately (see Fig. 2.10).

whose function is essentially intermediate between that of the DCT and the next segment, the initial collecting duct (CD) that is made up of the same epithelial cell type as the cortical CD (see Fig. 2.6). Two cell types make up the cortical CD: the predominant cell, the *principal* cell (or CD cell), is responsible for Na^+ reabsorption and K^+ secretion[17] (as well as regulated water reabsorption; see later discussion). Na^+ enters the principal cell from the lumen through apical epithelial sodium channels (ENaC) and exits by the basolateral Na^+,K^+-ATPase. This process is electrogenic and sets up a lumen-negative transepithelial potential difference. K^+ enters the principal cell by the same basolateral Na^+,K^+-ATPase and leaves by K^+ transport pathways in both membranes; however, the relative depolarization of the apical membrane (caused by Na^+ entry through ENaC) favors K^+ secretion into the lumen, the major route for which is through renal outer medullary potassium (ROMK) channels. The other cell type in the late distal tubule and cortical CD is the *intercalated* (IC) cell. Type A (or α) IC cells secrete H^+ into the tubular

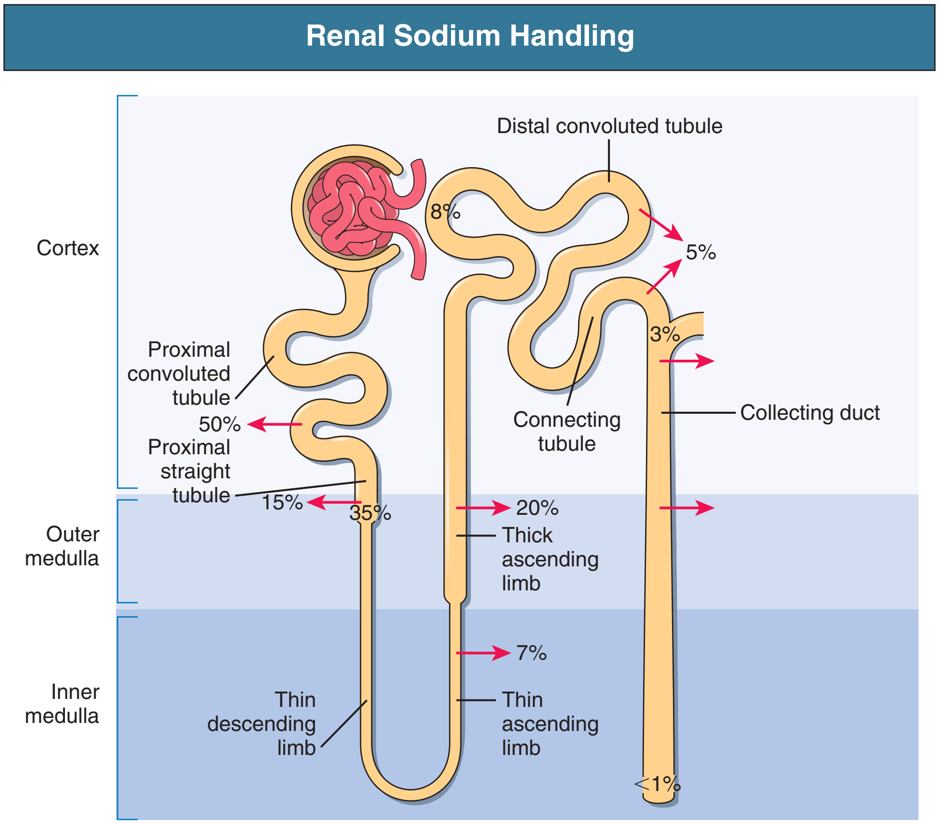

Fig. 2.7 **Renal sodium handling along the nephron.** Figures outside the nephron represent the approximate percentage of the filtered load reabsorbed in each region. Figures within the nephron represent the percentages remaining. Most filtered sodium is reabsorbed in the proximal tubule and loop of Henle; normal day-to-day control of sodium excretion is exerted in the distal nephron.

fluid via H$^+$-ATPase and H$^+$,K$^+$-ATPase. Type B (or β) IC cells mediate HCO_3^- secretion into the final urine, in exchange for Cl$^-$. An exchanger called pendrin, encoded by *SLC26A4*, mediates this process. Type B IC cells also express a Na$^+$-dependent chloride-bicarbonate exchanger (NDCBE; *SLC4A8*). Functionally coupled with pendrin, NDCBE achieves electroneutral sodium transport across the type B cell (see Fig. 2.6).[18]

In the medullary CD there is a gradual transition in the epithelium. There are increasingly fewer IC cells, whereas the principal-like cells are modified such that they reabsorb Na$^+$ but, lacking apical K$^+$ channels, do not secrete K$^+$.

Figs. 2.7 and 2.8 show the sites of Na$^+$ and K$^+$ reabsorption and secretion along the nephron. Table 2.2 outlines the pathophysiologic consequences of known genetic defects in some of the major transporters in the nephron (see Chapter 47 for details).

GLOMERULOTUBULAR BALANCE

Because the proportion of filtered Na$^+$ excreted in the urine is so small (normally <1%), it follows that without a compensatory change in reabsorption, even small changes in the filtered load would cause major changes in the amount excreted in the final urine. For example, if GFR were to increase by 10%, and the rate of reabsorption remained unchanged, Na$^+$ excretion would increase more than 10-fold. However, an intrinsic feature of tubular function is that the extent of Na$^+$ reabsorption in a given nephron segment is proportional to the Na$^+$ delivery to that segment. This process is called *glomerulotubular balance*. In perfect balance, both the reabsorption and the excretion of Na$^+$ would change in exactly the same proportion as the change in GFR, but glomerulotubular balance is usually less than perfect. Most studies have focused on the proximal tubule, because glomerulotubular balance in this segment stabilizes delivery of Na$^+$ and fluid to the distal nephron, permitting efficient secretion of K$^+$ and H$^+$. However, Na$^+$ reabsorption in the thick limb of Henle and distal tubule is also delivery-dependent. This partly explains why diuretics acting on the proximal tubule are less effective compared with those acting more distally. With distal-acting diuretics, there is less scope further downstream for compensatory Na$^+$ reabsorption. This also explains why combining two diuretics (acting at different nephron sites) can cause a more striking diuresis and natriuresis.

The mechanism of glomerulotubular balance is not fully understood. In the proximal tubule, physical factors (Starling forces) operating across peritubular capillary walls may be involved. Glomerular filtration of an essentially protein-free fluid means the plasma leaving the glomeruli in efferent arterioles and supplying the peritubular capillaries has a relatively high oncotic pressure, favoring reabsorption of fluid from the proximal tubules. If GFR were reduced in the absence of a change in RPF, the *filtration fraction* (GFR/RPF ratio) would fall. Peritubular capillary oncotic pressure would also be reduced, and the tendency of the peritubular vasculature to take up fluid reabsorbed from the proximal tubule would be diminished. Backflux of this fluid is thought to occur through the leaky tight junctions, reducing net reabsorption (Fig. 2.9). However, this mechanism could work only if GFR changed in the absence of a corresponding change in RPF; if the two changed in parallel, filtration fraction would stay constant, with no change in oncotic pressure.

A second contributory factor to glomerulotubular balance in the proximal tubule could be the filtered loads of glucose and amino acids:

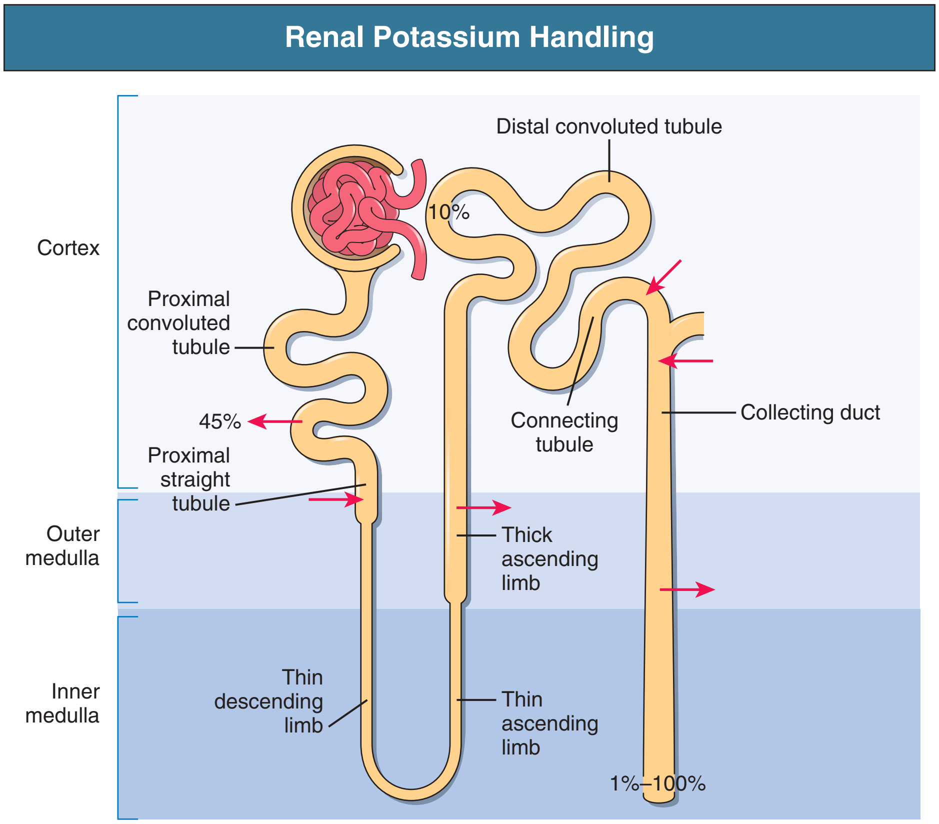

Fig. 2.8 **Renal potassium handling along the nephron.** Figures are not given for percentages reabsorbed or remaining in every region because quantitative information is incomplete, but most filtered potassium is reabsorbed in the proximal convoluted tubule and thick ascending limb of Henle; approximately 10% of the filtered load reaches the early distal tubule. Secretion by connecting tubule cells and principal cells in the late distal tubule–cortical collecting duct is variable and is the major determinant of potassium excretion.

if their loads increase, because of increased GFR, the rates of Na^+-coupled glucose and amino acid reabsorption in the proximal tubule will also increase. It has been proposed that the brush border microvilli of the proximal tubule serve a “mechanosensing” function, transmitting changes in torque (caused by altered tubular flow rates) to the tubular cells’ actin cytoskeleton and thereby modulating transporter activity.[19] The mechanisms are unknown, but the release of paracrine mediators such as ATP, dopamine, or Ang II into the lumen fluid may contribute.[20]

Although the renal sympathetic nerves and certain hormones can influence reabsorption in the proximal tubule and loop of Henle, under normal conditions the combined effects of autoregulation and glomerulotubular balance ensure a relatively constant load of glomerular filtrate is delivered to the distal tubule. It is the final segments of the nephron that exert normal day-to-day control of Na^+ excretion. Evidence indicates important roles for the late DCT[16] and the CNT,[21] in addition to the CD.[17] Aldosterone secreted from the adrenal cortex stimulates mineralocorticoid receptors within CNT cells and in principal cells. This leads to the generation and activation by phosphorylation of the regulatory protein serum- and glucocorticoid-inducible kinase 1 (SGK1), which promotes sodium transport by increasing the density of Na^+ channels (ENaC) in the apical membrane (see Fig. 2.6), and by activating the basolateral Na^+,K^+-ATPase. Na^+ transport across the principal cell is further enhanced and the apical membrane thereby maximally depolarized, thus facilitating K^+ secretion into the tubular fluid. The electrophysiologic coupling of Na^+ reabsorption to K^+ secretion explains why aldosterone promotes antinatriuresis and kaliuresis. However, under conditions of volume depletion, aldosterone promotes sodium retention *without* promoting urinary potassium excretion. The mechanism underlying this difference is now better understood. During hypovolemia, aldosterone and Ang II engage the WNK4 kinase network to differentially activate NCC in the DCT, promoting potassium-sparing sodium reabsorption, while also inhibiting ROMK channels to limit potassium secretion.[16] Recent studies have shown direct effects of small changes in plasma potassium concentration on the WNK kinase pathway and NCC activity that explains the natriuretic and blood pressure–lowering effects of increases in dietary potassium intake.[22] Ang II also activates NDBCE and pendrin in the type B IC cell to promote potassium-sparing sodium reabsorption.

The mineralocorticoid receptors have equal affinity in vitro for aldosterone and other adrenal corticosteroids, such as cortisol. The circulating concentrations of cortisol vastly exceed those of aldosterone, but in vivo the mineralocorticoid receptors show specificity for aldosterone because of the presence along the distal nephron of the enzyme 11β-hydroxysteroid dehydrogenase 2, which inactivates cortisol in the vicinity of the receptor.[23] Mutations in the gene that encodes 11β-hydroxysteroid dehydrogenase 2, or inhibition of the enzyme by derivatives of glycyrrhetinic acid (found in licorice), can cause hypertension from excessive and unregulated stimulation of Na^+ transport[24] and salt appetite[25] by cortisol (see also Chapter 38).

TABLE 2.2 Genetic Defects in Transport Proteins Resulting in Renal Disease*

Transporter	Consequence of Mutation
Proximal Tubule	
Apical Na^+-cystine cotransporter	Cystinuria
Apical Na^+-glucose cotransporter (SGLT2)	Renal glycosuria
Basolateral Na^+-HCO_3^- cotransporter	Proximal renal tubular acidosis
Intracellular H^+-Cl^- exchanger (ClC5)	Dent disease
Thick Ascending Limb	
Apical Na^+-K^+-$2Cl^-$ cotransporter	Bartter syndrome type 1
Apical K^+ channel	Bartter syndrome type 2
Basolateral Cl^- channel	Bartter syndrome type 3
Basolateral Cl^- channel accessory protein	Bartter syndrome type 4
Distal Convoluted Tubule	
Apical Na^+-Cl^- cotransporter	Gitelman syndrome
Collecting Duct	
Apical Na^+ channel (principal cells)	Overexpression: Liddle syndrome Underexpression: Pseudohypoaldosteronism type 1b
Aquaporin 2 channel (principal cells)	Nephrogenic diabetes insipidus
Basolateral Cl^-/HCO_3^- exchanger (intercalated cells)	Distal renal tubular acidosis
Apical H^+-ATPase (intercalated cells)	Distal renal tubular acidosis (with or without deafness)

*For more detailed coverage of these clinical conditions, see Chapter 47.

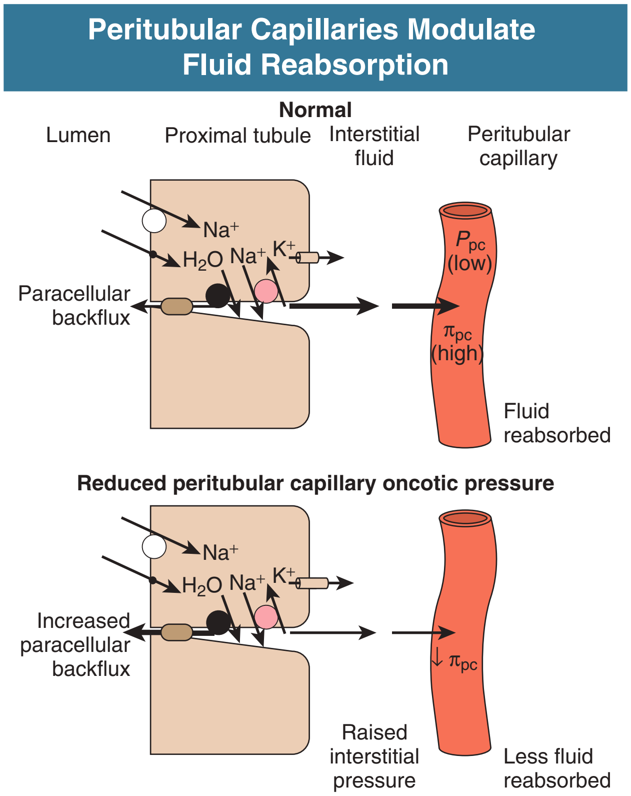

Fig. 2.9 **Physical factors and proximal tubular reabsorption.** Influence of peritubular capillary oncotic pressure on net reabsorption in proximal tubules. Uptake of reabsorbate into peritubular capillaries is determined by the balance of hydrostatic and oncotic pressures across the capillary wall. Compared with those in systemic capillaries, the peritubular capillary hydrostatic (P_{pc}) and oncotic (π_{pc}) pressures are low and high, respectively, so that uptake of proximal tubular reabsorbate into the capillaries is favored. If peritubular capillary oncotic pressure decreases (or hydrostatic pressure increases), less fluid is taken up, interstitial pressure increases, and more fluid may leak back into the lumen paracellularly; net reabsorption in proximal tubules would therefore be reduced.

COUNTERCURRENT SYSTEM

A major function of the loop of Henle is the generation and maintenance of the interstitial osmotic gradient that increases from the renal cortex (~290 mOsm/kg) to the tip of the medulla (~1200 mOsm/kg). As indicated in Chapter 1, the loops of Henle of superficial nephrons turn at the junction between outer and inner medulla, whereas those of deep nephrons (long-looped nephrons) penetrate the inner medulla to varying degrees. The anatomic loops of Henle reabsorb approximately 40% of filtered Na^+, mostly in the pars recta and the thick ascending limb, and approximately 25% of filtered water in the pars recta and the thin descending limbs of deep nephrons. Evidence suggests that the thin descending limb of superficial nephrons is relatively impermeable to water.[26] Both the thin ascending limb (found only in deep nephrons) and the thick ascending limb are essentially impermeable to water, although Na^+ is reabsorbed; passively in the thin ascending limb but actively in the thick ascending limb. The thick ascending limb also operates as a pump-leak system: the basolateral Na^+,K^+-ATPase maintains the electrochemical driving force for passive Na^+ entry from the lumen through the Na^+,K^+,$2Cl^-$ cotransporter (NKCC2) and to a smaller extent the NHE3 (Fig. 2.10). The apical NKCC2 is the site of action of loop diuretics such as furosemide and bumetanide. Na^+ exits the cell through the Na^+,K^+-ATPase, and Cl^- and K^+ exit via basolateral ion channels and a K^+-Cl^- cotransporter. K^+ also reenters the lumen through apical membrane channels. This "recycling" of K^+ into the tubular lumen is necessary for normal operation of the Na^+,K^+,$2Cl^-$ cotransporter, because the availability of K^+ is a limiting factor for the transporter (K^+ concentration in tubular fluid is much lower than Na^+ and Cl^-). Potassium recycling is also partly responsible for generating the lumen-positive transepithelial potential difference found in the thick ascending limb, which drives additional Na^+ reabsorption through the paracellular pathway; for each Na^+ reabsorbed by the transcellular route, another is reabsorbed paracellularly (see Fig. 2.10). Other cations (K^+, Ca^{2+}, Mg^{2+}) are also reabsorbed by this route. The reabsorption of NaCl along the thick ascending limb in the absence of significant water reabsorption means that the tubular fluid leaving this segment is hypotonic; the thick ascending limb is also called the *diluting segment.*

The reabsorption in the thick ascending limb of solute without water generates a "horizontal" osmotic gradient of about 200 mOsm/kg between the tubular fluid and interstitium. This separation is the *single osmotic effect.* The U-shaped arrangement of the loop of Henle, in which flow in the descending limb is opposite to that in the ascending limb, multiplies the single effect to generate a much larger vertical (corticomedullary) osmotic gradient by a process known as *countercurrent multiplication* (Fig. 2.11). Fluid entering the descending limb from the proximal tubule is isosmotic (~290 mOsm/kg). On encountering the hypertonicity of the medullary interstitial fluid (caused by NaCl reabsorption in the water-impermeable ascending limb), the fluid in the descending limb comes into osmotic equilibrium with its surroundings,

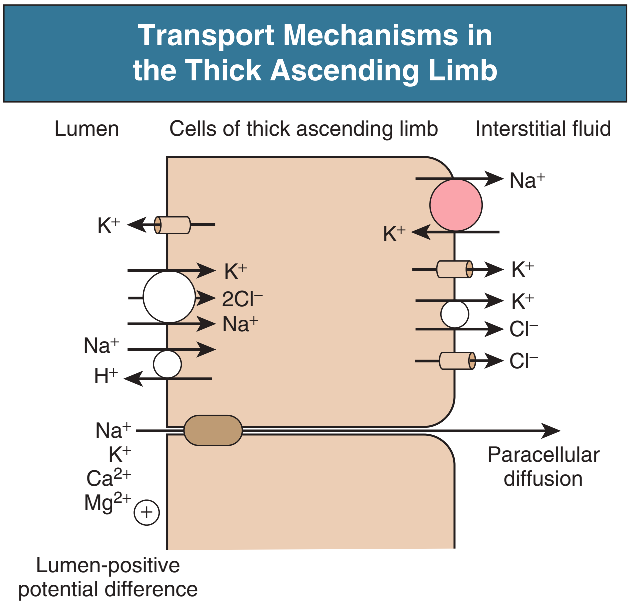
Transport Mechanisms in the Thick Ascending Limb
Lumen
Cells of thick ascending limb
Interstitial fluid
Na+
K+
K+
K+
2Cl–
Na+
K+
K+
Cl–
Na+
H+
Cl–
Na+
K+
Ca2+
Mg2+
+
Paracellular diffusion
Lumen-positive potential difference

Fig. 2.10 Transport mechanisms in the thick ascending limb of Henle. The major cellular entry mechanism is the Na^+-K^+-$2Cl^-$ cotransporter. The transepithelial potential difference drives paracellular transport of Na^+, K^+, Ca^{2+}, and Mg^{2+}.

either by solute entry into the descending limb (superficial nephrons) or by water exit by osmosis (deep nephrons). These events, combined with continuing NaCl reabsorption in the ascending limb, result in a progressive increase in medullary osmolality from the corticomedullary junction to the papillary tip. A similar osmotic gradient exists in the thin descending limb, and at any level in the ascending limb the osmolality is less than in the surrounding tissue. Thus hypotonic fluid (~100 mOsm/kg) is delivered to the distal tubule. Ultimately, the energy source for countercurrent multiplication is active Na^+ reabsorption in the thick ascending limb. As stated earlier, Na^+ reabsorption in the thin ascending limb is passive, although the mechanism is not yet understood.

Role of Urea

The thin limbs of the loop of Henle are relatively permeable to urea (ascending more permeable than descending), but the thick ascending limb and beyond are urea-impermeable up to the final section of the inner medullary CD. During antidiuresis, vasopressin-induced water reabsorption from the CDs concentrates urea, such that in the terminal inner medullary CD there is a large concentration gradient between the luminal fluid and interstitium. This section of the inner medullary CD expresses urea transporters (UT-A1 and UT-A3), allowing passive reabsorption of urea into the inner medullary interstitium. This process is also under the control of vasopressin (AVP, also known as antidiuretic hormone).[27] The interstitial urea exchanges with vasa recta capillaries

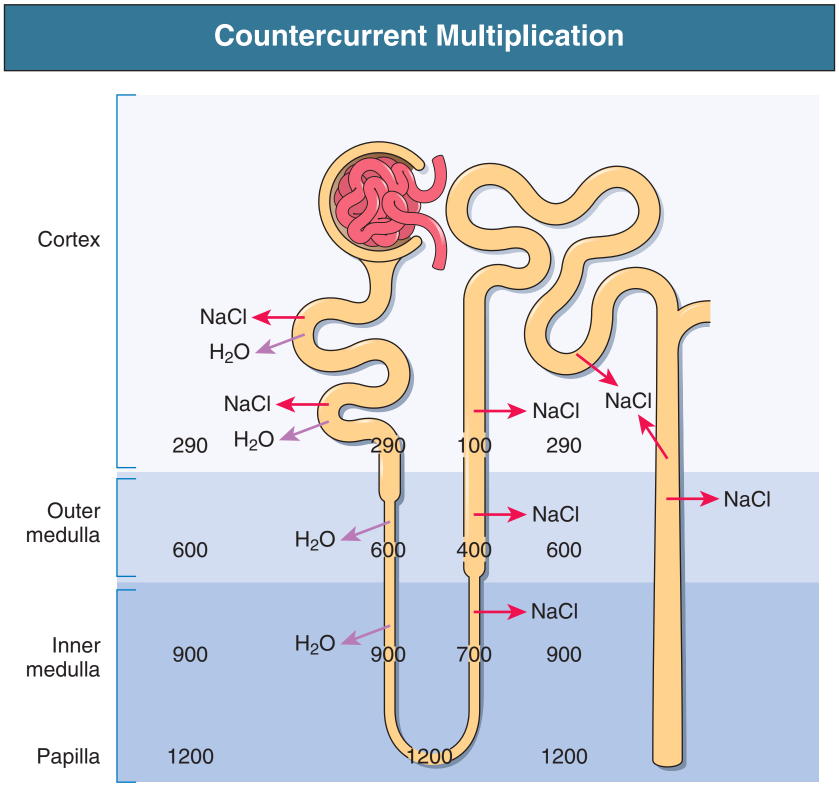
Countercurrent Multiplication
Cortex
Outer medulla
Inner medulla
Papilla
NaCl
H2O
NaCl
H2O
NaCl
NaCl
NaCl
NaCl
NaCl
H2O
H2O
290
290
100
290
600
600
400
600
900
900
700
900
1200
1200
1200

Fig. 2.11 Countercurrent multiplication by the loop of Henle. The nephron drawn represents a deep (long-looped) nephron. Figures represent approximate osmolalities (mOsm/kg). Osmotic equilibration occurs in the thin descending limb of Henle, whereas NaCl is reabsorbed in the water-impermeable ascending limb; hypotonic fluid is delivered to the distal tubule. In the absence of vasopressin, this fluid remains hypotonic during its passage through the distal tubule and collecting duct, despite the large osmotic gradient favoring water reabsorption. A large volume of dilute urine is therefore formed. During maximal vasopressin secretion, water is reabsorbed down the osmotic gradient, so that tubular fluid becomes isotonic in the cortical collecting duct and hypertonic in the medullary collecting duct. A small volume of concentrated urine is formed.

(see next section) and some urea enters the S_3 segment of the pars recta and the descending and ascending thin limbs; it is then returned to the inner medullary CDs to be reabsorbed. The net result of this urea recycling process is to add urea to the inner medullary interstitium, thereby increasing interstitial osmolality. The fact that the high urea concentration within the medullary CD is balanced by a similarly high urea concentration in the medullary interstitium allows large quantities of urea to be excreted without incurring the penalty of osmotic diuresis, because the urea in the CD is rendered osmotically inactive. Moreover, the high urea concentration in the medullary interstitium should also increase osmotic water abstraction from the thin descending limbs of deep nephrons, thus raising the intraluminal Na^+ concentration within the thin descending limbs.

Although until recently this process was thought to prepare for passive Na^+ reabsorption along the thin ascending limbs, mice with genetic deletion of the urea transporters UT-A1 and UT-A3 have a greatly reduced urea concentration in the inner medullary interstitium, but a normal interstitial NaCl gradient.[27] Therefore the mechanisms responsible for the inner medullary electrolyte gradients are still unclear. However, it is worth emphasizing that the ultimate driving force for countercurrent multiplication is active Na^+ reabsorption in the thick ascending limb. For this reason, loop diuretics disrupt the osmotic gradient and genetic mutations in the pathways contributing to efficient Na^+ reabsorption in the thick ascending limb cause salt-wasting Bartter syndrome (see Chapter 47).

Vasa Recta

If the capillaries that supply the renal medulla had a more conventional anatomic arrangement, these vessels would soon dissipate the medullary osmotic gradient because of equilibration of the hypertonic interstitium with the isotonic capillary blood. This does not happen to any appreciable extent, because the U-shaped arrangement ensures that solute entry and water loss in the descending vasa recta are offset by solute loss and water entry in the ascending vasa recta. This is the process of *countercurrent exchange* and is entirely passive (Fig. 2.12).

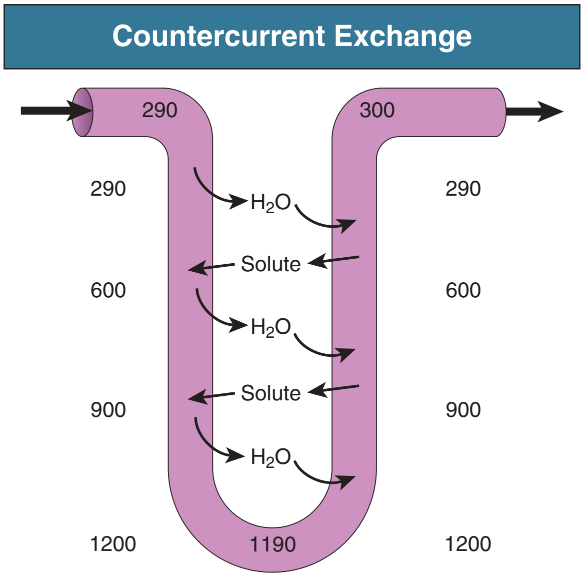

Fig. 2.12 Countercurrent exchange by the vasa recta. Figures represent approximate osmolalities (mOsm/kg). The vasa recta capillary walls are highly permeable, but the U-shaped arrangement of the vessels minimizes the dissipation of the medullary osmotic gradient. Nevertheless, because equilibration across the capillary walls is not instantaneous, a certain amount of solute is removed from the interstitium.

Renal Medullary Hypoxia

Countercurrent exchange by the medullary capillaries applies also to oxygen, which diffuses from descending to ascending vasa recta, bypassing the deeper regions. This phenomenon, combined with ongoing energy-dependent Na^+ transport in the (outer medullary) thick ascending limb, renders medullary tissue relatively hypoxic. Thus the partial pressure of oxygen normally decreases from about 50 mm Hg in the cortex to 10 mm Hg in the inner medulla.[28] Indeed, administration of furosemide, which inhibits oxygen consumption in the thick ascending limb, increases medullary oxygenation. As part of the adaptation to this relatively hypoxic environment, medullary cells have a higher capacity for glycolysis than cortical cells. Moreover, a number of *heat shock proteins* are expressed in the medulla, which assist cell survival by restoring damaged proteins and by inhibiting apoptosis.[28]

The degree of medullary hypoxia depends on the balance between medullary blood flow (influenced by contractile cells called *pericytes*) and oxygen consumption in the thick ascending limb. In health, this balance is modulated by a variety of autocrine/paracrine agents (e.g., NO, eicosanoids, ATP, adenosine; see later discussion), several of which can increase medullary oxygenation by simultaneously reducing pericyte contraction and thick ascending limb transport. Some cases of radiocontrast-induced nephropathy result from a disturbance in the balance between oxygen supply and demand, with consequent hypoxic medullary injury in which the normal cellular adaptations are overwhelmed, with subsequent apoptotic and necrotic cell death.

VASOPRESSIN (ANTIDIURETIC HORMONE) AND WATER REABSORPTION

Vasopressin, or antidiuretic hormone (AVP), is a nonapeptide synthesized in specialized neurons of the supraoptic and paraventricular nuclei. Vasopressin is transported from these nuclei to the posterior pituitary and released in response to increases in plasma osmolality and decreases in blood pressure. Osmoreceptors are found in the hypothalamus, and there is also input to this region from arterial baroreceptors and atrial stretch receptors. The actions of vasopressin are mediated by three receptor subtypes: V_{1a}, V_{1b}, and V_2. The V_{1a} receptors are found in vascular smooth muscle and are coupled to the phosphoinositol pathway; they cause an increase in intracellular Ca^{2+} resulting in contraction. V_{1a} receptors also have been identified in the apical membrane of several nephron segments; activation by luminal vasopressin can influence Na^+ transport in these segments. V_{1b} receptors are found in the anterior pituitary, where vasopressin modulates adrenocorticotropic hormone release. V_2 receptors are found in the basolateral membrane of principal cells in the late distal tubule and the whole length of the CD; they are coupled by a G_s protein to cyclic adenosine monophosphate generation, which ultimately leads to the insertion of aquaporin 2 (AQP2) water channels into the apical membrane of this otherwise water-impermeable segment (Fig. 2.13). In the X-linked form of nephrogenic diabetes insipidus, the most common inherited form, the V_2 receptor is defective.[29]

Several aquaporins have been identified in the kidney.[30] AQP1 is found in apical and basolateral membranes of all proximal tubules and of thin descending limbs of long-looped nephrons; it is largely responsible for the permanently high water permeability of these segments. AQP3 is constitutively expressed in the basolateral membrane of CNT cells and cortical and outer medullary principal cells. AQP4 is constitutively expressed in the basolateral membrane of outer medullary principal cells and inner medullary CD cells; however, AQP2 is responsible for the variable water permeability of the late distal tubule and CD. Acute vasopressin release causes shuttling of AQP2 from intracellular vesicles

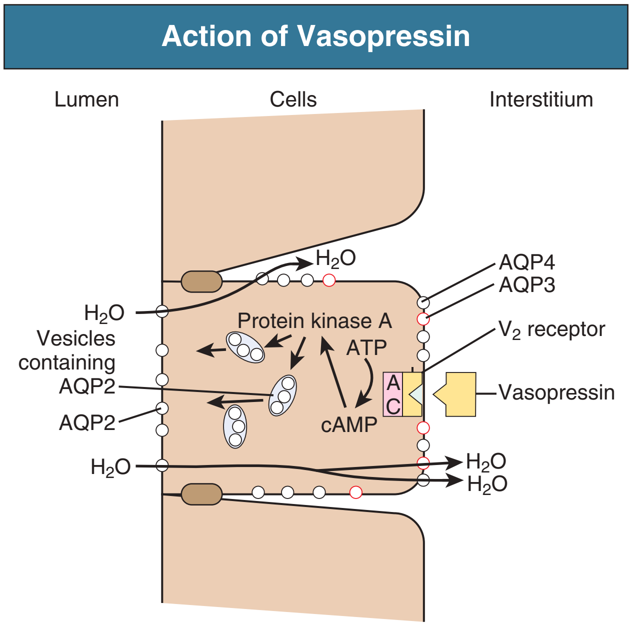

Fig. 2.13 Mechanism of action of vasopressin (antidiuretic hormone). Vasopressin binds to V_2 receptors on the basolateral membrane of collecting duct principal cells and increases intracellular cyclic adenosine monophosphate *(cAMP)* production, causing insertion of preformed aquaporin 2 *(AQP2)* water channels into the apical membrane through intermediate reactions involving protein kinase A. The water permeability of the basolateral membrane, which contains aquaporins 3 and 4, is permanently high. Therefore vasopressin secretion allows transcellular movement of water from lumen to interstitium. *AC,* Adenylate cyclase; *ATP,* adenosine triphosphate.

to the apical membrane, whereas chronically raised vasopressin levels increase transcription and translation of the gene encoding AQP2. The apical insertion of AQP2 allows reabsorption of water, driven by the high interstitial osmolality achieved and maintained by the countercurrent system. Vasopressin also contributes to the effectiveness of this system by stimulating Na^+ reabsorption in the thick ascending limb and urea reabsorption through the UT-A1 and UT-A3 transporters in the inner medullary CD. In the (rare) autosomal recessive and (even rarer) autosomal dominant forms of nephrogenic diabetes insipidus, AQP2 is abnormal and/or fails to translocate to the apical membrane.[29]

More frequently, defects in AQP2 shuttling contribute to the urine-concentrating defects associated with both hypokalemia and hypercalcemia. With chronic hypokalemia, AQP2 expression in the CD is reduced, possibly reflecting the generalized suppression of proteins central to urine concentration[31] and reduction in the medullary osmotic gradient. With hypercalcemia, increased intraluminal Ca^{2+} concentrations preventing insertion of AQP2 in the apical membrane. In addition, stimulation of the calcium receptor in the basolateral membrane of the thick ascending limb (a receptor similar to that in the parathyroid glands) reduces transcellular solute flux by inhibiting NKCC2 and ROMK channels and also by direct inhibition of paracellular permeability.[32] Overall this reduces the medullary osmotic gradient for water reabsorption.

INTEGRATED CONTROL OF RENAL FUNCTION

One of the major functions of the kidneys is the regulation of blood volume, through the regulation of *effective circulating volume,* a conceptual volume reflecting the degree of fullness of the vasculature. This is achieved largely by controlling the sodium content of the body. Chapter 7 describes the mechanisms involved in the regulation of effective circulating volume. This discussion introduces some of the more important mediator systems.

Renal Interstitial Hydrostatic Pressure and Nitric Oxide

Acute increases in arterial blood pressure lead to *pressure natriuresis.*[20] Because autoregulation is not perfect, part of this response is mediated by increases in RBF and GFR (see Fig. 2.3), but the main cause is reduced tubular reabsorption resulting from an increase in *renal interstitial hydrostatic pressure* (RIHP). An elevated RIHP reduces net reabsorption in the proximal tubule by increasing paracellular backflux through the tight junctions of the tubular wall (see Fig. 2.9). The increase in RIHP is thought to depend on intrarenally produced nitric oxide (NO) and modulated by reactive oxygen species.[20] Moreover, increased NO production in macula densa cells, which contain the neuronal (type I) isoform of nitric oxide synthase (nNOS), blunts the sensitivity of TGF, thereby allowing increased NaCl delivery to the distal nephron without incurring a TGF-mediated decrease in GFR.[20]

Another renal action of NO results from the presence of inducible (type II) nitric oxide synthase (iNOS) in glomerular mesangial cells. Local NO production counteracts the mesangial contractile response to agonists such as Ang II and endothelin (see later discussion). Furthermore, NO may contribute to the regulation of medullary blood flow. Locally synthesized NO offsets the vasoconstrictor effects of other agents on the pericytes of the descending vasa recta, and it reduces Na^+ reabsorption in the thick ascending limb; both actions help protect the renal medulla from hypoxia. NO also may promote natriuresis and diuresis through direct actions on the renal tubule. Thus, in addition to its effect on the thick ascending limb, locally produced NO inhibits Na^+ and water reabsorption in the CD.[33]

Renal Sympathetic Nerves

Reductions in arterial pressure and/or central venous pressure result in reduced afferent signaling from arterial baroreceptors and atrial volume receptors, which elicits a reflex increase in renal sympathetic nervous discharge. This reduces urinary Na^+ excretion in at least three ways: (1) constriction of afferent and efferent glomerular arterioles (predominantly afferent), thereby directly reducing RBF and GFR, and indirectly reducing RIHP; (2) direct stimulation of Na^+ reabsorption in the proximal tubule and the thick ascending limb of the Henle loop; and (3) stimulation of renin secretion by afferent arteriolar cells (see later discussion). Renal sympathetic overactivity has long been associated with Na^+ retention and experimental hypertension. The Symplicity-HTN trials initially indicated that bilateral sympathetic efferent denervation causes long-lasting reductions in blood pressure in patients with resistant hypertension.[34] This early promise from small studies was not supported in a larger single-blind, sham-controlled trial,[35] and on present evidence renal denervation is not advocated for treatment of resistant hypertension.

Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is central to the control of extracellular fluid volume (ECFV) and blood pressure. Renin is synthesized and stored in specialized afferent arteriolar cells that form part of the juxtaglomerular apparatus and is released into the circulation in response to (1) increased renal sympathetic nervous discharge, (2) reduced stretch of the afferent arteriole after a reduction in renal perfusion pressure, and (3) reduced delivery of NaCl to the macula densa region of the nephron (see Fig. 2.4).

Renin catalyzes the production of the decapeptide Ang I from circulating angiotensinogen (synthesized in the liver). Ang I is converted by the ubiquitous angiotensin-converting enzyme (ACE) to the octapeptide Ang II, which influences the control of ECFV and blood pressure as follows:

- Causes general arteriolar vasoconstriction, including renal afferent and (particularly) efferent arterioles, thereby increasing arterial pressure, but reducing RBF. The tendency of P_{gc} to increase is offset by Ang II–induced mesangial cell contraction, and reduced K_f and the overall effect on the GFR is unpredictable.
- Directly stimulates sodium reabsorption in the proximal tubule.
- Directly stimulates thiazide-sensitive NaCl cotransport.[36]
- Stimulates aldosterone secretion from the zona glomerulosa of adrenal cortex. As described earlier, aldosterone stimulates sodium reabsorption in the distal tubule and CD.

Eicosanoids

Eicosanoids are a family of metabolites of arachidonic acid (AA) produced enzymatically by three systems: *cyclooxygenase,* with two isoforms, COX-1 and COX-2, both expressed in the kidney; *cytochrome P-450* (CYP-450); and *lipoxygenase.* The major renal eicosanoids produced by the COX system are the prostaglandins E_2 (PGE_2) and I_2 (PGI_2), both of which are renal vasodilators and buffer the effects of renal vasoconstrictor agents (e.g., Ang II, norepinephrine) and the vasoconstrictor thromboxane A_2. Under normal circumstances, PGE_2 and PGI_2 have minimal effects on renal hemodynamics, but during stressful situations such as hypovolemia, they help protect the kidney from excessive functional changes. Consequently, NSAIDs, which are COX inhibitors, can cause significant falls in GFR. PGE_2 also has tubular effects, inhibiting Na^+ reabsorption in the thick ascending limb of the Henle loop, as well as both Na^+ and water reabsorption in the CD.[37] The action of PGE_2 in the thick ascending limb, together with a dilator effect on vasa recta pericytes, is another paracrine regulatory mechanism that helps protect the renal medulla from hypoxia. This may explain why inhibition of COX-2 can reduce medullary blood flow and cause apoptosis of medullary interstitial cells.

The metabolism of AA by renal CYP-450 enzymes yields epoxyeicosatrienoic acids (EETs), 20-hydroxyeicosatetraenoic acid (20-HETE), and dihydroxyeicosatrienoic acids (DHETs). These compounds appear to have multiple autocrine/paracrine/second messenger effects on the renal vasculature and tubules still to be fully unraveled. As with prostaglandins, EETs are vasodilator agents, whereas 20-HETE is a potent renal arteriolar constrictor and may be involved in the vasoconstrictor effect of Ang II, as well as the TGF mechanism. 20-HETE also constricts vasa recta pericytes and may be involved in the control of medullary blood flow. Some evidence suggests that locally produced 20-HETE and EETs can inhibit sodium reabsorption in the proximal tubule and thick ascending limb. Indeed, CYP-450 metabolites of AA may contribute to the reduced proximal tubular reabsorption seen in pressure natriuresis.[38]

The third enzyme system that metabolizes AA, the lipoxygenase system, is activated (in leukocytes, mast cells, and macrophages) during inflammation and injury and is not considered here.

COX-2 is present in macula densa cells and has a critical role in the release of renin from juxtaglomerular cells (granular cells) in response to reduced NaCl delivery to the macula densa.[38] A low-sodium diet increases COX-2 expression in the macula densa and simultaneously increases renin secretion; the renin response is virtually abolished in COX-2 knockout mice or during pharmacologic inhibition of COX-2. Therefore it is likely that the low renin observed during administration of NSAIDs is largely a consequence of COX-2 inhibition. In addition to COX-2, the enzyme PGE synthase is expressed in macula densa cells, and the principal COX-2 product responsible for enhancing renin secretion is PGE_2, acting on specific receptors identified in juxtaglomerular cells. It is not clear whether PGI_2 is also synthesized in macula densa cells. As previously discussed, nNOS (type I isomer) is also present in macula densa cells and produces NO that blunts TGF. NO also has a permissive role in renin secretion, although the mechanism is not understood. The increase in macula densa COX-2 expression induced by a low-sodium diet is attenuated during administration of selective nNOS inhibitors, which has led to speculation that NO is responsible for the increase in COX-2 activity and the resulting increase in juxtaglomerular renin secretion. Fig. 2.14 shows the established and proposed roles of COX-2 and nNOS in the macula densa.

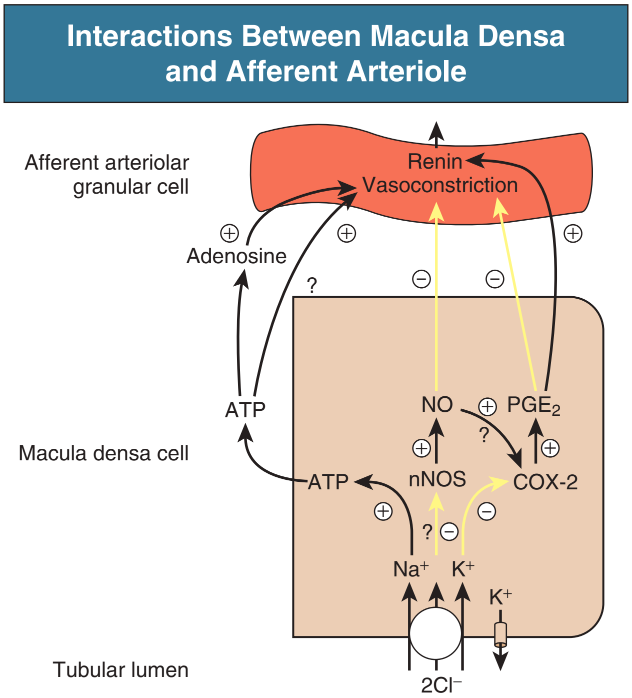

Fig. 2.14 **Interactions between macula densa and afferent arteriole: proposed mediators of renin secretion and tubuloglomerular feedback.** Both cyclooxygenase-2 *(COX-2)* and neuronal nitric oxide synthase *(nNOS)* enzyme systems are present in macula densa cells. Increased NaCl delivery to the macula densa stimulates NaCl entry into the cells through the Na^+-K^+-$2Cl^-$ cotransporter. This causes afferent arteriolar constriction through adenosine or adenosine triphosphate *(ATP)* and also inhibits COX-2 activity; the latter effect might be mediated partly through inhibition of (nNOS-mediated) nitric oxide *(NO)* production. Generation of prostaglandin E_2 (*PGE_2*) by COX-2 stimulates renin release. PGE_2 also modulates vasoconstriction, as does NO.

Atrial Natriuretic Peptide

If blood volume increases significantly, the resulting atrial stretch stimulates the release of atrial natriuretic peptide (ANP) from atrial myocytes. This hormone increases sodium excretion by suppressing renin and aldosterone release and through a direct inhibitory effect on sodium reabsorption in the medullary CD. ANP may also increase GFR, because high doses cause afferent arteriolar vasodilation and mesangial cell relaxation (thus increasing K_f; see Table 2.1).

Endothelins

Endothelins are potent vasoconstrictor peptides to which the renal vasculature is exquisitely sensitive.[39] Endothelins function primarily as autocrine or paracrine agents. The kidney is a rich source of endothelins, the predominant isoform being endothelin-1 (ET-1). ET-1 is generated throughout the renal vasculature, including afferent and efferent arterioles, where it causes vasoconstriction, possibly mediated by 20-HETE, and mesangial cells, where it causes contraction (i.e., decreases K_f). Consequently, renal ET-1 can cause profound reductions in RBF and GFR (see Table 2.1).

In contrast to its effect on GFR, ET-1 can act on the renal tubule to increase urinary Na^+ and water excretion. ET-1 levels are highest in the renal medulla—in the thick ascending limb, and, more prominently, the inner medullary CD. The distribution of renal endothelin receptors (ET_A and ET_B) reflects the sites of production; the predominant receptor in the inner medulla is ET_B.[39] Mice with CD-specific deletions of either ET-1 or ET_B receptors exhibit salt-sensitive hypertension, whereas duct-specific ET_A deletion results in no obvious renal phenotype. ET-1 knockout mice also show a greater sensitivity to vasopressin than do wild-type mice. There is mounting evidence that NO mediates the natriuretic and diuretic effects of medullary ET_B stimulation.[39] Taken together with evidence that ET-1 can inhibit Na^+ reabsorption in the medullary thick ascending limb (also likely mediated by NO), these findings highlight the potential importance of ET-1/NO interactions in the control of Na^+ and water excretion.

Purines

Increasing evidence indicates that extracellular purines such as ATP, adenosine diphosphate (ADP), adenosine, and uric acid can act as autocrine or paracrine agents within the kidneys by activating specific cell surface receptors.[9] *Purinoceptors* are subdivided into P1 and P2 receptors. P1 receptors are responsive to adenosine and are more usually known as *adenosine receptors* (A_1, A_{2a}, A_{2b}, and A_3). P2 receptors are responsive to nucleotides (e.g., ATP, ADP) and are further subdivided into P2X (ligand-gated ion channel) and P2Y (metabotropic) receptors, each category having a number of subtypes.[40] As indicated earlier, A_1 and $P2X_1$ receptors are found in afferent arterioles and mediate vasoconstriction. Purinoceptors are also found in the apical and basolateral membranes of renal tubular cells. Stimulation of A_1 receptors enhances proximal tubular reabsorption and inhibits CD Na^+ reabsorption, whereas stimulation of P2 receptors generally has an inhibitory effect on tubular transport.[40] Thus luminally applied nucleotides, acting on a variety of P2 receptor subtypes, can inhibit Na^+ reabsorption in the proximal tubule, distal tubule, and CD, and stimulation of $P2Y_2$ receptors in the CD inhibits vasopressin-sensitive water reabsorption.

Exosomes, Other Extracellular Vesicles and Luminal Factors

Extracellular vesicles are released into the urine from all cells of the nephron. Exosomes are a subtype of vesicles that are approximately 100 nm. They contain proteins, mRNA, and microRNA specific to their cell of origin and have generated much interest as a reservoir for kidney disease biomarker discovery. Recent studies also show that exosomes can signal between cells along the urinary tract. Studies in renal cells lines and in mice find that these vesicles are shuttled to a recipient cell, taken up under hormonal control, and then can influence recipient cell function.[41] Finally, recent studies have also shown the importance and potential clinical relevance of enzymes (serine proteases) in urine that can activate ENaC and thereby affect Na^+ reabsorption, particularly in proteinuric diseases such as the nephrotic syndrome.[42]

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SELF-ASSESSMENT QUESTIONS

1. Filtration at the glomerulus is a passive process. Which of the following statements is true?
   A. Albumin is too large to be filtered.
   B. Albumin is not filtered because the glomerular barrier is positively charged.
   C. Hydrostatic pressure in the glomerular capillaries is the only force for filtration.
   D. Dilation of the afferent arteriole, but not the efferent arteriole, can increase filtration rate.
   E. Mesangial cells do not influence filtration rate.
2. Fanconi syndrome is a disorder of the proximal tubule. Patients can present with glycosuria, polyuria, hypercalciuria, hyperphosphaturia, and low-molecular-weight proteinuria. These features can be explained because the proximal tubule normally:
   A. Reabsorbs about 100% of the filtered glucose
   B. Reabsorbs approximately 65% of the filtered water, because of a large transepithelial osmotic gradient
   C. Actively reabsorbs calcium through Ca^{2+}-ATPase in the apical membrane
   D. Secretes phosphate through the organic anion transporter system
   E. Is a tight epithelium, impermeable to paracellular movement of proteins
3. The corticomedullary osmotic gradient is required for urine concentration. Which of the following would diminish this gradient?
   A. Increased circulating vasopressin
   B. Increased blood flow through the renal medulla
   C. Activation of the sympathetic nervous system
   D. Activation of the renin-angiotensin-aldosterone system
   E. Increased urea recycling through the collecting duct system

3

Assessment of Glomerular Filtration Rate

Lesley A. Inker, Andrew S. Levey

The level of glomerular filtration rate (GFR) is widely accepted as the best overall index of kidney function in health and disease. GFR decline is correlated with decline in other excretory functions of the kidney, such as tubular reabsorption and secretion, as well as with decline in endocrine and metabolic functions of the kidney. Decreased GFR is strongly associated with complications of acute and chronic kidney disease (CKD), and decreased GFR is one criterion in the definition and staging of acute and CKD. GFR estimating equations are now recommended for routine use in clinical practice, and estimated GFR is routinely reported when serum creatinine is measured.

GLOMERULAR FILTRATION RATE

GFR is the product of the average filtration rate of each nephron, the filtering unit of the kidneys, multiplied by the number of nephrons in both kidneys. The normal level for GFR is approximately 130 ml/min/1.73 m^2 for men and 120 ml/min/1.73 m^2 for women, with considerable variation among individuals according to age, gender, body size, physical activity, diet, pharmacotherapy, hyperglycemia, and physiologic states such as pregnancy. To standardize GFR for differences in kidney size, which is proportional to body size, GFR is indexed for body surface area (BSA), computed from height and weight, and is expressed per 1.73 m^2 BSA, the mean BSA of young men and women when indexing was proposed. Even after adjustment for BSA, GFR is approximately 8% higher in young men than in women and declines with age; the mean rate of decline is approximately 0.75 ml/min/yr after 40 years of age, but the variation is wide and the sources of variation are poorly understood. During pregnancy, GFR increases by about 50% in the first trimester and returns to normal immediately after delivery. GFR has a diurnal variation and is 10% lower at midnight compared with the afternoon. In an individual, GFR is relatively constant over short intervals of time but varies considerably among people, even after adjustment for the known variables.

Reductions in GFR may result from a decline in the nephron number or in the single-nephron (SN) GFR from physiologic or hemodynamic alterations. An increase in SNGFR caused by increased glomerular capillary pressure or glomerular hypertrophy can compensate for a decrease in nephron number; therefore the level of GFR may not reflect the loss of nephrons. As a result, there may be substantial kidney damage before GFR decreases.

MEASUREMENT AND ESTIMATION OF THE GLOMERULAR FILTRATION RATE

The GFR cannot be measured directly in humans. Instead, it is assessed from clearance measurements or serum levels of filtration markers, exogenous or endogenous solutes that are mainly eliminated by glomerular filtration. Both measured GFR (mGFR) and estimated GFR (eGFR) are associated with systematic and random error (bias and imprecision, respectively) in their determination and thus may differ from the "true GFR."

The classic method for GFR measurement described by Homer Smith is the urinary clearance of inulin and remains the reference (gold standard) against which other clearance methods and filtration markers are evaluated.[1] However, this technique is cumbersome in practice. Therefore many alternative clearance methods and filtration markers are used in clinical centers and as a research tool (Table 3.1). Recently, methods to estimate the GFR from serum levels of endogenous filtration markers have been developed to simplify GFR assessment without requiring administration of exogenous filtration markers and without performing clearance measurements. The principles of GFR estimation are similar in adults and children, but we discuss only GFR estimating equations developed in adults.

CLEARANCE MEASUREMENTS

Concept of Clearance

Clearance of a substance is defined as the volume of plasma cleared of a marker per unit of time. The clearance of substance *x* (C_x) can be calculated as $C_x = A_x/P_x$, where A_x is the amount of *x* eliminated from the plasma, P_x is the average plasma concentration, and C_x is expressed in units of volume per time. Clearance does not represent an actual volume; rather, it is a virtual volume of plasma that is completely cleared of the substance per unit of time. The value for clearance is related to the efficiency of elimination: the greater the efficiency of elimination, the higher the clearance. Clearance of substance *x* is the sum of the urinary and extrarenal clearance; for substances that are eliminated by renal and extrarenal routes, plasma clearance exceeds urinary clearance. By convention we refer to concentration in plasma when discussing physiologic principles and serum when discussing clinical measures. In practice, laboratory measurements of markers of glomerular

TABLE 3.1 Exogenous Filtration Markers for Estimation of Glomerular Filtration Rate

Marker	Method of Administration	Comments
Inulin	Continuous IV infusion	Gold standard.
Iothalamate	Bolus IV injection or subcutaneous injection	Can be administered as radioactive compound with iodine 125 (^{125}I) as the tracer or in nonradioactive form, with assay using HPLC or MS methods in plasma and whole blood. In radioactive form, potential problem of thyroid uptake of ^{125}I. Iothalamate is secreted, leading to overestimation of GFR.
^{99m}Tc-DTPA	Bolus IV injection	Dissociation of ^{99m}Tc leads to plasma protein binding and underestimation of GFR.
^{51}Cr-EDTA	Bolus IV injection	10% lower clearance than inulin.
Iohexol	Bolus IV injection	Low incidence of adverse effects; assay using HPLC or MS methods in plasma and whole blood. Lower urinary clearance than iothalamate.

^{51}*Cr-EDTA,* Chromium 51–labeled ethylenediaminetetraacetic acid; *GFR,* glomerular filtration rate; *HPLC,* high-performance liquid chromatography; *IV,* intravenous; *MS,* mass spectrophotometric; ^{99m}*Tc-DTPA,* technetium 99m–labeled diethylenetriaminepentaacetic acid.

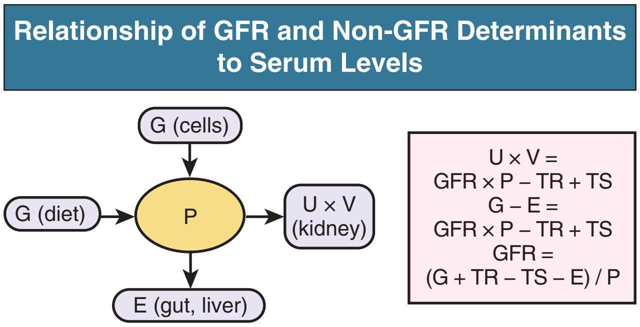


Fig. 3.1 **Relationship of GFR and non-GFR determinants to serum levels.** *G,* Generation; *GFR,* glomerular filtration rate; *E,* extrarenal elimination; *P,* plasma; *TR,* tubular reabsorption; *TS,* tubular secretion. (Modified from reference 50.)

filtration are similar in plasma and serum and are generally referred to as serum concentrations.

Urinary Clearance

The amount of substance *x* excreted in the urine can be calculated as the product of the urinary flow rate *(V)* and the urinary concentration (U_x). Therefore urinary clearance is defined as follows:

$$C_x = (U_x \times V)/P_x$$

Urinary excretion of a substance depends on filtration, tubular secretion, and tubular reabsorption. Substances that are filtered but not secreted or reabsorbed by the tubules are ideal filtration markers because their urinary clearance can be used as a measure of GFR. For substances that are filtered and secreted, urinary clearance exceeds GFR, and for substances that are filtered and reabsorbed, urinary clearance is less than GFR.

Measurement of urinary clearance requires a timed urine collection for measurement of urine volume, as well as urine and plasma concentrations of the filtration marker. The classic protocol of Smith[1] used a continuous intravenous infusion to achieve a steady state and bladder catheterization with multiple timed urine collections. Alternative protocols to assess urinary clearance have been validated, including bolus intravenous or subcutaneous administration rather than continuous intravenous infusion and spontaneous bladder emptying rather than bladder catheterization. Bolus administration of the marker results in declining plasma levels of the filtration markers during the clearance measurement, which may cause errors in determining the average plasma concentration during the clearance measurement.

Plasma Clearance

Measurement of plasma clearance avoids the need for a timed urine collection. GFR is calculated from plasma clearance (C_x) after bolus intravenous administration of an exogenous filtration marker, with the clearance (C_x) computed from the amount of the marker administered (A_x) divided by the average plasma concentration (P_x), which can be computed from the area under the curve of plasma concentration versus time.

$$C_x = A_x/P_x$$

The decline in plasma levels is secondary to the immediate disappearance of the marker from the plasma into its volume of distribution (fast component) and to renal excretion (slow component). Plasma clearance is best estimated by use of a two-compartment model that requires blood sampling early (usually two or three time points until 60 minutes) and late (one to three time points from 120 minutes onward).[2] Novel methods are under investigation to shorten the time required for clearance measurements.[3] As with urinary clearance, plasma clearance of a substance depends on filtration, tubular secretion, and tubular reabsorption, but, in addition, extrarenal elimination and the time course for equilibration of the filtration marker between plasma and its volume of distribution. Edematous conditions prolong the distribution from plasma to extracellular fluid and may cause error in GFR. Extrarenal elimination has been demonstrated for several filtration markers.

ESTIMATION OF THE GLOMERULAR FILTRATION RATE

Fig. 3.1 shows the relationship of plasma concentration of substance *x* to its generation (G_x) by cells and dietary intake, urinary excretion ($U_x \times V$), and extrarenal elimination (E_x) by gut and liver. The plasma level is related to the reciprocal of the level of GFR, but it is also influenced by generation, tubular secretion and reabsorption, and extrarenal elimination, collectively termed *non-GFR determinants* of the plasma level.[4]

In the steady state, a constant plasma level of substance *x* is maintained because generation is equal to urinary excretion and extrarenal elimination. Estimating equations incorporate demographic and clinical variables as surrogates for the non-GFR determinants and provide a more accurate estimate of GFR than the reciprocal of the plasma level alone. eGFR may differ from mGFR if a discrepancy exists between the true and average values for the relationship of the surrogate to the non-GFR determinants of the filtration marker. Other sources of errors include measurement error in the filtration marker (e.g., failure to calibrate assay for filtration marker to assay used in development of equation), measurement error in GFR in development of the equation, and regression to the mean. In principle, all these errors are likely to be greater at higher values for GFR, although such errors may be more clinically significant at lower measured GFR.

Filtration Markers

Solutes with molecular weight less than approximately 20,000 daltons and not bound to plasma proteins are freely filtered by the glomeruli and are candidate filtration markers.

Exogenous Filtration Markers

Iothalamate, iohexol, ethylenediaminetetraacetic acid, and diethylenetriaminepentaacetic acid, often chelated to radioisotopes for ease of detection, are commonly used alternatives to inulin (see Table 3.1). Deviations from ideal behavior can be inferred from differences from inulin clearance during simultaneous clearance measurements.

Endogenous Filtration Markers

Endogenous filtration markers are substances generated in the body at a relatively constant rate and eliminated largely by glomerular filtration. Therefore the plasma level correlates highly with measured GFR after accounting for the non-GFR determinants. Currently identified endogenous filtration markers include low-molecular-weight metabolites (such as creatinine and urea) and plasma proteins (such as cystatin C) (Table 3.2). Filtered metabolites may undergo reabsorption or secretion, which may be assessed by comparing their urinary clearance to urinary clearance of exogenous filtration markers. By contrast, filtered plasma proteins are reabsorbed and degraded within the tubule with minimal appearance in the urine. For metabolites excreted in the urine, urinary clearance can be computed from a timed urine collection and a single measurement of serum concentration. If the plasma level is not constant during the urine collection, as in acute kidney disease or when residual kidney function is assessed in patients undergoing intermittent dialysis, it is necessary to obtain additional blood samples during the urine collection to estimate the average plasma concentration.

CREATININE

Metabolism and Excretion

Creatinine is a 113-d end product of muscle catabolism. Advantages of creatinine include its ease of measurement and the low cost and widespread availability of assays (see Table 3.2). Disadvantages include the large number of conditions affecting its non-GFR determinants, leading to a wide range of GFR for a given serum creatinine level (Table 3.3). For example, a serum creatinine level of 1.5 mg/dl (132 μmol/l) may correspond to a GFR from approximately 20 to 90 ml/min/1.73 m^2.

Creatinine is derived by the metabolism of phosphocreatine in muscle, as well as from dietary meat intake or creatine supplements. Creatinine generation is proportional to muscle mass, which can be estimated from age, gender, race, and body size, but many other factors can affect

TABLE 3.2 Creatinine, Cystatin C, and Urea as Endogenous Filtration Markers

Variable	Creatinine	Cystatin C	Urea
Molecular Properties			
Weight (daltons)	113	13,000	60
Structure	Amino acid derivative	Nonglycosylated basic protein	Organic molecular product of protein metabolism
Physiologic Determinants of Serum Level			
Generation	Varies, according to muscle mass and dietary protein; lower in elderly persons, women, and whites	Thought to be mostly constant by all nucleated cells; increases in hyperthyroid state and with steroid use; lower in elderly persons and women	Varies, according to dietary protein intake and catabolism
Handling by kidney	Filtered, secreted, and excreted in urine	Filtered, reabsorbed, and catabolized	Filtered, reabsorbed, and excreted in urine
Extrarenal elimination	Yes; increases at reduced GFR	Preliminary evidence of increases at reduced GFR	Yes; increases at reduced GFR
Use in Estimating Equations for GFR			
Demographic and clinical variables as surrogates for physiologic determinants	Age, gender, and race; related to muscle mass	Age, sex	Not applicable
Accuracy	Accurate for GFR <60 ml/min/1.73 m^2	Unknown	Not applicable
Assay			
Method	Colorimetric or enzymatic	PENIA, PETIA, or ELISA	Direct measurement, enzymatic colorimetric, and electrochemical
Assay precision	Very good except at low range	Precise throughout range, but difficult to standardize	Precise throughout range
Clinical laboratory practice	Multiple assays; widely used nonstandard calibration	Not on most autoanalyzers; not standardized	Multiple assays; enzymatic and colorimetric more common
Standardized recommendation materials (SRMs)	SRM 967	ERM-DA471/IFCC	SRM 912a
Reference assay	IDMS	PENIA, PETIA, or ELISA	IDMS

ELISA, Enzyme-linked immunosorbent assay; *GFR,* glomerular filtration rate; *IDMS,* isotope-dilution–mass spectroscopy; *PENIA,* particle-enhanced nephelometric immunoassay; *PETIA,* particle-enhanced turbidimetric immunoassay.

TABLE 3.3 Factors Affecting Serum Creatinine and Cystatin C Concentrations Independent From Glomerular Filtration Rate

Factors	Effect on Creatinine (Direction/*Mechanism*)	Effect on Cystatin C (Direction/*Mechanism*)
Age	Decrease *Lower creatinine generation caused by age-related decline in muscle mass*	Decrease *Presumed lower cystatin C generation caused by age-related decreased cellular mass, smaller impact than creatinine*
Female sex	Decrease *Lower creatinine generation caused by lower muscle mass*	Decrease *Presumed lower cystatin C generation caused by lower cellular mass, smaller impact than creatinine*
Race		
African American	Increase *Higher creatinine generation caused by higher average muscle mass in African Americans; not known how muscle mass in other races compares with that of African Americans or Caucasians*	No effect
Diet		
Vegetarian	Decrease *Lower creatinine generation*	No effect
Ingestion of cooked meats and creatinine supplements	Increase *Transient increase in creatinine generation, although this may be blunted by transient increase in GFR*	No effect
Body Habitus		
Larger muscle mass	Increase *Higher muscle generation caused by increased muscle mass and/or increased protein intake*	No effect
Smaller muscle mass (e.g., amputation, anorexia)	Decrease *Lower creatinine generation caused by reduced muscle mass and/or reduced protein intake*	No effect
Malnutrition, muscle wasting, in context of chronic illness	Decrease *Lower creatinine generation caused by reduced muscle mass and/or reduced protein intake*	Possible increase *Presumed higher cystatin C generation in conditions associated with inflammation*
Obesity	No change *Excess fat mass, not muscle mass, which does not contribute to creatinine generation*	Increase *Presumed higher cystatin C generation by excess fat mass*
Medications		
Trimethoprim, cimetidine, fibric acid derivatives other than gemfibrozil	Increase *Reduced tubular secretion of creatinine*	No known effects, not studied
Ketoacids, some cephalosporins	Interference with alkaline picrate assay for creatinine	No known effects, not studied

creatinine generation. Creatinine is distributed in total body water, not protein bound, and freely filtered across the glomerulus and secreted by the tubules. Several medications, such as cimetidine, trimethoprim, and possibly fenofibrate, competitively inhibit creatinine secretion, leading to a rise in the serum creatinine concentration without an effect on GFR.

In addition, creatinine is contained in intestinal secretions and can be degraded by bacteria; gastrointestinal elimination of creatinine is increased at higher levels of serum creatinine but can be reduced by changes in gut flora due to antibiotic use. Clinically, it can be difficult to distinguish a rise in serum creatinine concentration caused by inhibition of creatinine secretion or extrarenal elimination from a decline in GFR.

Creatinine clearance (Clcr) is usually computed from the creatinine excretion in a 24-hour urine collection and single measurement of serum creatinine in the steady state. Creatinine excretion rates vary with age, gender, and race, with mean levels of approximately 20 to 25 mg/kg/day and 15 to 20 mg/kg/day in a complete collection in healthy young men and women, respectively. Deviations from estimated creatinine excretion (based on age, gender, weight, and other variables)[5] can indicate errors in timing or completeness of urine collection, but cannot be relied on because of wide variability in creatinine generation.

Creatinine Assay

Historically, the most common assay for measurement of serum creatinine was the alkaline picrate (Jaffe) assay that generates a color reaction. Chromogens other than creatinine can interfere with the assay, causing errors of up to 20% in normal individuals. Reference materials traceable to an isotope-dilution–mass spectrometry (IDMS) reference are now available to standardize creatinine measurements, and most manufacturers have now calibrated their instruments using these reference materials.[6,7] Standardization has reduced, but not eliminated the error in estimating GFR at higher levels.

Estimated Glomerular Filtration Rate From Serum Creatinine

GFR can be estimated from serum creatinine (eGFR$_{cr}$) by equations that use age, gender, race, and body size as surrogates for creatinine generation. Despite ongoing refinements in recent years, GFR estimates remain imprecise; none of the equations is expected to work as well in patients with extreme levels for creatinine generation, such as amputees, large or small individuals, patients with muscle-wasting conditions, or people with atypical pattern of meat consumption (see Table 3.3). Also, equations developed in one racial or ethnic group are unlikely to be accurate in multiethnic populations. As discussed later, further improvements will probably require additional filtration markers.

Equation Currently Recommended for Use

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation was developed from a large database of people, including those with and without kidney disease, diabetes, and a history of organ transplantation.[8] The equation includes age, race, and sex and standardized serum creatinine. It uses a two-slope "spline" to model the relationship between GFR and serum creatinine and is accurate across the full range of GFR. It is accurate across a wide range of patient characteristics, including age, gender, race, body mass index (BMI), and presence or absence of diabetes or history of organ transplantation. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that clinical laboratories use CKD-EPI creatinine equations to report eGFR in all adults whenever serum creatinine is measured or use other equations if shown to be superior to CKD-EPI equation in that population (Box 3.1).[9]

Equations Previously Recommended for Use

The Cockcroft-Gault equation, developed in 1977, estimates Clcr from age, gender, and body weight, in addition to serum creatinine.[10] Comparison to normal values for Clcr requires computation of BSA and adjustment to 1.73 m^2. The Cockcroft-Gault formula has several limitations. First, it is not precise, in particular in the GFR range above 60 ml/min. Second, it estimates Clcr rather than GFR and thus is expected to overestimate GFR. Third, the formula was derived by older assay methods for serum creatinine, which cannot be calibrated to newer assay methods and would be expected to lead to a systematic bias in estimating Clcr. Fourth, it systematically overestimates Clcr in edematous or obese patients. Fifth, the large age term means that all older adults will have lower levels of estimated GFR.

BOX 3.1 LINKS TO RELEVANT GUIDELINES AND GLOMERULAR FILTRATION RATE CALCULATOR

KDIGO Guideline 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[9]
http://kdigo.org/guidelines/ckd-evaluation-and-management/

Guideline for Acute Kidney Injury[42]
http://kdigo.org/guidelines/acute-kidney-injury/

KDIGO Clinical Practice Guideline on the Evaluation and Follow-Up Care of Living Kidney Donors[45]
http://kdigo.org/guidelines/living-kidney-donor/

KDIGO Controversy Conference on Drug Prescribing in Kidney Disease: Initiative for Improved Dosing[49]
http://www.kdigo.org/pdf/Section%20topic%20summaries.pdf

Chronic Kidney Disease Epidemiology Collaboration (CKP-EPI)
http://ckdepi.org/equations/gfr-calculator/

The Modification of Diet in Renal Disease (MDRD) study equation[11] is similar to the CKD-EPI equation and more accurate than the Cockcroft-Gault equation. However, it was derived from a study population with CKD, so it underestimates the measured GFR in populations with higher levels of GFR, and numeric values cannot be reported for GFR levels greater than 60 ml/min/1.73 m^2.[12]

Other Equations That Could Be Considered for Use in Selected Populations

Several equations developed in Europe and North America and using standardized creatinine appear to be as accurate as the CKD-EPI equation for whites, but are not applicable for African American or other races.[13-15] Other equations have been developed in Asian and African populations that improve the accuracy of GFR estimates in the study population; however, these equation modifications do not generalize well to other populations.[16-21]

CYSTATIN C

Metabolism and Excretion

Cystatin C is a 122–amino acid protein with molecular weight of 13 kd (see Table 3.2).[22] Cystatin C is produced in all nucleated cells and is distributed in extracellular fluid. Approximately 99% of the filtered cystatin C is reabsorbed by the proximal tubular cells, where it is almost completely catabolized, with the remainder eliminated in the urine largely intact.[23] Some evidence suggests the existence of tubular secretion as well as extrarenal elimination, the latter estimated at 15% to 21% of renal clearance. Smoking, inflammation, adiposity, thyroid diseases, certain malignant neoplasms, and use of glucocorticoids appear to be associated with higher cystatin C levels independent of mGFR.[24,25] Therefore factors other than GFR must be considered in interpreting cystatin C levels.

Cystatin C Assay

Several assays are available (all more expensive than those for creatinine). The International Federation of Clinical Chemists (IFCC) has developed reference material for standardization of cystatin C, but international standardization of the assay is still in process and important differences remain.[26-28]

Estimated Glomerular Filtration Rate From Serum Cystatin C

Cystatin C is less affected by muscle than creatinine, but eGFR based on serum cystatin C (eGFR$_{cys}$) is not more accurate than eGFR$_{cr}$, because of variation in conditions affecting non-GFR determinants of serum cystatin C. However, equations combining both these filtration markers (eGFR$_{cr\text{-}cys}$) appear to be more precise than equations using either marker alone. The 2012 CKD-EPI cystatin C and creatinine–cystatin C equations are expressed for use with standardized serum creatinine and cystatin C and are recommended by the 2012 KDIGO guidelines (see Box 3.1).[9,29] The equation using cystatin C without creatinine includes age and sex, but does not require specification of race. In patients with reduced muscle mass (e.g., neuromuscular or liver disease, low BMI) or in patients with diabetes, eGFR$_{cys}$ may be more accurate than eGFR$_{cr}$. Other recent equations using cystatin C have been developed;

regional modifications appear to be less important for $eGFR_{cys}$ than for $eGFR_{cr}$.[14,30,31]

Some studies show that a lower $eGFR_{cys}$ is a better predictor of the risk for cardiovascular disease and total mortality than is a lower $eGFR_{cr}$.[32] In our view, this is likely due to confounding by non-GFR determinants of cystatin C and creatinine. Because of better accuracy and risk prediction, $eGFR_{cr\text{-}cys}$ is recommended as a confirmatory test for CKD, but full implementation will require standardization, greater availability, and cost reductions of cystatin C assays, as well as better understanding of non-GFR determinants of serum cystatin C (see Box 3.1).[9,29]

UREA AND OTHER METABOLITES

The serum urea level has limited value as an index of GFR, in view of widely variable non-GFR determinants, primarily urea generation and tubular reabsorption (see Table 3.2).

Urea is a 60-d end product of protein catabolism by the liver. Factors associated with the increased generation of urea include protein loading from hyperalimentation and absorption of blood after a gastrointestinal hemorrhage. Catabolic states caused by infection, corticosteroid administration, or chemotherapy also increase urea generation. Decreased urea generation is seen in patients with severe malnutrition and liver disease.

Urea is freely filtered by the glomerulus and then passively reabsorbed in both proximal and distal nephrons. As a result of tubular reabsorption, urinary clearance of urea underestimates GFR. Reduced kidney perfusion in the patient with volume depletion and states of antidiuresis are associated with increased urea reabsorption. This leads to a greater decrease in urea clearance than the concomitant decrease in GFR. At GFR of less than about 20 ml/min/1.73 m^2, the overestimation of GFR by Clcr resulting from creatinine secretion approximates the underestimation of GFR by urea clearance from urea reabsorption; thus the average of creatinine and urea clearance approximates the measured GFR.

Recent advances in assays for metabolites have revealed a number of compounds, such as pseudouridine and acetylthreonine, that are highly correlated with GFR and may have promise for GFR estimation.[33,34]

OTHER LOW-MOLECULAR-WEIGHT SERUM PROTEINS

β_2-Microglobulin (β_2M) and β-trace protein (βTP) are low-molecular-weight serum proteins being evaluated as filtration markers for estimating GFR and for their role in prognosis. As with cystatin C, β_2M and βTP are freely filtered by the glomerulus and extensively reabsorbed and degraded by the proximal tubule, with only small amounts excreted in the urine under normal conditions.

Serum β_2M and βTP levels are more strongly correlated with measured GFR than serum creatinine and are similar to cystatin C. Like cystatin C, serum β_2M and βTP are less influenced by age, sex, and race than creatinine, but GFR estimating equations using these markers are not more accurate than equations using creatinine and cystatin C.[24,35] In addition, studies have shown that β_2M and βTP are better predictors of adverse health outcomes than creatinine and are potentially as accurate as cystatin C in the general population and in patients with CKD.[36]

A recent study shows that serum β_2M and βTP can be used to estimate residual kidney function in patients on dialysis.[37] The likely explanation is that they are too large to be filtered by conventional dialysis membranes, so their serum concentrations reflect residual kidney function rather than the dialysis dose.

CLINICAL APPLICATION OF ESTIMATED GLOMERULAR FILTRATION RATE

Chronic Kidney Disease

Estimation of GFR is necessary for the detection, evaluation, and management of patients with CKD. GFR less than 60 ml/min/1.73 m^2 for 3 months or longer is one of the criteria for the definition of CKD (see Box 3.1).[9] Current guidelines recommend testing of patients at increased risk for CKD for decreased GFR as well as albuminuria, as a marker of kidney damage, and recommend staging of kidney disease severity and estimating prognosis using levels of albuminuria and GFR (see Box 3.1).[9] The Kidney Failure Risk Equation, a recently developed and validated prediction instrument uses age, sex, GFR, and urine albumin-to-creatinine ratio to predict the risk for onset of kidney failure within 2 or 5 years.[38]

Use of serum creatinine alone as an index of GFR is not recommended and can lead to delays in detection of CKD and misclassification of the severity of CKD. Use of estimating equations allows direct reporting of eGFR by clinical laboratories whenever serum creatinine is measured. Current estimating equations are less accurate in people with factors affecting serum creatinine concentration other than GFR (see Table 3.3). In these patients, more accurate GFR estimates require additional testing, such as measurement with an endogenous filtration marker (e.g., cystatin C, β_2M, βTP), a timed urine Clcr measurement, or clearance measurement using an exogenous marker. The KDIGO CKD guidelines recommend use of $eGFR_{cr}$ as an initial test followed by $eGFR_{cr\text{-}cys}$ or a clearance measurement for confirmation in conditions in which eGFR may be inaccurate (Fig. 3.2). Examination of consistency of the results in GFR estimates and clearance measurements is recommended. If the results are inconsistent, clinicians should consider possible reasons for the inconsistency, such as differences in expected creatinine excretion and non-GFR determinants of creatinine and cystatin C, and eliminate the inconsistent value from consideration, repeating the measurement, or performing a measured GFR using an exogenous marker.

Change in serum creatinine is routinely used to assess the progression of kidney disease, and quantitative associations with risk for end-stage renal disease (ESRD) are now available. For those with GFR less than 60 ml/min/1.73 m^2, a decline in eGFR within 2 years of 30%, 40%, and 57% (corresponding to a 1.3-, 1.5-, and 2.0-fold increase in serum creatinine), corresponded to a 5.4, 10.2, and 32.1 times higher risk for developing ESRD in the subsequent 2 to 4 years compared with a stable eGFR.[39] Similar results were observed for those with a GFR greater than 60 ml/min/1.73 m^2. The current level of eGFR was more strongly associated with ESRD risk than the rate of decline.[40] Similar results were observed for associations with mortality.

Acute Kidney Disease

Change in GFR induces a non-steady state in the serum levels of endogenous filtration markers (Fig. 3.3). After a decline in GFR, there is a lag before the rise in serum level because of the time required for retention of an endogenous filtration marker. Conversely, after recovery of GFR, there is a lag before the excretion of the retained marker. During the non-steady state, neither the serum level nor the GFR estimated from the serum level accurately reflects the measured GFR. Nonetheless, a change in the eGFR in the non-steady state can be a useful indication of the magnitude and direction of the change in measured GFR. If the eGFR is decreasing, the decline in eGFR is less than the decline in mGFR. Conversely, if the eGFR is increasing, the rise in eGFR is greater than the rise in mGFR. The more rapid the change in eGFR, the greater is the change in measured GFR. When eGFR reaches a new steady state, it more accurately reflects measured GFR. A GFR estimating equation

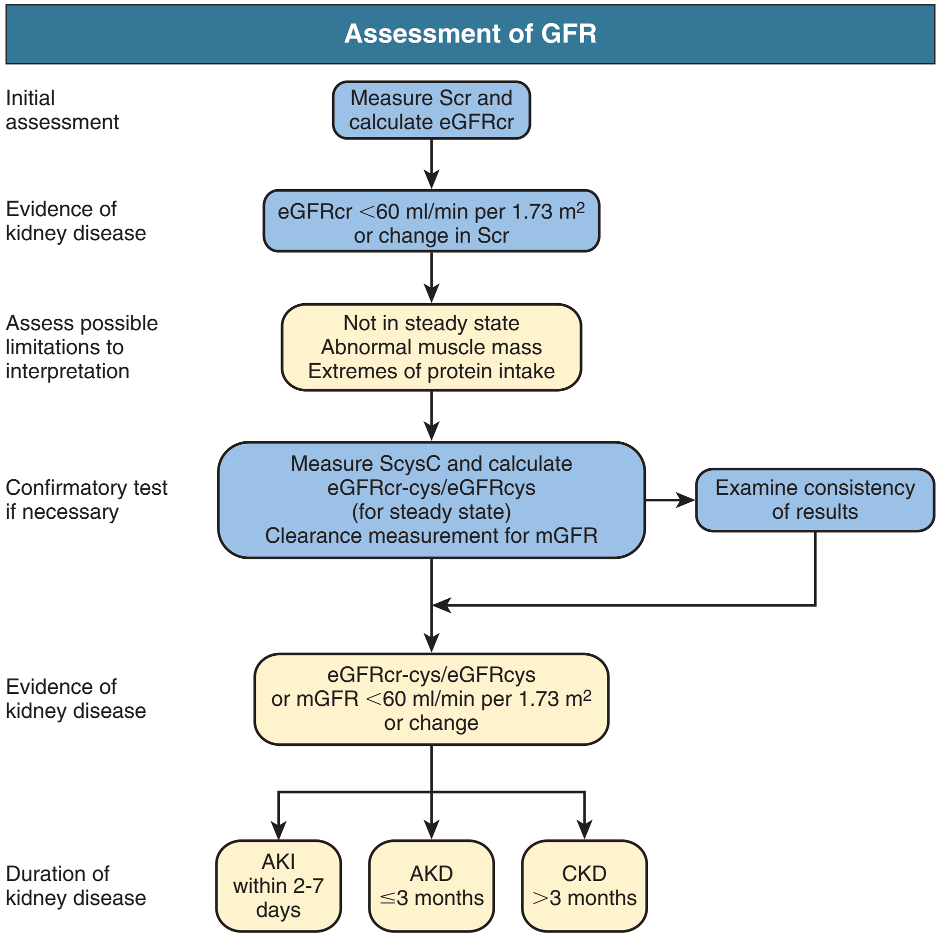

Assessment of GFR
Initial assessment
Measure Scr and calculate eGFRcr
Evidence of kidney disease
eGFRcr <60 ml/min per 1.73 m2 or change in Scr
Assess possible limitations to interpretation
Not in steady state
Abnormal muscle mass
Extremes of protein intake
Confirmatory test if necessary
Measure ScysC and calculate eGFRcr-cys/eGFRcys (for steady state)
Clearance measurement for mGFR
Examine consistency of results
Evidence of kidney disease
eGFRcr-cys/eGFRcys or mGFR <60 ml/min per 1.73 m2 or change
Duration of kidney disease
AKI within 2-7 days
AKD ≤3 months
CKD >3 months

Fig. 3.2 Algorithm for GFR assessment in acute and chronic kidney diseases. *AKD,* Acute kidney disease; *AKI,* acute kidney injury; *CKD,* chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *eGFR*$_{cr}$, eGFR from serum creatinine; *eGFR*$_{cr\text{-}cys}$, eGFR from creatinine and cystatin C; *eGFR*$_{cys}$, eGFR from cystatin C; *mGFR,* measured glomerular filtration rate; *Scr,* serum creatinine; *ScysC,* cystatin C.

for use in the non-steady state has been proposed, but has not yet been validated.[41]

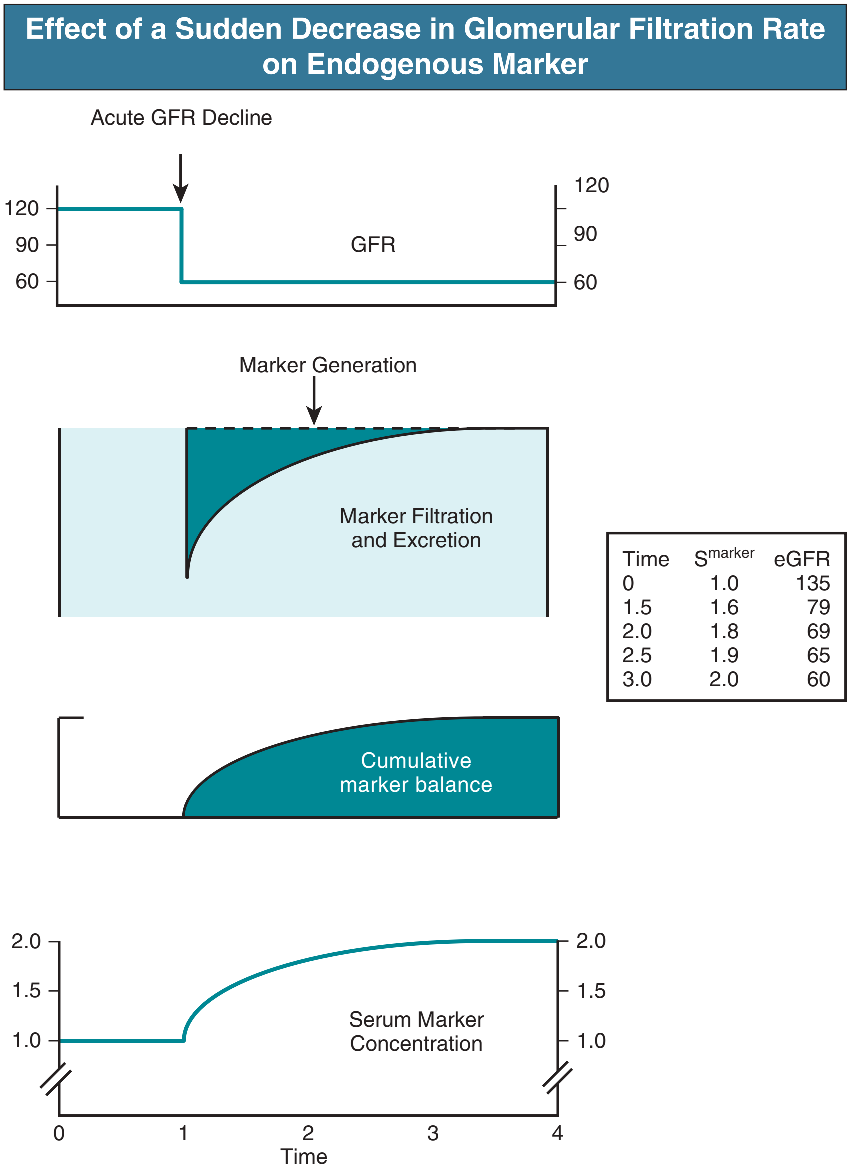
An increase in serum creatinine by 0.3 mg/dl over 48 hours or by 50% over 7 days are criteria for the definition of acute kidney injury (AKI) (see Box 3.1).[42] The absolute and proportionate increase in serum creatinine are influenced by the baseline GFR as well as the magnitude of decline in GFR (Fig. 3.4).[43] In patients with AKI, serum cystatin C appears to increase more rapidly than serum creatinine.[44] More data are required to establish whether changes in serum cystatin C are a more sensitive indicator of rapidly changing kidney function than changes in serum creatinine. In addition, similar to CKD, eGFR$_{cr}$ might be inappropriate in patients with differences in muscle mass or dietary protein intake, and in such patients it would be possible to confirm the change in eGFR$_{cr}$ with changes in eGFR$_{cys}$ or clearance measures (see Fig. 3.2).

LIVING KIDNEY DONOR CANDIDATES

Despite the larger imprecision of GFR estimates at higher levels of GFR, recent KDIGO guidelines on evaluation of the living kidney donor state that eGFR could be used in the evaluation of living kidney donor candidates (see Box 3.1).[45] In the United States, where evaluation of living kidney donor candidates requires a measured clearance, eGFR could be used as a first test with measured clearance as a confirmatory test.[46,47] Performance of multiple tests and assessment of the consistency of their results is helpful to identify possible sources of error. Elsewhere, eGFR could be used to accept or decline donor candidates if the probability is very high that mGFR is above or below, respectively, the thresholds for decision making.[48]

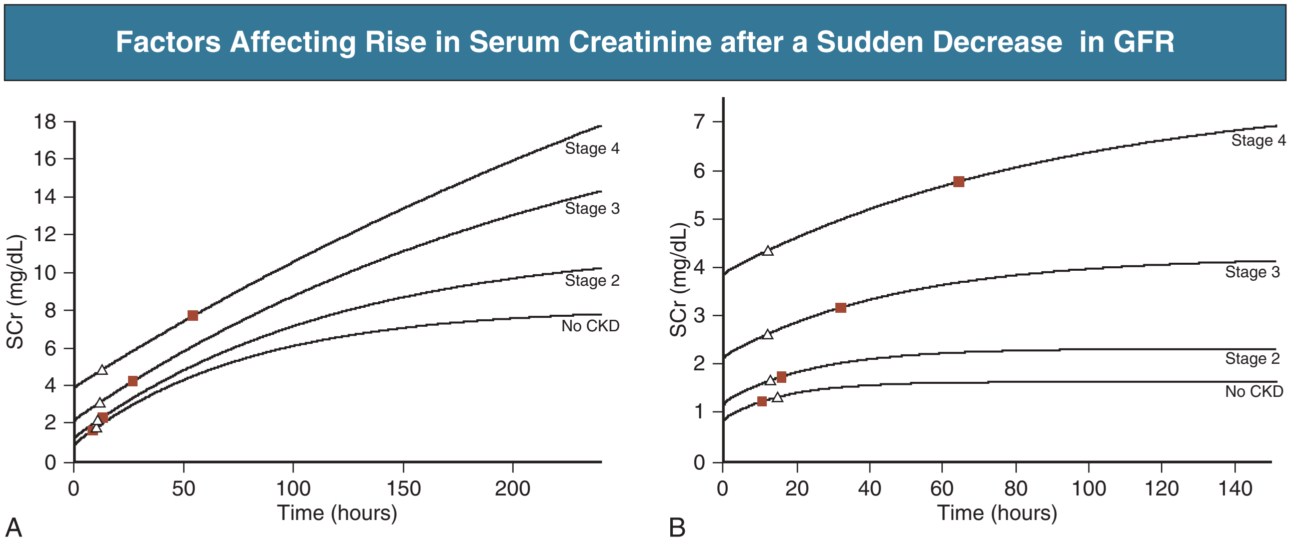
DRUG DOSING

Pharmacokinetic properties of many drugs are affected by acute and chronic kidney disease. Drug dosing must be adjusted in patients with alterations in GFR to ensure therapeutic levels. The Cockcroft-Gault formula was widely used to assess pharmacokinetic properties of drugs in patients with impaired kidney function, but, because of the limitations described previously, the KDIGO Controversies Conference Report recommends that GFR, as it is best evaluated in an individual patient, be used to assess kidney function for drug dosing, rather than a specific equation (see Box 3.1).[49] For drug dosing, GFR should be expressed without indexing for BSA. To convert from ml/min/1.73 m^2 to ml/min, multiply by BSA/1.73 m^2.



Time	S^{marker}	eGFR
0	1.0	135
1.5	1.6	79
2.0	1.8	69
2.5	1.9	65
3.0	2.0	60

Fig. 3.3 **Change in serum ceatinine and eGFR after a sudden decrease in GFR.** Graphs show the effect of acute GFR decline *(top)* on generation, filtration and excretion, balance of endogenous marker *(middle)*, and concentration of serum marker (S^{marker}) *(bottom)*.



Factors Affecting Rise in Serum Creatinine after a Sudden Decrease in GFR

Fig. 3.4 **Factors affecting rise in serum creatinine after a sudden decrease in GFR.** (A) Serum creatinine concentrations after an abrupt 90% reduction in GFR, superimposed on four different levels of baseline kidney function (no CKD and stages 2 through 4 CKD). *Solid squares* show the point at which a 100% increase in serum creatinine has occurred; *open triangles* show the point at which a 1.0-mg/dl increase in serum creatinine has occurred. (B) Serum creatinine concentrations after an abrupt 50% reduction in GFR, superimposed on four different levels of baseline kidney function (no CKD and CKD stages 2 through 4). *Solid squares* show the point at which a 100% increase in serum creatinine has occurred; *open triangles* show the point at which a 1.0-mg/dl increase in serum creatinine has occurred. (Modified from reference 43.)

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SELF-ASSESSMENT QUESTIONS

1. A 59-year-old, 100-kg, 193-cm-tall white man has a serum creatinine concentration of 1.5 mg/dl. Estimated glomerular filtration rate (GFR) using the chronic kidney disease Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation and standardized serum creatinine is 50 ml/min/1.73 m^2, but measured GFR is 90 ml/min/1.73 m^2. What factor most likely explains the underestimation of measured GFR?
   A. Non-steady state of serum creatinine
   B. Drug-induced inhibition of tubular secretion of creatinine
   C. Decreased extrarenal elimination of creatinine
   D. Increased creatinine generation from large muscle mass or diet
2. An 80-year-old white woman has a serum creatinine concentration of 1.0 mg/dl for 3 months. Her estimated GFR using the CKD-EPI creatinine equation and standardized serum creatinine is 53 ml/min/1.73 m^2. She has no chronic kidney disease risk factors. What laboratory tests could be performed to confirm the diagnosis of chronic kidney disease?
   A. Measure urine albumin-to-creatinine ratio.
   B. Measure GFR using an exogenous filtration marker.
   C. Measure serum cystatin C and calculate $eGFR_{cys}$.
   D. Image the kidneys and urinary tract.
   E. Examine the urine sediment.
   F. Any of the above.
3. A 40-year-old man with type 1 diabetes mellitus and urine albumin-to-creatinine ratio of 450 mg/g begins angiotensin-converting enzyme (ACE) inhibitor therapy to slow the progression of kidney disease. Within 2 weeks, $eGFR_{cr}$ declines from 75 to 65 ml/min/1.73 m^2. What is the most likely cause for decline in eGFR?
   A. Effect of ACE inhibitor on serum creatinine assay
   B. Effect of ACE inhibitor on GFR
   C. Effect of ACE inhibitor on tubular secretion of creatinine
   D. Effect of ACE inhibitor on muscle mass

4

Urinalysis

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DEFINITION

Urinalysis is one of the key tests to evaluate kidney and urinary tract disease. When a patient is first seen by a nephrologist, urinalysis must always be performed. Reagent strips are still the most widely used method for urinalysis to supply physicochemical information. However, the nephrologist should be aware of their limitations and ask for more sensitive and specific measurements by other methods in the case of reagent strip abnormalities (e.g., the accurate measurement of proteinuria in case of reagent strip positivity for albumin).[1]

As well as physiochemical findings, urine sediment examination is an integral part of urinalysis[2,3] and ideally should be performed by nephrologists, who may be able to identify particles of clinical relevance that escape laboratory personnel.[4]

THE URINE SAMPLE

The use of an early morning urine sample is suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) guideline,[1] especially for the measurement of albumin (see later discussion).

However, the 24-hour urine collection is still widely used for the measurement of multiple parameters, even though errors caused by improper timing and missed samples can lead to overcollection or undercollection of urine. Errors can be minimized by giving the patient clear written instructions (e.g., at 7:00 AM discard the first urine of the morning; then collect in a capacious—of at least 2.5 L—and graduated container *all* the urine produced, including that passed at 7:00 AM of the day after; measure the volume of urine carefully and record it). Written instructions should also be provided for other types of urine samples—for example, when testing for orthostatic proteinuria, one sample produced while the patient has been recumbent for some hours, and another sample produced while the patient has been standing.

Strenuous physical exercise (e.g., running, soccer) should be avoided for at least 24 hours before the urine sample delivery to avoid exercise-induced proteinuria and hematuria or urinary casts. In women, urinalysis must be avoided during menstruation because of the high probability of blood contamination.

For urine microscopy, a midstream sample of the first morning urine is recommended by some international guidelines because this urine is the most concentrated and acidic and theoretically the best for the preservation of particles.[5] On the other hand, the prolonged persistence in the bladder may favor the lysis of cells and casts, which may lead to false-negative urine sediment examination. For this reason, we use a combined dipstick and urine microscopy on the second morning urine.[6]

For a urine sediment sample, after the washing of hands, women should spread the labia of the vagina and men withdraw the foreskin of the glans. The external genitalia are washed and wiped dry with a paper towel, and the midstream urine is collected after the first portion is discarded. The same procedures can be used for children. For small infants, bags for urine are often used, even though these carry a high probability of contamination. A suprapubic bladder puncture may occasionally be necessary. In special situations, urine can also be collected through a bladder catheter, although this procedure may cause hematuria. Permanent indwelling catheters are almost invariably associated with bacteriuria, leukocyturia, hematuria, and candiduria.

The container for urine should be clean, have a capacity of at least 50 ml, and have a diameter opening of at least 4 cm to allow easy collection. It should have a wide base to avoid accidental spillage and should be capped. The label should identify the patient and the hour of urine collection.[5]

Several elements (but especially leukocytes) can lyse rapidly after collection; thus ideally the sample should be handled and examined as soon as possible. We recommend analysis within 3 hours from collection. If this is not possible, refrigeration of specimens at +4° to +8° C assists preservation but may cause precipitation of phosphates or urates, which can hamper examination. Alternatively, chemical preservatives such as formaldehyde or glutaraldehyde can be used.

PHYSICAL CHARACTERISTICS

Color

The color of normal urine ranges from pale yellow to amber, depending on the concentration of the urochrome. Abnormal changes in color can be caused by pathologic conditions, drugs, or foods.

The most frequent color changes are caused by hematuria, hemoglobinuria, or myoglobinuria (pink, red, brown, or black urine); bilirubinuria (dark-yellow to brown urine); and massive uric acid crystalluria (pink urine). Less frequent causes are urinary infection, mainly from *Klebsiella* spp., *Proteus mirabilis, Escherichia coli, Providencia stuartii,* or *Enterococcus* spp. in patients with a permanent bladder catheter (purple urine, known as "purple urine bag syndrome")[7]; chyluria (white milky urine); porphyrinuria (associated with the excretion in the urine of porphobilinogen); and alkaptonuria (red urine turning black on standing).

The main drugs responsible for abnormal urine color are rifampin; phenazopyridine (yellow-orange to red urine); desferrioxamine (pinkish urine); phenytoin (red urine); chloroquine and nitrofurantoin (brown urine); triamterene, propofol, and blue dyes of enteral feeds (green urine); methylene blue (blue urine); and metronidazole, methyldopa, and imipenem-cilastatin (darkening on standing).

Among foods are beetroot (red urine), senna and rhubarb (yellow to brown or red urine), and carotene (brown urine).

Turbidity

Normal urine is transparent. Urine can be turbid because of a high concentration of any urine particle, especially cells, crystals, and bacteria. The most frequent causes of turbidity are urinary tract infection (UTI), heavy hematuria, and genital secretions. The absence of turbidity is not a reliable criterion by which to judge a urine sample because pathologic urine can be transparent.

Odor

A change in urine odor may be caused by the ingestion of some foods, such as asparagus. A pungent odor, caused by the production of ammonia, is typical of most bacterial UTIs, whereas there is often a sweet or fruity odor with ketones in the urine. Some rare conditions confer a characteristic odor to the urine. These include maple syrup urine disease (maple syrup odor), phenylketonuria (musty odor), isovaleric acidemia (sweaty feet odor), and hypermethioninemia (rancid butter or fishy odor).

Relative Density

Relative density can be measured by specific gravity or osmolality. *Specific gravity* (SG) refers to the weight of a volume of urine compared with the weight of the same volume of distilled water and depends on the mass and number of the dissolved particles. SG is most frequently evaluated by reagent strip (see discussion of chemical characteristics), which measures the ionic concentration of urine. In the presence of ions, protons are released by a complexing agent and produce a color change in the indicator bromothymol blue from blue to blue-green to yellow. Underestimation occurs with urine of pH above 6.5, whereas overestimation is found with urine protein concentration above 7.0 g/l. Because nonionized molecules, such as glucose and urea, are not detected by dipstick, this method does not strictly correlate with the results obtained by refractometry and osmolality.

Refractometry measures SG through the refraction of light while it passes through a drop of urine on a glass plate. This measures the number of solutes per unit volume and measures all solutes rather than just ionic substances. Therefore refractometry is more accurate than reagent strip, despite being influenced by urine temperature, although temperature-compensated refractometers are available. We suggest refractometry for everyday practice, because refractometers are inexpensive, simple to use, and require only one drop of urine. SG of 1.000 to 1.003 is seen with marked urinary dilution, as observed in patients with diabetes insipidus or water intoxication. SG of 1.010 is often called *isosthenuric* urine because it is of similar SG (and osmolality) to plasma, so it is often observed in conditions in which urinary concentration is impaired, such as acute tubular necrosis (ATN) and chronic kidney disease (CKD) with renal dysfunction. SG above 1.040 almost always indicates the presence of some extrinsic osmotic agent, such as radiocontrast.

Osmolality is measured by an osmometer, which evaluates the freezing-point depression of a solution and supplies results as milliosmoles per kilogram (mOsm/kg) of water. Osmolality depends only on the number of particles present and is not influenced by urine temperature or protein concentrations. However, high glucose concentrations significantly increase osmolality (10 g/l of glucose = 55.5 mOsm/l). Measurement of osmolality is more reliable than SG by either reagent strip or refractometry.

CHEMICAL CHARACTERISTICS

Chemical characteristics of urine are most frequently evaluated by reagent strips. These plastic strips bear several pads (the most used are SG, pH, glucose, hemoglobin, albumin, leukocyte esterase, nitrites, bile pigments, and ketones), each pad being impregnated with chemical reagents meant to detect a specific urine feature. In wealthy countries, the reagent strip reading is performed by automated reader devices, using reflectance spectrometry. Alternatively, the reading is performed manually, which is simple and quick; however, it must be performed correctly, that is, rapid plunging of the strip in the urine; removal of the urine in excess on the pads to avoid color carryover from one pad to the close ones; adherence to the time interval between removal of the strip from urine and the reading of results as indicated by the manufacturer; matching the color developed in the pad with the color scale reported on the strip box in adequate light conditions.

Reagent strips have the advantages of simplicity and low cost and supply a full urinary profile within 2 to 3 minutes. Disadvantages include semiquantitative results only, susceptibility to interference by substances and urine discoloration. Sensitivity and specificity of reagent strips greatly differ across studies and partly depend on the brand used (there is no standardization across manufacturers). Table 4.1 summarizes the

TABLE 4.1 Urine Reagent Strip Testing

Constituent	False-Negative Results	False-Positive Results
Specific gravity (SG)	Urine pH >6.5	Urine protein >7.0 g/l
pH	Reduced values in presence of formaldehyde	—
Hemoglobin	High urine SG Ascorbic acid Formaldehyde (0.5 g/l) used to preserve samples	Myoglobin Microbial peroxidases
Glucose	Ascorbic acid Bacteria	Oxidizing detergents Very acid urine pH
Albumin	Albumin <0.25-0.30 g/l Low urine SG Tubular proteins Monoclonal heavy/light chains	Urine SG ≥1.030 Urine pH >8.0 Quaternary ammonium detergents Chlorhexidine Polyvinylpyrrolidone
Leukocyte esterase	Ascorbic acid Glucose ≥20 g/l Protein >5.0 g/l Cephalothin (+++) Tetracycline (+++) Cephalexin (++) Tobramycin (+) High urine SG	Formaldehyde (0.4 g/l) Imipenem Meropenem Clavulanate Abnormally colored urine
Nitrites	Bacteria that do not reduce nitrates to nitrites No vegetables in diet Short bladder incubation time	Abnormally colored urine
Ketones	Improper storage	Free sulfhydryl groups (e.g., captopril) Levodopa Abnormally colored urine

(Main false-negative and false-positive results of urine reagent strips. False results also may occur when time-expired strips are used.)

main false-negative and false-positive results that can occur with strip reagent testing.

pH

The pH is determined by a strip that covers the pH range of 5.0 to 8.5 or to 9.0, with intervals of only 0.5, which limits precision. Moreover, significant deviations from true pH are observed for values below 5.5 and above 7.5. In the presence of formaldehyde, the strip supplies reduced pH values; no causes of increased pH values are known. When an accurate measurement of pH is necessary, a pH meter with a glass electrode is mandatory.

Urine pH reflects the presence of hydrogen ions (H^+), but this does not necessarily reflect the overall acid load in the urine because most of the acid is excreted as ammonia. Low pH is often observed with metabolic acidosis (in which acid is secreted), high-protein meals (which generate more acid and ammonia), and volume depletion (in which aldosterone is stimulated, resulting in an acid urine). In addition, low urine pH may help distinguish pre-renal acute kidney injury (AKI) from ATN, which is typically associated with a higher pH. High pH is often observed with renal tubular acidosis, vegetarian diets (caused by minimal nitrogen and acid generation), and infection due to urease-positive organisms (e.g., *Proteus*) that generate ammonia from urea.

Measurement of urine pH is also needed for a correct interpretation of other urine parameters (e.g., specific gravity, albumin) and several urine sediment findings.

Hemoglobin

Hemoglobin is detected by a dipstick based on the pseudoperoxidase activity of the heme moiety of hemoglobin, which catalyzes the reaction of a peroxide and a chromogen to form a colored product. The presence of hemoglobin is shown as green spots, which result from intact erythrocytes, or as a homogeneous, diffuse green pattern. The latter can result from marked hematuria because of the high number of erythrocytes that cover the whole pad surface; from lysis of erythrocytes favored by delayed examination, alkaline urine pH, or low SG; or from hemoglobinuria secondary to intravascular hemolysis.

False-negative results are most frequently caused by high SG or by ascorbic acid, a strong reducing agent, which can result in low-grade microhematuria being completely missed. Some reagent strips also include a vitamin C pad to reduce these false-negative results.[8]

The most important causes of false-positive results are myoglobinuria, resulting from rhabdomyolysis, and a high concentration of bacteria with pseudoperoxidase activity (Enterobacteriaceae, staphylococci, and streptococci).[9]

Glucose

The reagent strip uses glucose oxidase as catalyst: glucose is first oxidized to gluconic acid and hydrogen peroxide. Through the catalyzing activity of a peroxidase, hydrogen peroxide then reacts with a reduced colorless chromogen to form a colored product. This test detects concentrations of 0.5 to 20 g/l. When more precise quantification of urine glucose is needed, enzymatic methods such as hexokinase must be used.

False-negative results for glucose occur in the presence of ascorbic acid and bacteria. False-positive findings may be observed in the presence of oxidizing detergents and very acid urine pH.

Protein

Although there has been no consistent definition of proteinuria,[10] the definitions in the KDIGO guideline are increasingly used.[1] It is accepted that physiologic proteinuria does not exceed 150 mg/24 h for adults[1] and 140 mg/m^2 for children,[10] in whom, however, the normal values do vary by age.[1] Three different approaches can be used for the evaluation of proteinuria, as described next.

Albumin Reagent Strip

The albumin reagent strip test is based on the effect of albumin on a buffer (tetrabromophenol blue), which causes a change in pH proportional to the concentration of the albumin itself. The pad changes color, from pale green to green and blue, according to the pH changes induced by the albumin. The strip is sensitive to albumin but has a very low sensitivity to other proteins, such as tubular proteins and light-chain immunoglobulins; thus it will not detect tubular proteinuria or overflow proteinuria, which can occur in monoclonal gammopathies. Moreover, the detection limit is 0.25 to 0.3 g/l, so does not identify microalbuminuria and is influenced by hydration status (false-negative results may occur at low urine SG, and vice versa) and urine pH (false-positive results at strongly alkaline pH). The reagent strip supplies only a semi-quantitative measurement of urine albumin, which is expressed on a scale from 0 to +++ or ++++. Some manufacturers also supply numerical results, although these represent only approximate quantitative measurements. Some reagent strips also include a creatinine pad, which supplies an albumin-to-creatinine ratio (ACR) and reduces the variability caused by changing diuresis and urine dilution.[11] Nevertheless, for accurate quantification other methods are needed.

24-Hour Protein Excretion

The 24-hour protein excretion averages the variation of proteinuria caused by the circadian rhythm and is still considered the reference method,[1] especially for monitoring proteinuria during treatment.[12-14] The measurement of proteinuria can be done by chemical assays (e.g., biuret or Folin-Lowry reaction), turbidimetric techniques (e.g., trichloroacetic acid, benzethonium chloride, ammonium chloride), or dye-binding techniques (e.g., Ponceau S, Coomassie brilliant blue G-250, pyrogallol red molybdate), which quantify total proteins rather than only albumin. However, the 24-hour urine collection can be impractical in some settings (e.g., children, outpatients, elderly patients) and is subject to error from overcollection or undercollection.

Protein-to-Creatinine Ratio and Albumin-to-Creatinine Ratio on Random Urine Sample

The protein-to-creatinine ratio (PCR) measured on an early morning urine sample represents a practical alternative to the 24-hour urine collection because the sample is easy to supply and is not influenced by variation in water intake or rate of diuresis.[1] The PCR is obtained by the ratio between urine protein excretion and creatinine excretion, expressed as milligrams per milligrams or milligrams per millimole. A close correlation between the PCR in a random urine sample and the 24-hour protein excretion has been demonstrated in a wide range of patients,[10,15] including those with different types of glomerulonephritis (GN) evaluated longitudinally during treatment.[16] However, the results may be influenced by a reduced creatinine excretion because of low muscle mass. Thus, in elderly and female patients, PCR values can be higher than in young men. Some investigators consider a normal PCR sufficient to rule out pathologic proteinuria, but an elevated PCR should be confirmed and quantified with a 24-hour collection.[12] Others have found poor correlation between PCR and 24-hour proteinuria at high levels of protein excretion[16] or that PCR is an unreliable method to monitor some patients with lupus nephritis.[17]

The KDIGO guideline suggests ACR rather than PCR as first measurement of proteinuria in adults because albuminuria is a reliable marker of the outcome of CKD, it provides a specific and sensitive measure of changes in glomerular permeability in several renal diseases, and the measurement of total proteins is problematic in several respects.[1]

However, false-negative results may occur with ACR,[18] especially in tubulointerstitial diseases and monoclonal gammopathies, in which urine proteins are mostly composed of tubular proteins and monoclonal light chains, respectively. In children, KDIGO guidelines[1] recommend the measurement of PCR rather than ACR because the latter can miss the identification of congenital disorders associated with nonalbumin proteinuria.[1]

Specific Proteins

Albuminuria. *Albuminuria* is the term that should be used now, according to the KDIGO guideline, instead of *microalbuminuria*,[1] defined as urine albumin in the range of 30 to 299 mg/24 h. In persons with diabetes it identifies increased risk for developing overt diabetic nephropathy and, in the general population, subjects at increased risk of CKD, cardiovascular morbidity, and overall mortality. Semiquantitative reagent strips are available to screen for urine albumin in this range.[19] Once the reagent strip is positive, a quantitative method on early morning urine must be used for confirmation.[1] Because of its great simplicity, immunoturbidometry is most frequently used.

Tubular proteins. When an isolated tubular lesion is suspected, specific tubular proteins such as α_1-microglobulin, retinol-binding protein, or β_2-microglobulin should be measured.[1] This can be done by qualitative analysis of urine proteins, using electrophoresis on cellulose acetate or agarose after protein concentration or using very sensitive stains such as silver and gold, or sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE).

Bence Jones proteinuria. Bence Jones proteinuria indicates the presence of free monoclonal immunoglobulin (heavy or light chains) as occurs with monoclonal gammopathies. Bence Jones proteinuria is revealed by urine electrophoresis, whereas light-chain identification requires urine immunofixation.[20]

Leukocyte Esterase

The leukocyte esterase dipstick test evaluates the presence of leukocytes based on the activity of an indoxyl esterase released from lysed neutrophil granulocytes. Leukocyte esterase may be positive but microscopy negative when leukocytes are lysed because of low SG, alkaline pH, or a delay in sample handling and examination.

False-negative results derive from vitamin C,[8] high glucose (≥20 g/l) or high protein (≥5 g/l) concentration or from the presence of antibiotics such as cephalothin and tetracycline (strong inhibition), cephalexin (moderate inhibition), or tobramycin (mild inhibition). The sensitivity is also reduced by high SG, because this prevents leukocyte lysis. False-positive results may occur when formaldehyde is used as a urine preservative, from the presence in the urine of imipenem, meropenem, or clavulanate,[21] and with all discolored urine.

Nitrites

The dipstick nitrites test detects bacteria that reduce nitrates to nitrites by nitrate reductase activity. This includes most gram-negative uropathogenic bacteria, but not *Pseudomonas, Staphylococcus albus,* or *Enterococcus*. False-negative results also may occur on a diet with low content of nitrate (vegetables), which form the substrate for nitrite production and short bladder incubation time. Thus the sensitivity of the dipstick nitrites test is low, whereas specificity is high.[22] False-positive results may occur in the presence of abnormally colored urine.

Ketones

The ketone dipstick tests for acetoacetate and acetone (but not β-hydroxybutyrate), which are excreted into urine during diabetic acidosis or during fasting, vomiting, or strenuous exercise. It is based on the reaction of the ketones with nitroprusside.

URINE MICROSCOPY

Methods

We instruct the patient to deliver the second urine specimen of the morning because it avoids the lysis of particles that can occur in the bladder overnight (Box 4.1). We centrifuge an aliquot of urine within 3 hours from collection and concentrate it by removal of a fixed aliquot of supernatant urine. After this, the sediment is resuspended with a Pasteur pipette, and a fixed aliquot is transferred to the slide and prepared using a coverslip with a fixed surface. Some suggest the use of noncentrifuged urine, because centrifugation may cause the damage and/or lysis of particles during the procedure. On the other hand, with this approach, clinically important particles (e.g., erythrocyte casts), when in small numbers, can easily be missed.

Phase contrast microscopy is recommended because it improves the identification of almost all particles, especially cells and casts, whereas polarized light is mandatory for the correct identification of lipids and crystals, especially when they have uncommon morphologies.[6]

At least 20 microscopic fields, in different areas of the sample, should be examined at both low magnification (e.g., ×100 or ×200) and high magnification (e.g., ×400). More extensive examination may be required in certain clinical settings, such as isolated microhematuria of unknown origin, for which we suggest examination of 50 low-power fields (lpfs) to look for erythrocyte casts.[23]

For correct examination, both pH and SG of the sample must be known. Both alkaline pH (≥7.0) and low SG (especially ≤1.010) favor the lysis of erythrocytes and leukocytes, which can cause discrepancies between dipstick readings and the microscopic examination (see earlier discussion). Alkaline pH also impairs the formation of casts and favors the precipitation of amorphous phosphates. On the contrary, high SG (≥1.030) may reduce the sensitivity of reagent strips for hemoglobin and leukocyte esterase.

We quantify the particles seen as number per microscopic field, whereas if counting chambers are used, the elements are quantified as number per volume. Counting chambers allow a precise quantitation but are not frequently used in everyday practice.

BOX 4.1 Procedures for Preparation and Examination of Urine Sediment*

- Written instructions for the patient to deliver a correct urine sample (i.e., the second urine of the morning after discarding the first few milliliters of urine [midstream urine] collected in a proper container).
- Sample handling and examination within 3 hours of collection.
- Centrifugation of a 10-ml aliquot of urine at 400 g for 10 minutes.
- Removal by suction of 9.5 ml of supernatant urine.
- Gentle but thorough resuspension with a Pasteur pipette of sediment in remaining 0.5 ml of urine.
- Transfer by a precision pipette of 50 µl of resuspended urine to a slide.
- Covering of sample with a 24- × 32-mm coverslip.
- Examination of the urine sediment with a phase contrast microscope at ×160 and ×400.
- Use of polarized light to identify doubtful lipids and crystals.
- Matching of the microscopic findings with reagent strip for pH, specific gravity, hemoglobin, leukocyte esterase, nitrites, and albumin.
- Cells expressed as lowest/highest number seen per high-power field (hpf), casts as number per low-power field (lpf), and all other elements (e.g., bacteria, crystals) on scale from 0 to ++++.

*Procedures used in the authors' laboratory.

Cells

Erythrocytes

Urinary erythrocytes have a mean diameter of approximately 6 µm. In the urine, there are two main types of erythrocytes: *isomorphic*, with regular shapes and contours, derived from the urinary excretory system; and *dysmorphic*, with irregular shapes and contours, which are of glomerular origin (see Fig. 4.1A and B).[24] Erythrocyte dysmorphism is thought to result from deformation of the erythrocytes as they pass through gaps in the glomerular basement membrane, followed by physicochemical insults while the erythrocytes pass through the tubular system.[25]

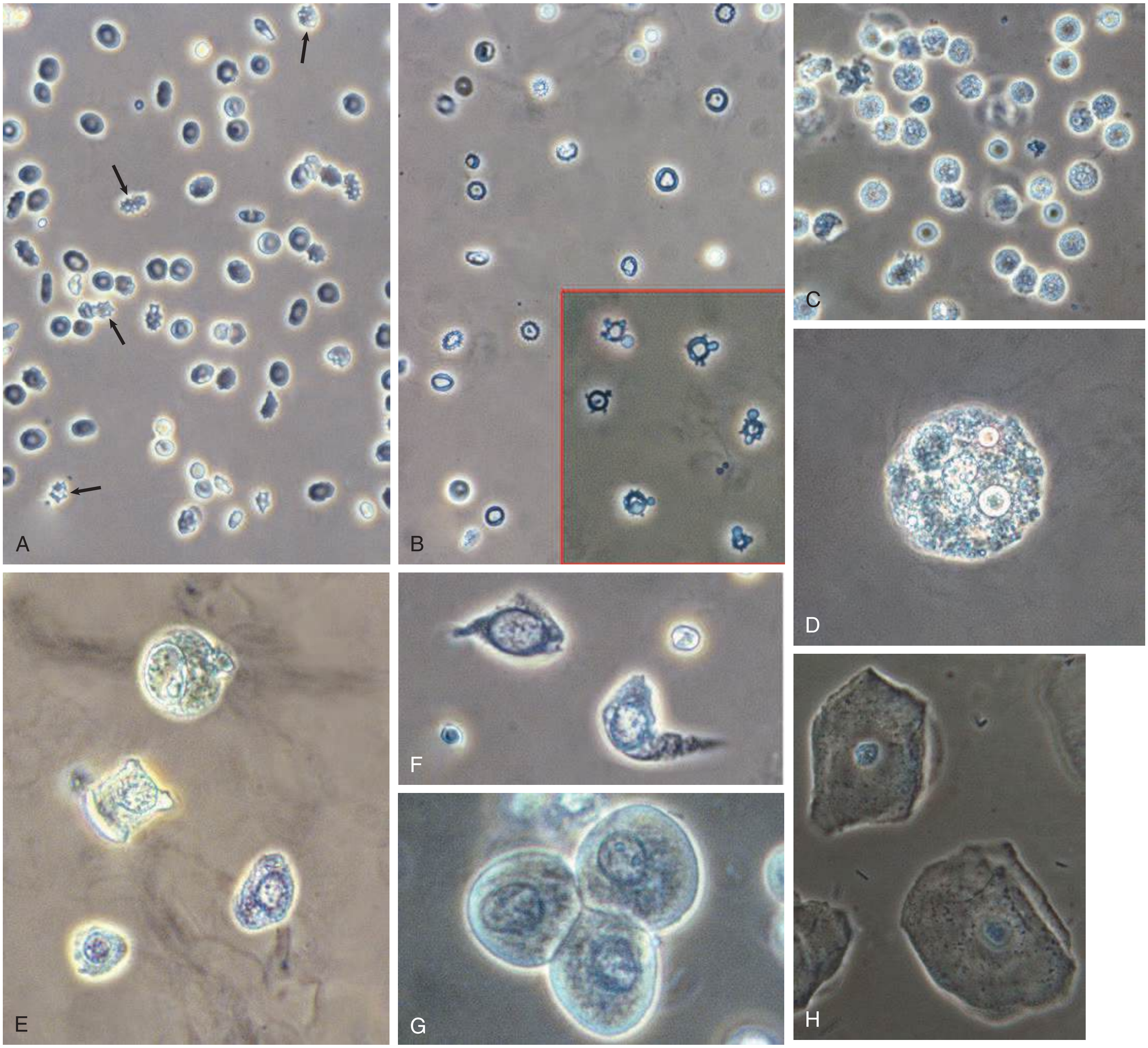

Fig. 4.1 Urinary sediment cells. (A) Isomorphic nonglomerular erythrocytes (diameter ~6 µm). The *arrows* indicate the so-called crenated erythrocytes, which are a finding in nonglomerular hematuria. (B) Dysmorphic glomerular erythrocytes (diameter ~6 µm). The dysmorphism consists mainly of irregularities of the cell membrane. *Inset,* Acanthocytes, with their typical ring-formed cell bodies with one or more blebs of different sizes and shapes. (C) Neutrophils (diameter ~10 µm). Note their typical lobulated nucleus and granular cytoplasm. (D) Granular phagocytic macrophage (diameter ~60 µm). (E) Different types of renal tubular epithelial cells (diameter ~14 µm). (F) Two cells from deep layers of uroepithelium (diameter ~18 µm). (G) Three cells from superficial layers of uroepithelium (diameter ~25 µm). Note the difference in shape, size, and ratio of nucleus to cytoplasm between the two types of uroepithelial cells. (H) Squamous epithelial cells (diameter ~50 µm). (All images by phase contrast microscopy; original magnification ×400.)

Unfortunately, there is no agreement on the criteria to classify hematuria as glomerular or nonglomerular. Some define glomerular hematuria as more than 80% of erythrocytes being dysmorphic; others define the discriminating cut-off as low as 10% or 15%.[6] Still, others define hematuria as glomerular when at least 5% of erythrocytes examined are *acanthocytes,*[26] a subtype of dysmorphic erythrocytes with a distinguishing appearance easily identifiable by the presence of one or more blebs of different size and shape protruding from a ring-shaped body (see Fig. 4.1B, *inset*).

In our laboratory, glomerular hematuria is diagnosed when there are 40% or more dysmorphic erythrocytes and/or 5% or more acanthocytes and/or one or more red blood cell casts/50 lpf (×160). With this criterion, a good correlation was found between urinary sediment and renal biopsy findings in 16 patients with long-standing isolated microhematuria.[23]

The distinction between glomerular and nonglomerular hematuria is of special value in the evaluation of patients with isolated microhematuria, in whom it is important to decide whether nephrologic or urologic investigation is needed.

Rare types of erythrocytes found in the urine include sickle cells, elliptocytes, spherocytes, dacryocytes, etc. The finding in the urine of such cells reflects their presence in the circulation.[27]

Leukocytes

Urinary *neutrophils* have an average diameter of approximately10 µm and are the most frequently found leukocytes in the urine. Neutrophils are identified by their granular cytoplasm and lobulated nucleus (see Fig. 4.1C). In most patients, neutrophils indicate UTI, but they may also result from urine contamination caused by genital secretions, especially in fertile women. Variable numbers of neutrophils are often, but not always, found in acute interstitial nephritis. Neutrophils can be found in low numbers in chronic interstitial nephritis and in proliferative GN, intermingled with high numbers of erythrocytes.[28]

Eosinophils, which can be identified only by the use of stains (e.g., Hansel), were once considered a marker of acute allergic interstitial nephritis. However this is not specific,[29] because eosinophils may be present in various types of GN, prostatitis, chronic pyelonephritis, urinary schistosomiasis, and cholesterol embolism.

Lymphocytes, whose identification also requires staining, may indicate acute cellular rejection in renal allograft recipients, although this is not sufficiently reliable to avoid renal biopsy. Lymphocytes are also a typical finding in patients with chyluria.

Macrophages are mononucleated or multinucleated cells of variable size (13 to 95 µm in diameter) and variable appearance: some are granular (see Fig. 4.1D). In patients with nephrotic syndrome, macrophages may be engorged with lipid droplets, appearing as "oval fat bodies." Macrophages have been found in the urine of patients with active GN. In our experience, macrophages are frequently seen in the urine of kidney transplant recipients with BK virus infection (see later discussion). However, urinary macrophages are not yet diagnostic of any specific condition.

Renal Tubular Epithelial Cells

The renal tubular epithelial cells (RTECs) derive from the exfoliation of the tubular epithelium. In the urine, RTECs can differ in size (diameter ~9 to 25 µm, average 14 µm) and shape, from roundish to rectangular or columnar, with a central or peripheral large nucleus (see Fig. 4.1E). RTECs are not found in the normal individual but can be found when there is acute tubular damage, including ATN,[30] acute interstitial nephritis, and acute cellular rejection. In smaller numbers, RTECs also can be found in glomerular diseases.[28] In ATN, these cells are frequently damaged and necrotic and may be present in casts (so-called epithelial casts).

Transitional Epithelial Cells

The transitional epithelial cells derive from the exfoliation of the uroepithelium, which lines the urinary tract from the calyces to the bladder in women and to the proximal urethra in men. This multilayered epithelium has small cells in the deep layers and larger cells in the superficial layers. When cells of the deep epithelial layers (average diameter 18 µm, see Fig. 4.1F) are present in large numbers (e.g., ≥1/high-power field [hpf]), this suggests severe uroepithelial damage, such as caused by neoplasia, stones, obstruction, or long-standing bladder catheters or ureteral stents.[6] Transitional cells of the superficial layers (average diameter ~25 µm; see Fig. 4.1G) are a common finding associated with mild uroepithelial damage, as may occur in cystitis.

Squamous Epithelial Cells

Squamous epithelial cells (SECs) (average diameter 50 µm; see Fig. 4.1H) derive from the urethra or from the external genitalia. In small numbers, SECs are a normal finding, but in large numbers, they indicate urine contamination from genital secretions.

Lipids

Lipids are found in the urine as *drops,* which are spherical, translucent, yellowish particles of different size that can be isolated or in clusters (see Fig. 4.2A); as *oval fat bodies,* which are RTECs or macrophages gorged with lipid droplets; as *fatty casts,* cylindrical structures containing variable amounts of fatty droplets or even oval fat bodies; and *cholesterol crystals* (see Crystals). All these particles contain mainly cholesterol esters and free cholesterol. Under polarized light, drops, oval fat bodies, and casts give the appearance of Maltese crosses with symmetric arms (see Fig. 4.2B), whereas cholesterol crystals are nonbirefringent.

These lipids are typical of glomerular diseases associated with marked proteinuria, usually but not invariably in the nephrotic range.

In Fabry disease, urine sediment may contain fatty particles even in the absence of proteinuria. These particles contain glycosphingolipids (especially globotriaosylceramide-3) and have irregular shape and size, variable protrusions or an internal lamellar structure, and irregular or truncated Maltese crosses under polarized light (see Fig. 4.2C).[31]

Casts

Casts are cylindrical structures that form in the lumen of distal renal tubules and collecting ducts. Their matrix is made of Tamm-Horsfall glycoprotein, today known as uromodulin, which is secreted by the cells of the thick ascending limb of Henle loop. Trapping of particles within the cast matrix results in casts with different appearances, each of which may have specific clinical significance (Table 4.2). Because casts form in the renal tubules, whatever particle is contained in a cast derives from the kidneys. Specific casts include the following:

- *Hyaline casts* are colorless with a low refractive index (see Fig. 4.3A). They are easily seen with phase contrast microscopy but can be overlooked when bright-field microscopy is used. Hyaline casts may occur in normal urine, especially when it is concentrated and acidic (both conditions favor precipitation of uromodulin). In patients with renal disease, hyaline casts are usually associated with other types of casts.
- *Hyaline-granular casts* contain variable amounts of granules within the hyaline matrix (see Fig. 4.3B) and are the most common mixed casts (see later discussion). Hyaline-granular casts are rare in normal individuals but are common in patients with renal diseases such as GN[28] and acute interstitial nephritis.[32]
- *Granular casts* can be finely granular (see Fig. 4.3C) or coarsely granular. Both types indicate renal disease. In patients with AKI, granular casts together with RTECs[30] or with epithelial casts[33] are a sensitive marker of ATN.

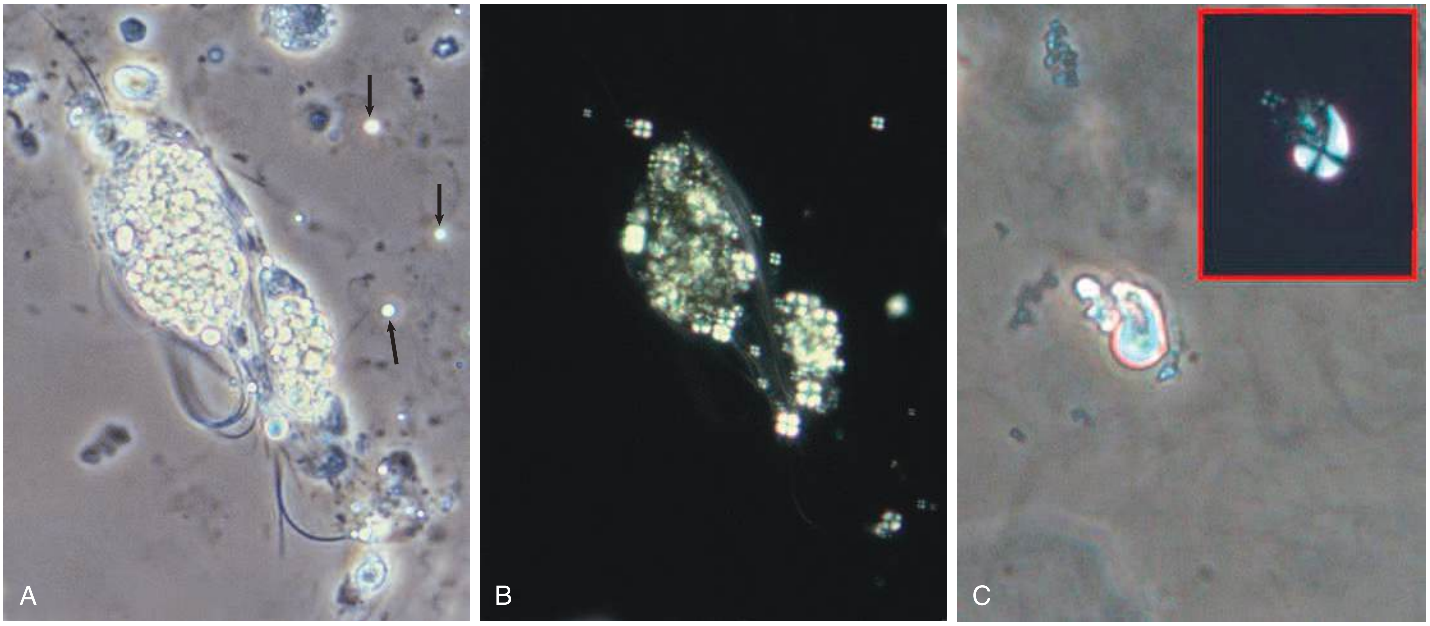

Fig. 4.2 Fatty particles. (A) Lipid droplets, both aggregated and isolated *(arrows)*, and filaments also made up of cholesterol by phase contrast microscopy. (B) Same lipid droplets in *A* under polarized light, showing typical Maltese crosses with symmetric arms. (C) Fatty particle with protrusions, as found in Fabry disease (phase contrast microscopy). *Inset*, Same particle under polarized light. Note the truncated and asymmetric Maltese cross. (Original magnification ×400.)

TABLE 4.2 Types of Casts and Their Main Clinical Associations

Cast	Main Clinical Associations
Hyaline	Normal individual; renal disease
Hyaline-granular	Normal individual; renal disease
Granular	Renal disease; acute tubular necrosis
Waxy	Renal disease with possible functional impairment
Fatty	Proteinuria; nephrotic syndrome
Erythrocyte	Glomerular hematuria; proliferative/ necrotizing GN; acute interstitial nephritis
Leukocyte	Acute interstitial nephritis; acute pyelonephritis; proliferative GN
Renal tubular epithelial cell (so-called epithelial casts)	Acute tubular necrosis; acute interstitial nephritis; proliferative GN; nephrotic syndrome
Hemoglobin	Same as for erythrocyte cast; hemoglobinuria caused by intravascular hemolysis
Myoglobin	Rhabdomyolysis
Bilirubin	Jaundice caused by increased direct bilirubin
Bacterial, fungal	Bacterial or fungal infection in the kidney
Containing crystals	Renal stone disease; crystalline nephropathies
Mixed	According to components present in the cast

AKI, Acute kidney injury; *GN,* glomerulonephritis.

- *Waxy casts* derive their name from their appearance, which is similar to that of melted wax (see Fig. 4.3D). They are typically found in patients with renal disease associated with impaired renal function, whether acute, rapidly progressive, or chronic.[34]
- *Fatty casts* contain variable amounts of lipid droplets, isolated, in clumps, or packed or even oval fat bodies or cholesterol crystals. Fatty casts are typical of glomerular diseases associated with marked proteinuria or the nephrotic syndrome.
- *Erythrocyte casts* may contain a few erythrocytes (see Fig. 4.3E) or so many that the matrix of the cast cannot be identified. Erythrocyte casts are usually considered a marker of glomerular bleeding, although a recent report found them in 28% of patients with acute interstitial nephritis.[32]
- *Hemoglobin casts* generally have a brownish hue and a coarsely granular appearance, which derives from the degradation of erythrocytes entrapped within the cast matrix (see Fig. 4.3F). In such cases, hemoglobin casts have the same clinical significance as erythrocyte casts. However, hemoglobin casts also may derive from hemoglobinuria, as may occur in intravascular hemolysis. In these patients, hemoglobin casts have a smooth surface.
- *Leukocyte casts* contain variable amounts of polymorphonuclear leukocytes (see Fig. 4.3G). They can be found in patients with acute pyelonephritis and acute interstitial nephritis, as well as in active proliferative GN.[28]
- *Renal tubular epithelial cell casts* (so-called epithelial casts) contain variable numbers of RTECs, which can be identified by their prominent nucleus (see Fig. 4.3H). Epithelial casts indicate damage of the renal tubular epithelium and can therefore be found in the urine of patients with ATN,[30] acute interstitial nephritis, and glomerular disease.[28]
- *Myoglobin casts* are pigmented cylinders, with the myoglobin providing their color. They may be similar to hemoglobin casts

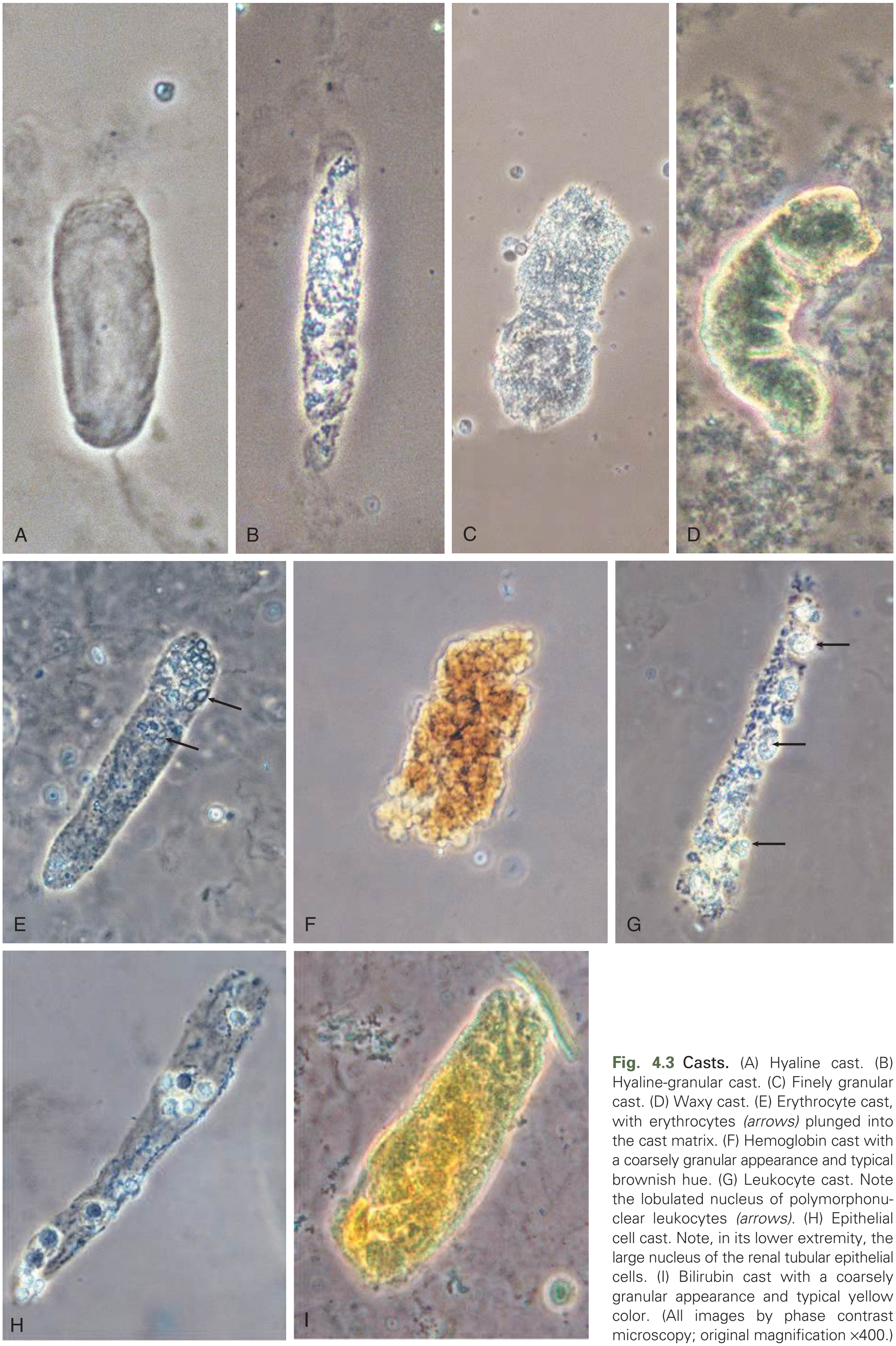

Fig. 4.3 Casts. (A) Hyaline cast. (B) Hyaline-granular cast. (C) Finely granular cast. (D) Waxy cast. (E) Erythrocyte cast, with erythrocytes *(arrows)* plunged into the cast matrix. (F) Hemoglobin cast with a coarsely granular appearance and typical brownish hue. (G) Leukocyte cast. Note the lobulated nucleus of polymorphonuclear leukocytes *(arrows)*. (H) Epithelial cell cast. Note, in its lower extremity, the large nucleus of the renal tubular epithelial cells. (I) Bilirubin cast with a coarsely granular appearance and typical yellow color. (All images by phase contrast microscopy; original magnification ×400.)

(see Fig. 4.3F), from which they can be distinguished by the clinical setting. Myoglobin casts are observed in the urine of patients with AKI associated with rhabdomyolysis.

- *Bilirubin casts* are cylinders pigmented with bilirubin, which can stain any particle contained in the cast (see Fig. 4.3I). They are observed in the urine of patients with jaundice associated with increased direct (conjugated) bilirubin.
- *Casts containing microorganisms* (bacteria and yeasts) indicate renal infection.
- *Casts containing crystals* indicate that crystals derive from the renal tubules. Crystal casts are an important diagnostic element in crystalline-induced nephropathies, such as acute urate nephropathy.[35]
- *Mixed casts* contain components of different nature, such as granules, cells, and lipids. This causes the appearance of pleomorphic cylinders, whose clinical significance is the same as that for the pure types of casts, of which mixed casts contain some components.

Crystals

Correct identification of urine crystals requires knowledge of crystal morphology, their appearance under polarized light, and urine pH. However, for unusual crystals, additional investigation may be needed, such as infrared spectroscopy, which is available only in specialized laboratories.[36] Examination of the urine for crystals is a key test in the assessment of patients with stone disease, with some rare inherited metabolic disorders (e.g., cystinuria, hyperoxaluria, phosphoribosyltransferase deficiency), and with suspected drug nephrotoxicity.[6] Crystals can be classified in four categories: common, pathologic, caused by drugs, and other crystals.

Common Crystals

Uric acid crystals and amorphous urates. Uric acid crystals have an amber color and a wide spectrum of appearances, most frequently rhomboids or barrels (see Fig. 4.4A) and, rarely, needle-like structures. Under polarized light they are strongly birefringent and polychromatic. They are found in acidic urine (pH 5.0 to 5.8).

Amorphous urates are tiny granules of irregular shape that polarize light and precipitate in acidic urine. They are identical to amorphous phosphates, which, however, precipitate in alkaline urine and do not polarize light.

Calcium oxalate crystals. There are two types of calcium oxalate crystals: bihydrated (or weddellite) crystals, which most often have a bipyramidal appearance (see Fig. 4.4B), and monohydrated (or whewellite) crystals, which are ovoid, dumbbell-shaped, or biconcave disks (see Fig. 4.4C). Monohydrated crystals always polarize light, whereas bihydrated crystals usually do not. Both types of calcium oxalate crystals precipitate at pH 5.4 to 6.7.

Calcium phosphate crystals (brushite) and amorphous phosphates. Calcium phosphate crystals are pleomorphic, appearing as prisms, star-like particles, or needles of various sizes and shapes (see Fig. 4.4D) that polarize light intensely. They also can appear as plates with a granular surface and do not polarize light. Both types of crystals precipitate in alkaline urine (pH ≥7.0).

Amorphous phosphates are tiny particles identical to amorphous urates, but they do not polarize light and precipitate at a pH of 7.0 or higher.

Triple phosphate (struvite) crystals. Triple phosphate crystals contain magnesium ammonium phosphate, and most frequently have the appearance of "coffin lids" (see Fig. 4.4E), although variants such as "flower-like, scissors-like" structures, etc., can be found. These crystals usually polarize light strongly and are found in alkaline urine (pH ≥7.0).

Pathologic Crystals

Cholesterol crystals. Cholesterol crystals are thin, transparent plates, often clumped together, with sharp edges (see Fig. 4.4F), which do not polarize light. They can be found in a wide spectrum of urine pH.

Cystine crystals. Cystine crystals occur in cystinuria and are hexagonal plates with irregular sides that are often heaped on one another (see Fig. 4.4G). They either do not polarize light or show a whitish biferingence. They are insoluble in a urine pH up to 7.4. Their persistence in urine and their number is significantly associated with the formation of cystine stones.[37]

2,8-dihydroxyadenine(2,8-DHA) crystals. 2,8-DHA crystal are spherical, brownish structures with a central umbilicus and a birefringent cross-like appearance under polarized light (see Fig. 4.4H). They are a marker of homozygous deficiency of the enzyme adenine phosphoribosyltransferase. Crystalluria is absent in heterozygotes and so allows specific identification of homozygotes in 100% of cases. The search for crystalluria is best performed on the first voided morning urine samples, which are the most concentrated.[38]

Other rare pathologic crystals are tyrosine, found in patients with acute liver disease and the rare hereditary disease tyrosinemia, and leucine, found in acute liver disease.

Crystals Caused by Drugs

Many drugs can cause crystalluria, especially in a setting of drug overdose, dehydration, or hypoalbuminemia in the presence of a urinary pH favoring drug crystallization. Examples include the antibiotics sulfadiazine, amoxicillin (see Fig. 4.4I), ciprofloxacin[6] (see Fig. 4.4J), and sulfamethoxazole[39]; the antiviral agents acyclovir, indinavir (see Fig. 4.4K),[6] atazanavir, and darunavir[40]; the vasodilators pyridoxylate and naftidrofuryl oxalate; the barbiturate primidone; the antiepileptic felbamate; the inhibitor of gastroenteric lipase orlistat; and intravenous vitamin C.[6] Most of these drugs cause crystals made of the drug, with unusual morphologies that differ from those of the crystals previously described. However, naftidrofuryl oxalate, orlistat, and vitamin C cause calcium oxalate crystals, which are indistinguishable from calcium oxalate crystals resulting from other causes.[6]

Other Crystals

Hippuric acid crystals, calcium carbonate crystals, and ammonium biurate crystals are rare and devoid of clinical significance.

Clinical Significance of Crystals

Uric acid, calcium oxalate, and calcium phosphate crystals may have no clinical significance because they can reflect transient supersaturation of the urine caused by ingestion of some foods (e.g., meat for uric acid, spinach or chocolate for calcium oxalate, milk or cheese for calcium phosphate) or mild dehydration. However, the persistence of calcium oxalate or uric acid crystalluria may reflect hypercalciuria, hyperoxaluria, or hyperuricosuria. In calcium stone formers, the evaluation of crystalluria is an important tool to assess calcium stone disease activity.[41]

Large numbers of uric acid crystals may be associated with AKI caused by acute urate nephropathy, whereas large numbers of monohydrated calcium oxalate crystals, especially with a spindle shape, may be associated with AKI from ethylene glycol intoxication. Triple phosphate crystals are usually associated with UTI caused by urea-splitting microorganisms such as *Proteus* sp., *Ureaplasma urealyticum,* and *Corynebacterium urealyticum.*

Cholesterol crystals are found in association with other fatty particles in patients with marked proteinuria. Cystine crystals are a marker of cystinuria, and 2,8-dihydroxyadenine crystals are associated with phosphoribosyltransferase enzyme deficiency. Crystalluria resulting from

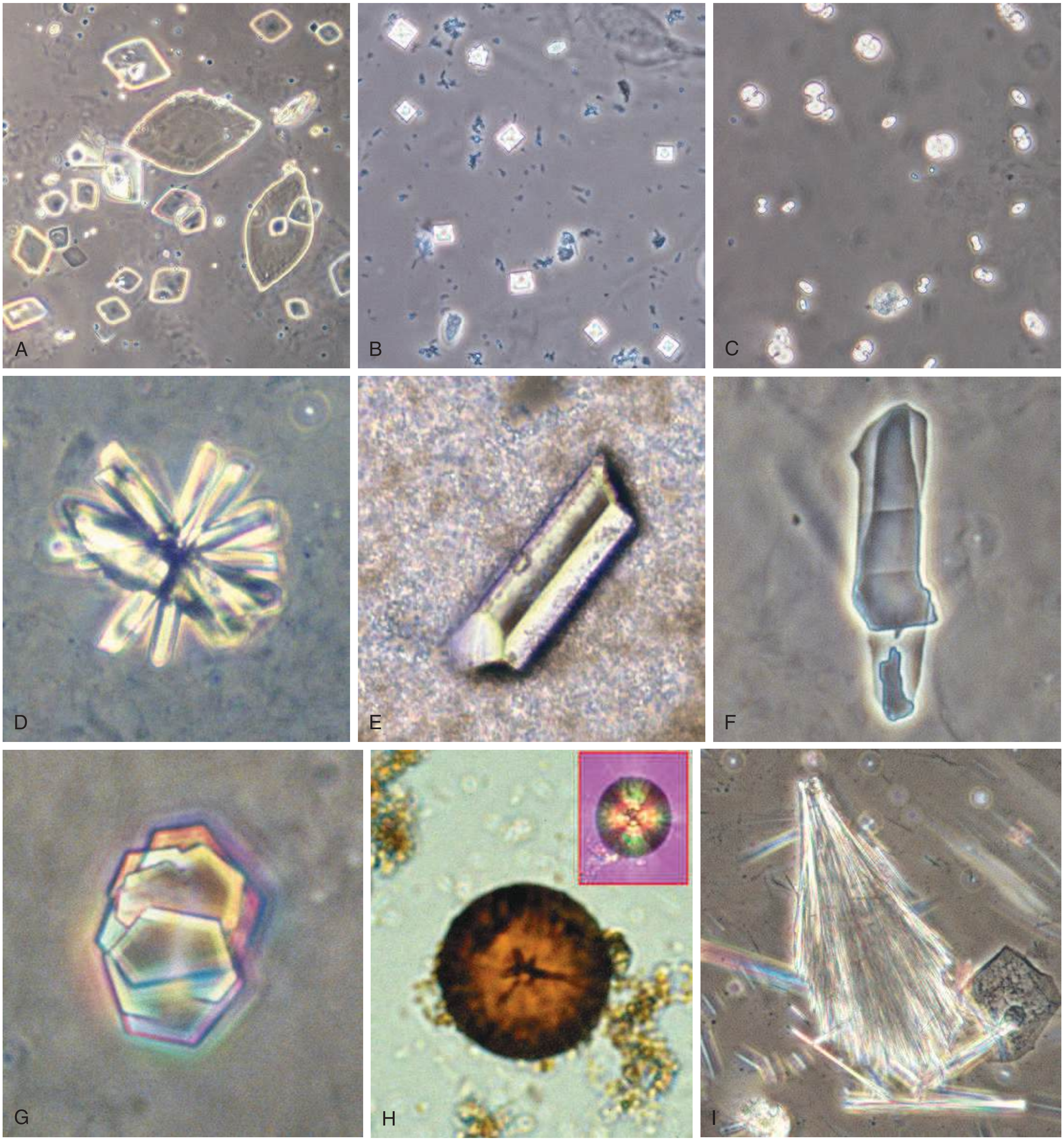

Fig. 4.4 Crystals. (A) Uric acid crystals. This rhomboid shape is the most common. (B) Bihydrated calcium oxalate crystals with typical "letter envelope" appearance. (C) Different types of monohydrated calcium oxalate crystals. (D) Star-like brushite (calcium phosphate) crystal. (E) Struvite (triple phosphate) crystal, on the background of a massive amount of amorphous phosphate particles. (F) Cholesterol crystal. (G) Cystine crystals heaped one on the other. (H) 2,8-Dihydroxyadenine crystal by bright-field microscopy; *inset*, by polarized light. (I) Amoxicillin crystal resembling a branch of a broom or bush.

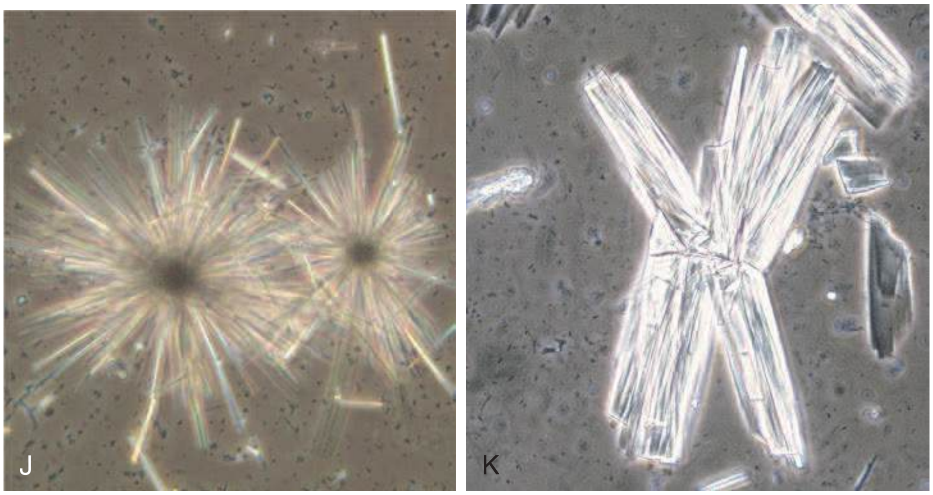

Fig. 4.4, cont'd (J) Star-like ciprofloxacin crystals. (K) Large crystal of indinavir. (All images by phase contrast microscopy; original magnification ×400.) (**H,** Courtesy Professor Michel Daudon, Paris.)

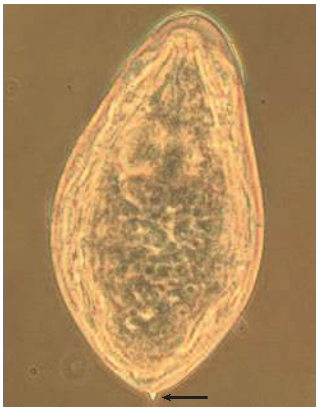

Fig. 4.5 Egg of *Schistosoma haematobium* (Diameter µm, ~100 µm). Note the thick shell, which contains the *miracidium,* and the typical terminal spike *(arrow).* (Phase contrast microscopy; original magnification ×400.)

drugs must be suspected whenever crystals with unusual morphology are seen. In this setting, crystalluria may be isolated and asymptomatic or associated with hematuria, obstructive uropathy, or AKI caused by the precipitation of crystals within the renal tubules.[6,35]

Organisms

Bacteria are a frequent finding because urine is usually collected and handled under nonsterile conditions and examination is often delayed. UTI should be suspected if bacteria are found in freshly voided midstream urine in association with leukocytes (in the absence of large amounts of SECs, which indicate likely contamination from genital secretions). *Candida* (yeasts), *Trichomonas vaginalis* (protozoon), and *Enterobius vermicularis* (parasite) are usually present as contaminants derived from genital secretions.

Examination of the urinary sediment is the most widely used, simplest, and fastest method for diagnosis of schistosomiasis because it shows the eggs of the *Schistosoma haematobium* parasite, with their typical terminal spike (see Fig. 4.5). The eggs are especially found in the urine collected between 10 AM and 2 PM, when the parasite female lays the eggs, and after physical exercise such as running, which favors the detachment of the eggs from the bladder mucosa.

Contaminants

A large number of particles can contaminate urine. These particles may come from the patient (e.g., spermatozoa; erythrocytes from menstruation; leukocytes from vaginitis, cloth or synthetic fibers, creams, or talcum), the laboratory (e.g., starch particles, glass fragments from coverslips), or the environment (e.g., pollens, plant cells, fungal spores).[6]

INTERPRETATION OF URINE SEDIMENT FINDINGS

Examination of the urine sediment, coupled with the quantity of proteinuria and other urine and blood findings, results in urine sediment profiles that aid in diagnosis of urinary tract diseases (Table 4.3).

Nephrotic Syndrome

The typical nephrotic sediment contains lipids, casts, and RTECs. Fatty, epithelial, granular, hyaline, and hyaline-granular casts are frequent, whereas erythrocyte or hemoglobin casts, leukocyte casts, and waxy casts are few or absent. Erythrocytes may be totally absent, especially in minimal change disease or may be in low to moderate numbers (e.g., 3-5/hpf to 20-30/hpf), which is seen especially in membranous nephropathy and focal segmental glomerulosclerosis. Leukocytes are usually not found.

Nephritic Syndrome

Erythrocytes with erythrocyte and hemoglobin casts are the hallmark of the nephritic sediment. Usually, the number of erythrocytes ranges from 30 to 40 cells/hpf to more than 100 cells/hpf, with the higher figure found especially in patients with extracapillary or necrotizing glomerular lesions. Leukocyturia is also common and is mild (e.g., 3-5/hpf) in most patients, but in those with acute postinfectious GN or active proliferative lupus nephritis, we have seen samples with up to 30 to 40 leukocytes/hpf. Leukocyte casts and waxy casts[34] also may be observed.

Acute Kidney Injury

In patients with AKI, the finding in the urine sediment of RTECs in association with granular casts and/or epithelial casts is the hallmark of ATN,[30,33] whereas these elements are rarely found in functional prerenal AKI.[30] A score based on the number of RTECs and granular casts significantly correlates with the severity of AKI, with new AKI urine biomarkers (NGAL, KIM-1, IL 18), with the progression of AKI, and with the need for dialysis and death.[30] Depending on the cause of the

TABLE 4.3 Main Urinary Profiles

Renal Disease	Hallmark	Associated Findings
Nephrotic syndrome (proteinuria: ++++)	Fatty particles	Renal tubular epithelial cells (RTECs) RTEC casts Erythrocytes (absent to moderate number)
Nephritic syndrome (proteinuria: + → ++++)	Erythrocytes (moderate to high number) Erythrocyte/hemoglobin casts	Leukocytes (low to moderate number) RTECs (low number) RTEC casts Waxy casts
AKI with ATN (proteinuria: absent to +)	RTECs RTEC casts Granular casts	Variable according to cause of ATN (e.g., myoglobin casts in rhabdomyolysis, uric acid crystals in acute urate nephropathy, erythrocytes in proliferative/active glomerulonephritis)
Urinary tract infection (proteinuria: absent)	Bacteria Leukocytes	Isomorphic erythrocytes Superficial transitional epithelial cells Struvite crystals (for infections caused by urease-producing bacteria) Leukocyte casts (in renal infection)
Polyomavirus BK infection (proteinuria: absent)	Decoy cells	Decoy cell casts (in BK virus nephropathy)
Urologic diseases (proteinuria: absent)	Isomorphic erythrocytes (low to high number) Leukocytes	Transitional cells (deep, superficial, atypical)

tubular damage, other elements can be seen. These include myoglobin-pigmented casts in rhabdomyolysis, uric acid crystals (usually in massive amounts) in acute uric acid nephropathy (tumor lysis syndrome), and erythrocytes (high numbers) and erythrocyte casts in proliferative glomerular diseases.

Urinary Tract Infection

Bacteria and leukocytes are the hallmarks of UTI, with or without superficial transitional epithelial cells and/or isomorphic erythrocytes. Struvite crystals also can be present when the infection is caused by urease-producing bacteria, such as *Proteus* sp., *U. urealyticum,* and *C. urealyticum.* In patients with renal infection, leukocyte casts and casts containing microorganisms may be found.

The correlation between the urine sediment findings and the urine culture is usually good. False-positive results may be caused by urine contamination from genital secretions (in which case large amounts of SECs are usually found, especially in women) or bacterial overgrowth on standing. False-negative results may be caused by the lysis of leukocytes or misinterpretation of cocci with other tiny particles, such as amorphous urates or phosphates.

BK Virus Infection

The KDIGO clinical practice guideline in kidney transplant recipients recommends that the monitoring of BK polyomavirus (BKV) reactivation, which may lead to BKV nephropathy (BKVN) and graft loss, is carried out by the periodical measurement of viral nucleic acid in the blood (i.e., viremia).[42] This approach, however, is expensive and not always available.[43] As an alternative, the search of "decoy cells" on either smeared or cytocentrifuged alcohol-fixed and Papanicolaou-stained urine specimens, also provides satisfactory diagnostic accuracy.[43,44] However, decoy cells can be easily seen by phase contrast microscopy in routine unstained samples.[45] Four decoy cell phenotypes are recognized: (1) nuclear ground-glass or gelatinous appearance (see Fig. 4.6A), (2) intranuclear inclusion surrounded by a clear halo (cytomegalovirus-like) (see Fig. 4.6B), (3) multinucleated cells (see Fig. 4.6C), and (4) vesicular nuclei with clumped chromatin and nucleoli (see Fig. 4.6D). In addition, hybrid forms, which represent transitions between the different phenotypes cells are frequently seen, as well as cells with eccentric nucleus and comet-like appearance. The presence of decoy cells may just indicate the reactivation of BKV infection; however, when they persist over time, are

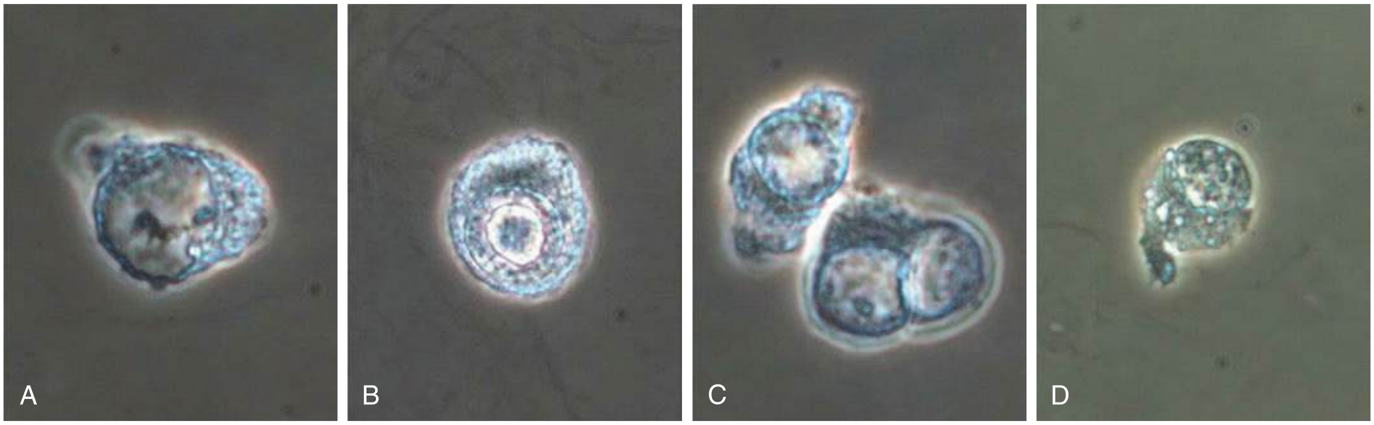

Fig. 4.6 **Decoy cells.** (A) Cell with nuclear ground-glass or gelatinous appearance (phenotype 1). (B) Cytomegalovirus-like cell with a large intranuclear inclusion surrounded by a clear halo (phenotype 2). (C) a binucleated cell (bottom, phenotype 3) and a cell with an enlarged ground glass nucleus (phenotype 1). (D) Cell with clumped chromatin (phenotype 4). (Phase contrast microscopy; original magnification ×400.)

in high numbers, or are found within urinary casts, they are a reliable marker of likely BKVN, which should be confirmed by measurement of BK viremia.[43,44,46]

Urologic Diseases

Urinary tract disorders such as cancer, urolithiasis, and hydronephrosis are associated with variable numbers of isomorphic urinary erythrocytes, which are often associated with leukocytes or transitional epithelial cells (from deep or superficial layers of uroepithelium). In addition, in uroepithelial cancer, malignant transitional cells can be found, which show abnormal size and shape, increased number and size of nuclei, and enlarged nucleoli. These cells also can be identified in unstained samples by phase contrast microscopy.[47]

Nonspecific Urinary Abnormalities

Some urine sediment findings are nonspecific. This occurs when variable numbers of hyaline or hyaline-granular casts are found with or without low numbers of erythrocytes (either isomorphic or dysmorphic), leukocytes, common crystals, or small numbers of superficial transitional epithelial cells.

AUTOMATED ANALYSIS OF URINE SEDIMENT

The three main types of automated instruments using different technology are flow cytometry, automated intelligent microscopy, and cuvette-based microscopy. Flow cytometry supplies quantitative results and graphics (“scattergrams”), but no images, of the identified particles. Compared with manual microscopy, the instrument shows a satisfactory correlation for red blood cells (RBCs), white blood cells (WBCs), and SECs, whereas for casts the correlation is not as good.[48]

Intelligent microscopy supplies quantitative results and images of the particles present in the sample, which are pooled and shown on the screen by categories (e.g., all SECs, all crystals found in the sample), with a good precision and accuracy for RBCs, WBCs, and SECs. For other particles, the accuracy may be improved by a trained technologist reviewing the images classified by the instrument.[49]

Cuvette-based microscopy also supplies quantitative results and black and white images of whole microscopic fields similar to those obtained with bright-field manual microscopy. This has good sensitivity for erythrocytes, leukocytes, SECs, and casts.[50]

Compared with manual microscopy, automated urine sediment analyzers offer several advantages. Small volumes of urine are required (1 to 3 ml), and high numbers of samples can be examined in a short time (up to 100/h). Drawbacks associated with centrifugation (time consumption, loss/lysis of particles) are avoided; there is acceptable accuracy for some particles, with quantitative results and small variation coefficients. Moreover, they signal to the operator the most complex samples, for which examination by manual microscopy is required. However, they also have limitations—they do not identify some clinically relevant epithelial cells (RTECs, transitional cells either deep or superficial, DCs); they underestimate casts, which they can only define as hyaline “non-hyaline” or “pathologic”; they identify only a few types of crystals; and they miss lipids completely.

Therefore automated urine sediment analyzers have their place in large clinical laboratories, in which hundreds of urine samples are tested every day, whereas they are not yet adequate for the examination of the most complex samples.

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SELF-ASSESSMENT QUESTIONS

1. The reagent strip for protein:
   A. Detects all types of proteins present in the urine
   B. Is not adequate for the evaluation of the renal patient
   C. Is not influenced by the pH of the urine
   D. Is not influenced by the specific gravity of the urine
2. Phase contrast microscopy coupled with polarized light:
   A. Is the correct approach for urine sediment examination
   B. Does not offer any advantage over bright-field microscopy alone
   C. Only phase contrast is useful
   D. Only polarized light is useful
3. The automated urine sediment analyzers available today:
   A. Are adequate for the evaluation of the renal patient
   B. Require high volumes of urine
   C. Identify renal tubular epithelial cells
   D. Are not adequate for the evaluation of the renal patient

5

Imaging

David T. G. Wymer, David C. Wymer

Imaging evaluation of patients with renal disease has changed significantly in recent years. Intravenous urography (IVU) is infrequently used and has mostly been replaced by ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine scanning. Rapidly changing computer-based data manipulation has resulted in major technologic advances in each of these modalities. Three-dimensional (3D) or even 4D (time-sensitive) image analysis is now available. *Molecular imaging,* which visualizes cellular function using biomarkers, is providing functional as well as anatomic information.

The American College of Radiology (ACR) has published Appropriateness Criteria,[1] guidelines that suggest the choice of imaging modality to provide a rapid answer to the clinical question while minimizing cost and potential adverse effects to the patient, such as contrast-induced adverse events and radiation exposure. Tables 5.1, 5.2, and 5.3 list relative radiation exposures, first-choice imaging modalities in renal disease, and risk estimates, respectively. Risks of imaging and cost need to be balanced against benefits.

ULTRASOUND

Ultrasound is relatively inexpensive and provides a rapid way to assess renal location, contour, and size without radiation exposure. Nephrologists are increasingly undertaking straightforward ultrasound examination; the practical techniques as well as the appropriate interpretative skills are discussed in Chapter 92. Portable ultrasound is available and is essential in the pediatric or emergency setting. Obstructing renal calculi can be readily detected, and renal masses can be identified as cystic or solid. In cases of suspected obstruction, the progression or regression of hydronephrosis is readily evaluated. Color Doppler imaging permits assessment of renal vascularity and perfusion. Unlike the other imaging modalities, ultrasound is highly dependent on operator skills. Limitations of ultrasound include lack of an acoustic window, body habitus, and poor patient cooperation.

Kidney Size

The kidney is imaged in transverse and sagittal planes and is normally 9 to 12 cm in length in adults. Differences in kidney size can be detected with all imaging modalities. Fig. 5.1 diagrams the common causes of enlarged and shrunken kidneys.

Renal Echo Pattern

The normal renal cortex is hypoechoic compared with the fat-containing echogenic renal sinus (Fig. 5.2A). The cortical echotexture is defined as isoechoic or hypoechoic compared with the liver or spleen. In children, the renal pyramids are hypoechoic (Fig. 5.2B) and the cortex is characteristically hyperechoic compared with the liver and the spleen. In adults, an increase in cortical echogenicity is a sensitive marker for parenchymal renal disease but is nonspecific (Fig. 5.3). Decreased cortical echogenicity can be found in acute pyelonephritis and acute renal vein thrombosis.

The normal renal contour is smooth, and the cortical mantle should be uniform and slightly thicker toward the poles. Two common benign pseudomasses that can be seen with ultrasound are the dromedary hump and the column of Bertin. The column of Bertin results from bulging of cortical tissue into the medulla; it is seen as a mass with an echotexture similar to that of the cortex, but it is found within the central renal sinus (Fig. 5.4). The renal pelvis and proximal ureter are anechoic. An *extrarenal pelvis* refers to the renal pelvis location outside the renal hilum. The ureter is not identified beyond the pelvis in nonobstructed patients.

Obstruction can be identified by the presence of hydronephrosis (Fig. 5.5). Parenchymal and pelvicalyceal nonobstructing renal calculi as well as ureteral obstructing calculi can be readily detected (Fig. 5.6). The upper ureter also will be dilated if obstruction is distal to the pelviureteral junction (see Fig. 5.5C). False-negative ultrasound examination findings with no hydronephrosis occasionally occur in early obstruction. Obstruction without ureteral dilation also may occur in retroperitoneal fibrosis and in transplanted kidneys as a result of periureteral fibrosis.

Renal Cysts

Cysts can be identified as anechoic lesions and are a frequent coincidental finding during renal imaging. Ultrasound usually readily identifies renal masses as cystic or solid (Figs. 5.7 and 5.8). However, hemorrhagic cysts may be mistakenly called solid because of increased echogenicity. Differentiation of cysts as simple or complex is required to plan intervention.

Simple Cysts

A simple cyst on ultrasound is anechoic, has a thin or imperceptible wall, and demonstrates through-transmission because of the relatively rapid progression of the sound wave through fluid compared with adjacent soft tissue.

Complex Cysts

Complex cysts contain calcifications, septations, and mural nodules. Instead of being anechoic, these masses may contain internal echoes representing hemorrhage, pus, or protein. Complex cysts may be benign or malignant; cyst wall nodularity, septations, and vascularity strongly suggest malignancy. The Bosniak classification of cystic renal masses is widely used (see Table 59.5). Complex cysts identified by ultrasound require further evaluation by contrast-enhanced CT (or MRI) to identify

TABLE 5.1 Relative Radiation Doses of Imaging Examinations

Examination	Effective Dose (mSv)
Chest: PA x-ray film	0.02
Lumbar spine	1.8
KUB abdomen	0.53
CT abdomen	10
CT chest	20-40
PET-CT	25
Ultrasound or MRI	0

CT, Computed tomography; *KUB,* kidney, ureter, bladder (plain film); *MRI,* magnetic resonance imaging; *mSv,* millisieverts; *PA,* posteroanterior; *PET,* positron emission tomography.

TABLE 5.2 Suggested Imaging in Renal Disease*

Renal Pathology	First-Choice Imaging
Acute kidney injury, chronic kidney disease	Ultrasound
Hematuria	Ultrasound or CT
Proteinuria, nephrotic syndrome	Ultrasound Multiphase CT urography
Hypertension with normal renal function	Ultrasound Consider CTA or MRA
Hypertension with impaired renal function	Ultrasound with Doppler
Renal infection	Contrast-enhanced CT
Hydronephrosis identified on ultrasound	Nuclear renogram
Retroperitoneal fibrosis	Contrast-enhanced CT
Papillary or cortical necrosis	Contrast-enhanced CT
Renal vein thrombosis	Contrast-enhanced CT
Renal infarction	Contrast-enhanced CT
Nephrocalcinosis	CT

Modified from reference 1.

*These recommendations assume availability of all common imaging modalities.

CT, Computed tomography; *CTA,* computed tomographic angiography; *MRA,* magnetic resonance angiography.

TABLE 5.3 Risk Estimates in Diagnostic Imaging

Imaging Risk	Estimated Risk
Cancer from 10 mSv of radiation (1 body CT)[2]	1 in 1000
Contrast-induced nephropathy in patient with renal impairment[4]	Uncertain but higher with diabetes or hyperuricemia
Nephrogenic systemic fibrosis[4,6]	1 in 25,000 to 1 in 30,000 (depends on gadolinium agent) Higher risk if GFR >30 ml/min
Death from iodine contrast anaphylaxis[5]	1 in 130,000
Death from gadolinium contrast anaphylaxis[6]	1 in 280,000

abnormal contrast enhancement of the cyst wall, mural nodule, or septum, which may indicate malignancy.

Bladder

Real-time imaging can be used to evaluate for bladder wall tumors and bladder stones. Color flow Doppler evaluation of the bladder in well-hydrated patients can be used to identify a ureteral jet, produced when peristalsis propels urine into the bladder. The incoming urine has a higher specific gravity relative to the urine already in the bladder (Fig. 5.9). Absence of the ureteral jet can indicate total ureteral obstruction.

Renal Vasculature

Color Doppler investigation of the kidneys provides a detailed evaluation of the renal vascular anatomy. The main renal arteries can be identified in most patients (Fig. 5.10). Power Doppler imaging is a more sensitive indicator of flow, but unlike color Doppler imaging, power Doppler provides no information about flow direction and cannot be used to assess vascular waveforms. However, power Doppler imaging is exquisitely sensitive for detection of renal parenchymal flow and has been used to identify cortical infarction.

Renal Artery Duplex Scanning

The role of gray-scale and color Doppler sonography in evaluating for renal artery stenosis is controversial. The principle is that a narrowing in the artery will cause a velocity change commensurate with the degree of stenosis, as well as a change in the normal renal artery waveform downstream from the lesion. The normal renal artery waveform demonstrates a rapid systolic upstroke and an early systolic peak (Fig. 5.11A). The waveform becomes damped downstream from a stenosis. This consists of a slow systolic acceleration (tardus) and a decreased and rounded systolic peak (parvus) (see Fig. 5.11B). It also results in a decrease in the *resistive index,* defined as the end-diastolic velocity (EDV) subtracted from the peak systolic velocity (PSV) divided by PSV: (PSV – EDV)/PSV. The normal resistive index is 0.70 to 0.72.

The entire length of the renal artery should be examined for the highest velocity signal. The origins of the renal arteries are important to identify because this area is often affected by atherosclerosis, but the arteries are often difficult to visualize because of overlying bowel gas. Within the kidney, medullary branches and cortical branches in the upper, middle, and lower thirds should be included to attempt detection of stenosis in accessory or branch renal arteries.

Proximal and distal criteria exist for diagnosis of significant renal artery stenosis, usually defined as stenosis greater than 60%. The *proximal* criteria detect changes in the Doppler signal at the site of stenosis and provide sensitivities and specificities ranging from, respectively, 0% to 98% and 37% to 98%.[7,8] Technical failure rates are typically 10% to 20%.[9] Renal artery stenosis also may be missed if PSV is low because of poor cardiac output or aortic stenosis. False-positive results can occur when renal artery velocity is increased because of high-flow states, such as hyperthyroidism or vessel tortuosity. The *distal* criteria are related to detection of a tardus-parvus waveform distal to a stenosis; sensitivities and specificities of 66% to 100% and 67% to 94%, respectively, have been reported.[10,11] Technical failure with distal criteria is much lower than with proximal evaluation (<5%). False-negative results can occur from stiff poststenotic vessels, which will decrease the tardus-parvus effect. The tardus-parvus effect also may be a result of aortic stenosis, low cardiac output, or collateral vessels in complete occlusion, giving a false-positive result.

Combining the proximal and distal criteria improves detection of stenoses. Sensitivity of 97% and specificity of 98% can be achieved

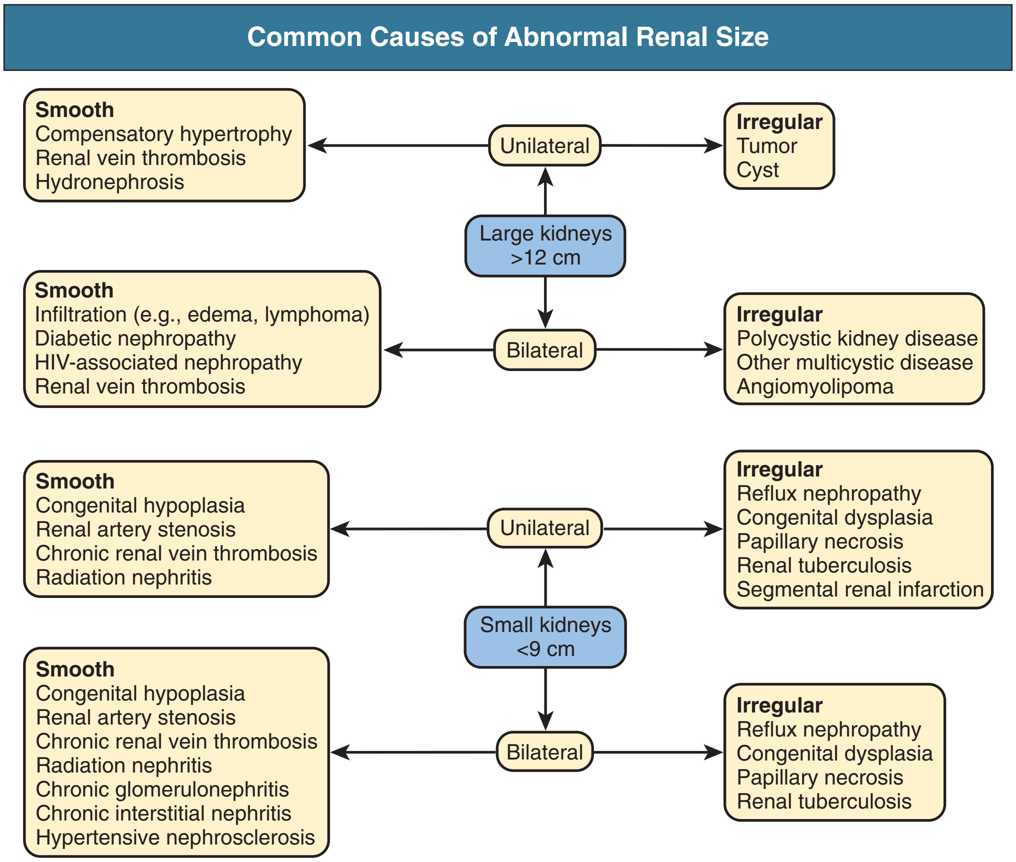
Common Causes of Abnormal Renal Size
Smooth
Compensatory hypertrophy
Renal vein thrombosis
Hydronephrosis
Unilateral
Irregular
Tumor
Cyst
Large kidneys >12 cm
Smooth
Infiltration (e.g., edema, lymphoma)
Diabetic nephropathy
HIV-associated nephropathy
Renal vein thrombosis
Bilateral
Irregular
Polycystic kidney disease
Other multicystic disease
Angiomyolipoma
Smooth
Congenital hypoplasia
Renal artery stenosis
Chronic renal vein thrombosis
Radiation nephritis
Unilateral
Irregular
Reflux nephropathy
Congenital dysplasia
Papillary necrosis
Renal tuberculosis
Segmental renal infarction
Small kidneys <9 cm
Smooth
Congenital hypoplasia
Renal artery stenosis
Chronic renal vein thrombosis
Radiation nephritis
Chronic glomerulonephritis
Chronic interstitial nephritis
Hypertensive nephrosclerosis
Bilateral
Irregular
Reflux nephropathy
Congenital dysplasia
Papillary necrosis
Renal tuberculosis

Fig. 5.1 Common causes of abnormal kidney size.

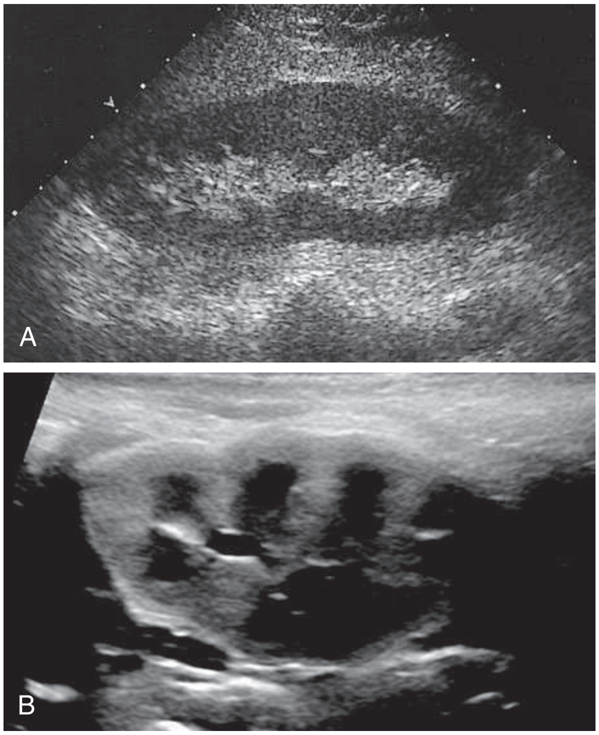

Fig. 5.2 Ultrasound images of kidney. (A) Normal sagittal renal ultrasound image. The cortex is hypoechoic compared with the echogenic fat containing the renal sinus. (B) Normal renal ultrasound image in an infant. Note the hypoechoic pyramids.

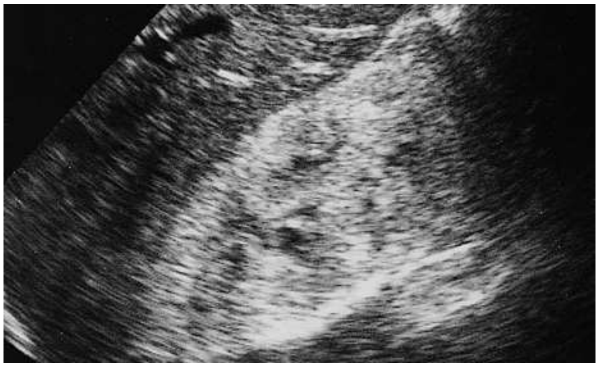

Fig. 5.3 Nephropathy associated with human immunodeficiency virus (HIV). Enlarged echogenic kidney with lack of corticomedullary distinction. Bipolar length of kidney is 14.2 cm.

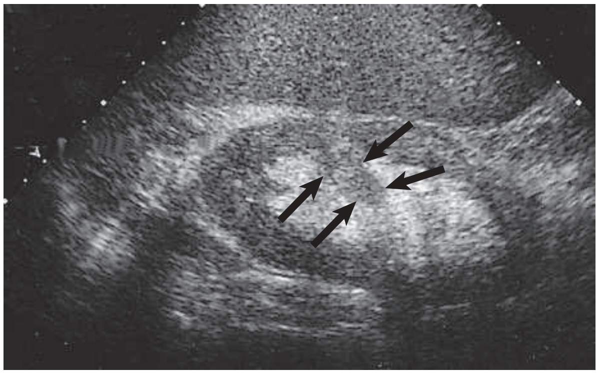

Fig. 5.4 Sagittal renal ultrasound image. Column of Bertin is present *(arrows)* and is easily identified because of echotexture similar to that of renal cortex.

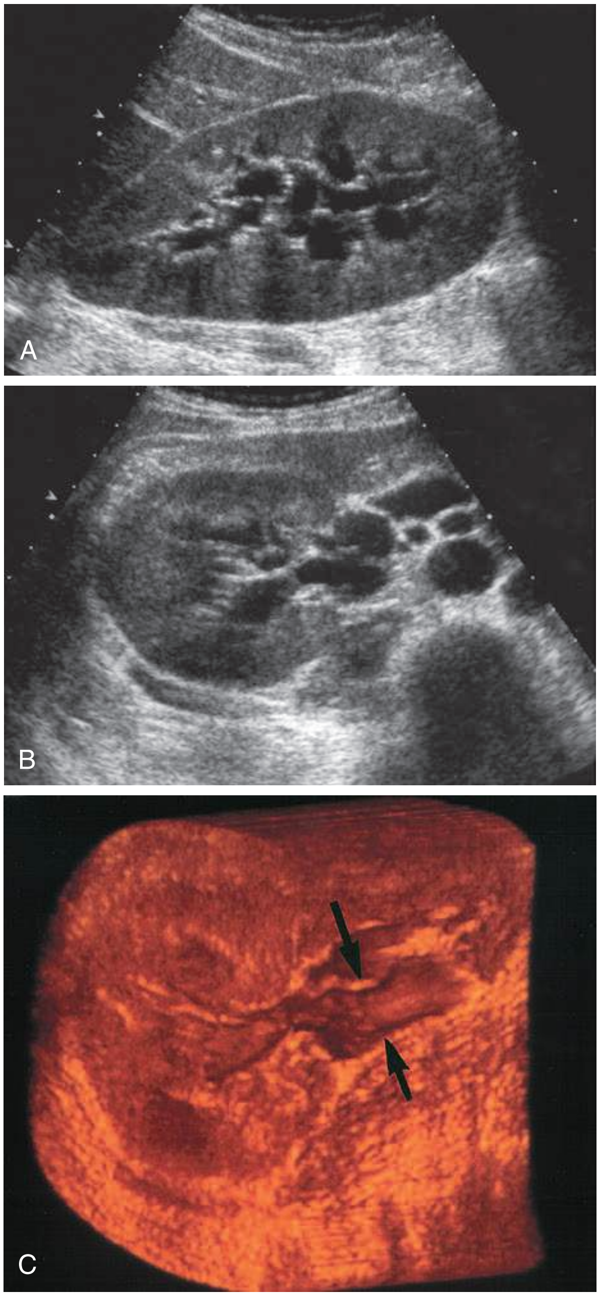

Fig. 5.5 Renal ultrasound study demonstrating hydronephrosis. (A) Sagittal ultrasound image. (B) Transverse image. (C) Transverse 3D surface-rendered image; *arrows* indicate the dilated proximal ureter.

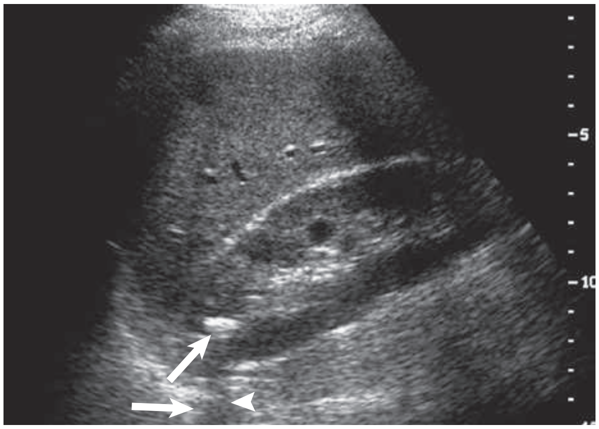

Fig. 5.6 Renal calculus *(arrow)* of upper pole. Note the acoustic shadowing *(arrowhead)* on sagittal ultrasound image.

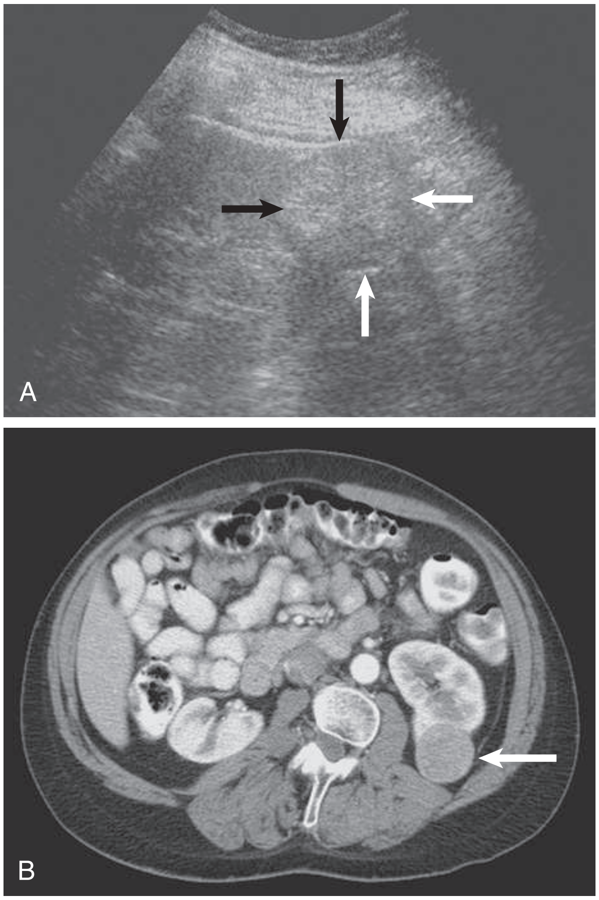

Fig. 5.7 Evaluation of renal mass. (A) Sagittal ultrasound image shows large hyperechoic mass arising from lower pole *(arrows)*. (B) Corresponding contrast-enhanced CT scan shows renal cell carcinoma *(arrow)*.

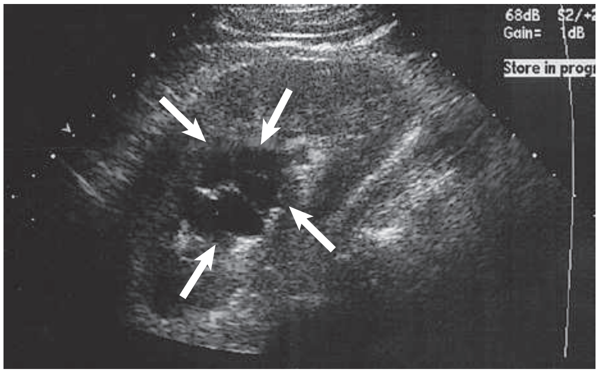

Fig. 5.8 Complex renal cyst *(arrows)*. Sagittal ultrasound image.

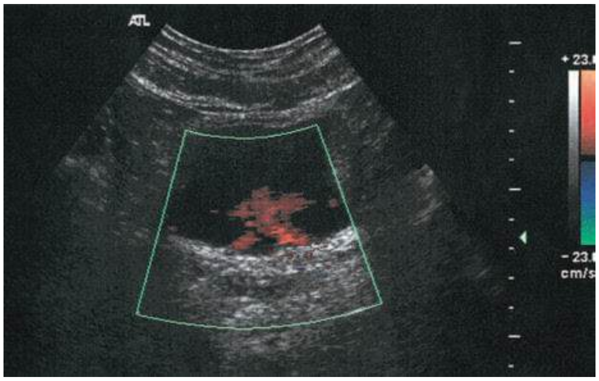

Fig. 5.9 Bilateral ureteral jets in bladder. Color Doppler ultrasound study detects this normal appearance.

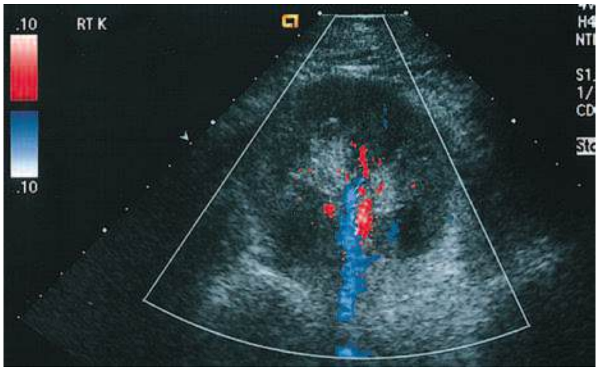

Fig. 5.10 **Ultrasound evaluation of kidney.** Transverse color Doppler image shows the artery as *red* and the vein as *blue.*

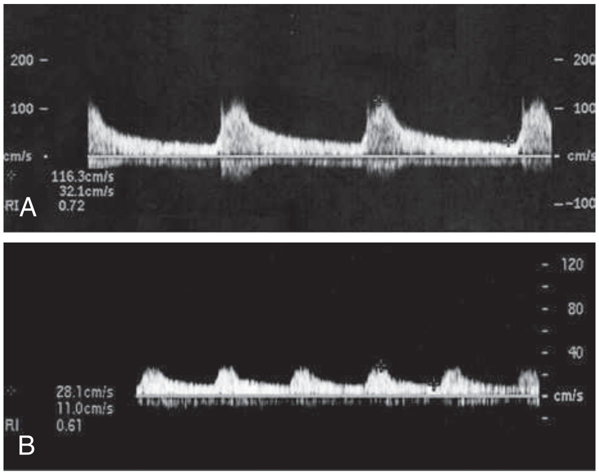

Fig. 5.11 **Renal artery color Doppler image and spectral tracing.** (A) Normal renal artery tracing shows rapid systolic upstroke and early systolic peak velocity (~100 cm/s). (B) Tardus-parvus waveform demonstrates slow systolic upstroke (acceleration) and decreased peak systolic velocity (~20 cm/s) associated with renal artery stenosis. Note different scales on vertical axis.

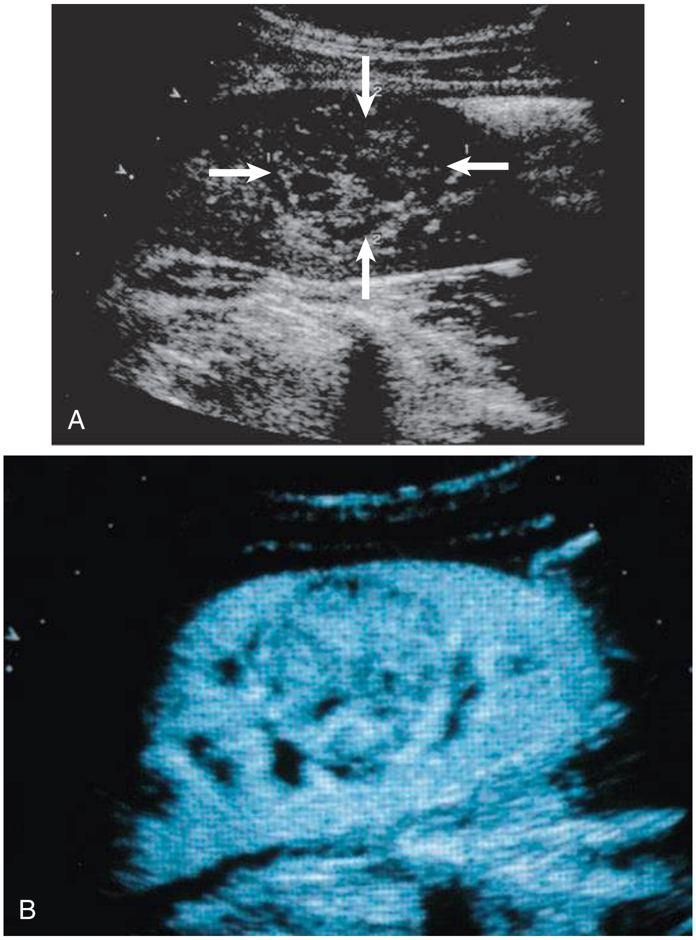

Fig. 5.12 **Contrast ultrasonography.** (A) Sagittal renal ultrasound image with a large, central renal cell cancer *(arrows).* (B) Central cancer better seen after injection of contrast material. (Courtesy Dr. Christoph F. Dietrich.)

when both the extrarenal and the intrarenal arteries are examined.[12] When it is technically successful, Doppler ultrasound has a negative predictive value of more than 90%.[12] However, reliable results require a skilled and experienced sonographer and a long examination time. Despite these limitations, Doppler studies also have several advantages. Noninvasive, inexpensive, and widely available, Doppler studies also allow structural and functional assessment of the renal arteries and imaging without exposure to radiation or contrast material.

Some physicians prefer computed tomography angiography (CTA) or magnetic resonance angiography (MRA) as a faster and more reliable test than ultrasound, but at present the choice should depend on local expertise and preference. For further discussion of the diagnosis and management of renovascular disease, see Chapter 41.

Contrast-Enhanced and Three-Dimensional Ultrasound

Ultrasound contrast agents, initially introduced to assess cardiac perfusion, are now being used to evaluate perfusion to other organs, such as the kidney. These intravenous agents are microbubbles 1 to 4 μm in diameter (smaller than erythrocytes) that consist of a shell surrounding the echo-producing gas core. The microbubbles oscillate in response to the ultrasound beam frequency and give a characteristic increased echo signal on the image. Preliminary studies evaluating renal perfusion in dysfunctional kidneys show reduced flow compared with normal kidneys, as well as improved lesion detection (Fig. 5.12). However, the clinical adoption of microbubble imaging in the kidney remains uncertain, particularly with the general availability and robustness of CT and MRI.

Two-dimensional ultrasound images can be reconstructed into 3D volume images by a process similar to 3D reconstructions for MRI and CT. Potential applications include vascular imaging and fusion with MRI or positron emission tomography (PET).

PLAIN RADIOGRAPHY AND INTRAVENOUS UROGRAPHY

The use of IVU has receded as cross-sectional imaging by CT and MRI has become more widely applied to the urinary tract. Although now with few primary indications in many centers, contrast urography may still be a key investigation in parts of the world where economic limitations mean that cross-sectional imaging is not available. However, plain radiography, often called KUB (kidneys, ureter, bladder) imaging, still has an important role in the identification of soft tissue masses, bowel gas pattern, calcifications, and renal location.

Renal Calcification

Most renal calculi are radiodense, although only about 60% of urinary stones detected on CT are visible on plain films.[13] CT demonstrates nonopaque stones, which include uric acid, xanthine, and struvite stones. However, neither CT nor plain radiography may detect calculi associated with protease inhibitor therapy.[14] Oblique films are sometimes obtained to confirm whether a suspicious upper quadrant calcification is renal in origin. Calculi that are radiolucent on plain films are usually detected as filling defects on IVU. IVU has higher sensitivity than radiography but lower sensitivity than CT. If available, CT is the imaging modality of choice for detection of urinary calculi.[15]

Nephrocalcinosis may be medullary (Fig. 5.13A and B) or cortical (C) and is localized or diffuse. The causes of nephrocalcinosis are discussed in Chapter 57 (see Box 57.7).

Intravenous Contrast Urography

Before contrast material is administered, an abdominal compression device may be placed, to compress the midureters against the bony pelvis. This retains the excreted contrast material in the upper tract and distends the renal pelvis and calyces. The first film is usually performed at 30 seconds after contrast injection, when the renal parenchyma is at peak enhancement. Subtle renal masses are often detected only on these early films. The compression device is then removed, and films of the entire abdomen are obtained at 5 minutes, when there is renal excretion of the contrast agent and the ureters are best evaluated. Films with the patient prone may be required to visualize the entirety of the ureter. A filled-bladder film is obtained. A postvoid film of the bladder assesses emptying and assists in evaluation of the distal ureters, which may be obscured by a distended contrast-filled bladder. The usual contrast volume injected for IVU is similar to that for routine abdominal CT. The primary difference is timing of imaging. IVU is contraindicated in patients with a history of allergic reactions to radiographic contrast agents. When the glomerular filtration rate (GFR) is less than 60 ml/min, IVU yields increasingly poor images.

Kidneys

Evaluation of the kidneys on IVU (as well as CT and MRI) should include their number, location, axis, size, contour, and degree of

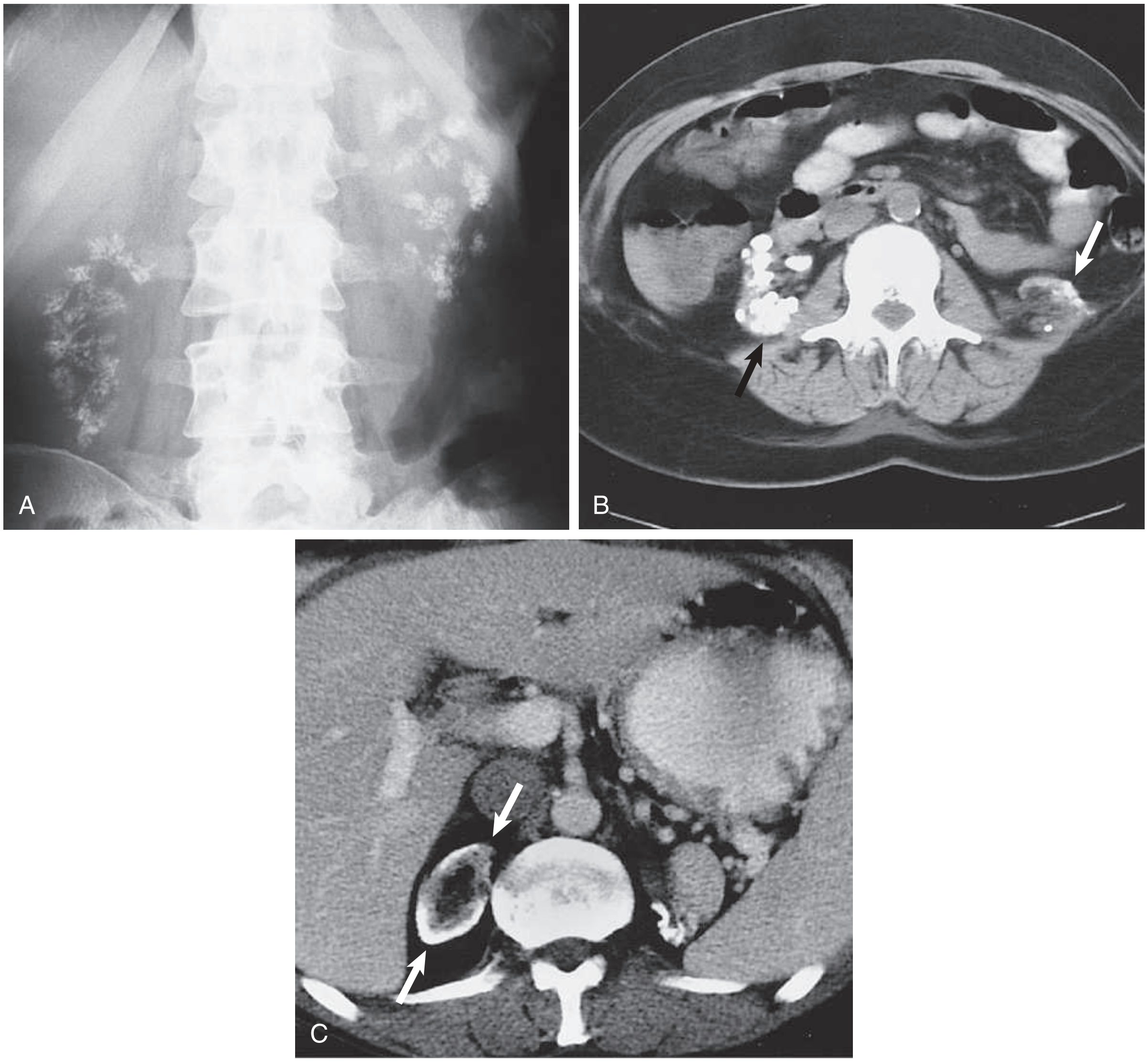

Fig. 5.13 Nephrocalcinosis. (A) Plain x-ray film shows bilateral medullary nephrocalcinosis in a patient with distal renal tubular acidosis. (B) Noncontrast CT scan in a patient with hereditary oxalosis and dense bilateral renal calcification *(arrows)*. The left kidney is atrophic. (C) Noncontrast CT scan shows cortical nephrocalcinosis in the right kidney *(arrows)* after cortical necrosis.

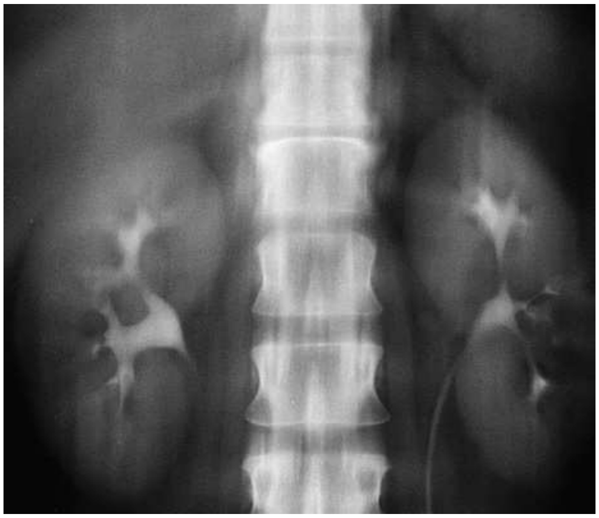

Fig. 5.14 **Normal parenchymal enhancement and normal renal excretion.** Early postcontrast tomogram in intravenous urography.

enhancement. Renal size is variable, but a normal kidney should be about three or four lumbar vertebral bodies in length. The renal outline should be smooth and sharply demarcated from the retroperitoneal fat. Renal enhancement after contrast administration should be symmetric and progress centrally from the cortex, with excretion evident in the ureters by 5 minutes. Asymmetry of renal enhancement may indicate renal artery disease.

Pelvicalyceal System

The pelvicalyceal system is best evaluated on the early postcontrast films. Normally, there are about 10 to 12 calyces per kidney. The calyces drain into the infundibula, which in turn empty into the renal pelvis (Fig. 5.14). The infundibulum and renal pelvis should have smooth contours without filling defects. In a common variant, vessels can cross the pelvicalyceal system or ureters, causing extrinsic compression defects that should not be mistaken for tumors or other urothelial lesions. When more than one calyx drains into an infundibulum, it is known as a *compound calyx,* most frequently seen in the poles. The normal calyx is gently cupped. Calyceal distortion occurs with papillary necrosis and reflux nephropathy.

Ureters

The ureters are often seen segmentally because of active peristalsis. The ureters should be free of filling defects and smooth. In the abdomen, the ureters lie in the retroperitoneum, passing anterior to the transverse processes of the vertebral bodies. In the pelvis, the ureters course laterally and posteriorly, eventually draining into the posteriorly located vesicoureteral junction. At the vesicoureteral junction, the ureters gently taper. Medial bowing or displacement of the ureter is often abnormal and can be seen secondary to ureter displacement from retroperitoneal masses, lymphadenopathy, and retroperitoneal fibrosis.

Bladder

The bladder should be rounded and smooth-walled. Benign indentations on the bladder include the uterus, prostate gland, and bowel. In chronic bladder outlet obstruction and neurogenic bladder, numerous trabeculations and diverticula may be seen around the bladder outline. Other incidental bladder diverticula, such as the Hutch diverticulum, can be seen and are usually of no significance unless they are large and do not empty completely on voiding.

RETROGRADE PYELOGRAPHY

Retrograde pyelography is performed when the ureters are poorly visualized on other imaging studies or when samples of urine need to be obtained from the kidney for cytology or culture. Patients who have severe allergies to contrast agents or impaired renal function can be evaluated with retrograde pyelography. The examination is performed by placing a catheter through the ureteral orifice under cystoscopic guidance and advancing it into the renal pelvis. With use of fluoroscopy, the catheter is slowly withdrawn while radiocontrast is injected (see Figs. 58.2 and 58.11). This technique provides excellent visualization of the renal pelvis and ureter and also can be used for cytologic sampling from suspect areas.

ANTEGRADE PYELOGRAPHY

Antegrade pyelography is performed through a percutaneous renal puncture and is used when retrograde pyelography is not possible. Ureteral pressures can be measured, hydronephrosis evaluated, and ureteral lesions identified (see Fig. 58.14). The examination is often performed as a prelude to nephrostomy placement. Both antegrade and retrograde pyelography are invasive and should be performed only when other studies are inadequate.

IMAGING ILEAL CONDUITS

After cystectomy or bladder failure, numerous types of continent or incontinent urinary diversions can be surgically created. One of the most common diversions is the ileal conduit; an ileal loop is isolated from the small bowel, and the ureters are implanted into the loop. This end of the loop is closed, and the other end exits through the anterior abdominal wall. This type of conduit can be evaluated by an excretory or a retrograde study. The excretory or *antegrade* study is performed and monitored in the same way as an IVU. A *retrograde* examination, also referred to as a "loop-o-gram," is obtained when the ureters and conduit are suboptimally evaluated on the excretory study. A Foley catheter is placed into the stoma and contrast slowly instilled. The ureters should fill by reflux because the ureteral anastomoses are not of the antireflux variety (Fig. 5.15).

CYSTOGRAPHY

A cystogram is obtained when more detailed radiographic evaluation of the bladder is required. *Voiding* cystography is performed to identify ureteral reflux and assess bladder function and urethral anatomy. A urethral catheter is placed into the bladder, the urine drained, contrast infused, and the bladder filled under fluoroscopic guidance. Early frontal and oblique films with the patient supine are obtained while the bladder is filling. Ureteroceles are best identified on early films. When the bladder is full, multiple films are obtained with varying degrees of obliquity. Reflux may be seen on these films. To obtain a voiding cystogram, the catheter is removed, the patient voids, and the contrast is followed into the urethra. Occasionally, bladder diverticula are seen only on the voiding films. When the patient has completely voided, a final film is used to assess the amount of residual urine and the mucosal pattern.

Radionuclide cystography is an alternative often used in children. It is useful in the diagnosis of reflux, but it does not provide the detailed anatomy seen with contrast cystography.

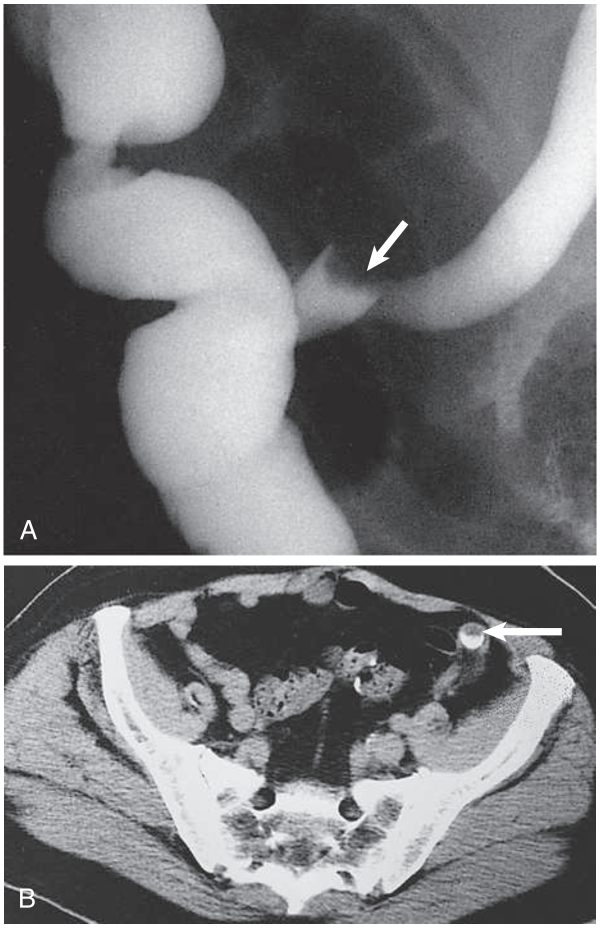

Fig. 5.15 Imaging of an ileal conduit. (A) Loop-o-gram. A recurrent transitional carcinoma is present in the reimplanted left ureter *(arrow)*. (B) CT scan clearly shows the tumor as a filling defect in anterior aspect of the opacified ureter *(arrow)*.

COMPUTED TOMOGRAPHY

Computed tomography examination of the kidneys is performed to evaluate suspect renal masses, locate ectopic kidneys (Figs. 5.16 and 5.17), investigate calculi, assess retroperitoneal masses, and evaluate the extent of parenchymal involvement in patients with acute pyelonephritis (Figs. 5.18 and 5.19). Helical CT scanners allow the abdomen and pelvis to be scanned at submillimeter intervals with single breath-held acquisitions, which eliminates motion artifact. Newer multidetector row CT results in multiple slices of information (64-slice and even 320-slice machines are now common) being acquired simultaneously, allowing the entire abdomen and pelvis to be covered in very fast acquisition times of less than 30 seconds. Although the improved CT imaging usually comes at a price of increased radiation exposure to the patient, new reconstruction software with *iterative reconstruction* significantly reduces radiation exposure by as much as 30%. The CT data can be reconstructed in multiple planes and even 3D for improved anatomic visualization and localization.

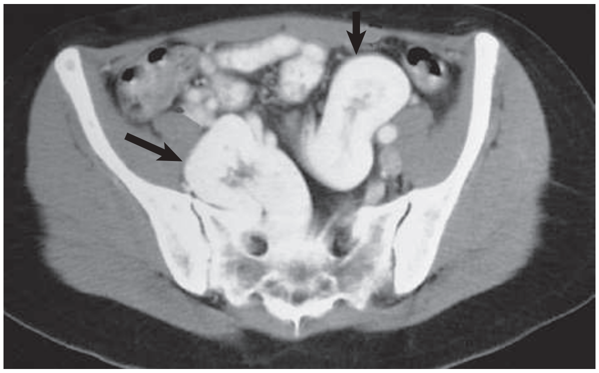

Fig. 5.16 Bilateral pelvic kidneys *(arrows)* on CT.

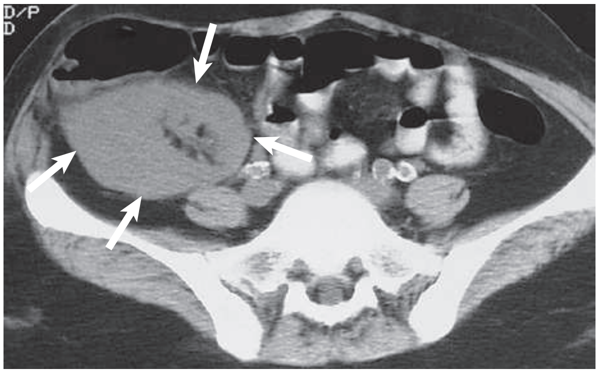

Fig. 5.17 Normal renal transplant *(arrows)* on CT.

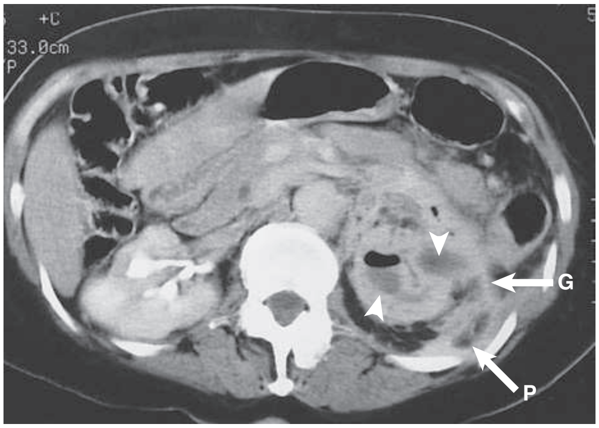

Fig. 5.18 **Emphysematous pyelonephritis.** Contrast-enhanced CT scan shows gas *(arrowheads)* within an enlarged left kidney and marked enhancement of the Gerota fascia *(G)* and posterior perirenal space *(P)*, indicative of inflammatory involvement.

Tissue Density

The Hounsfield unit (HU) scale is a measurement of relative densities determined by CT. Distilled water at standard pressure and temperature is defined as 0 HU; the radiodensity of air is defined as −1000 HU. All other tissue densities are derived from this (Table 5.4). Tissues can vary in their exact HU measurements and will also change with contrast enhancement. Water, fat, and soft tissue often can look identical on the scan, depending on the window and level settings of the image, so actual HU measurement is essential to characterize the tissues accurately.

Contrast-Enhanced and Noncontrast Computed Tomography

CT examination of the kidneys can be performed with or without intravenous administration of contrast material. Noncontrast imaging

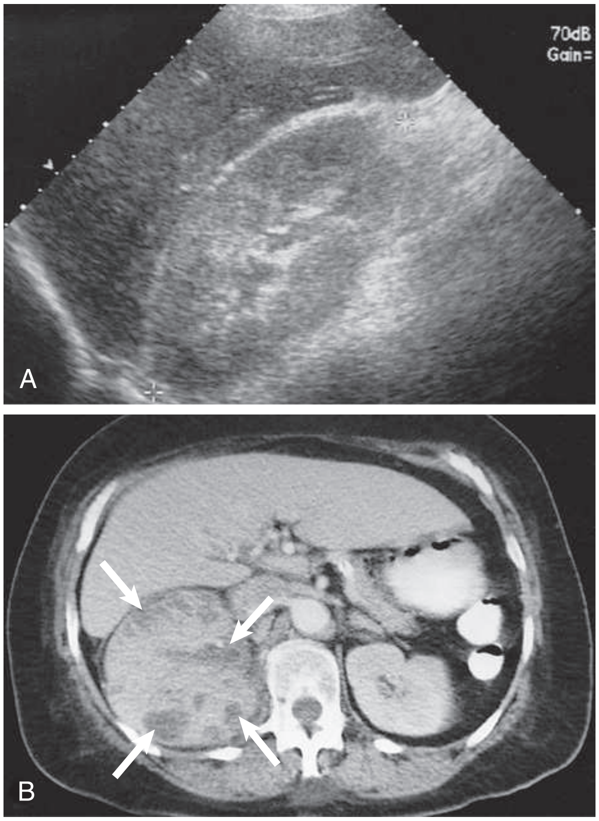

Fig. 5.19 **Acute pyelonephritis.** (A) Ultrasound image demonstrates an enlarged echogenic kidney. Bipolar length of kidney is 12.9 cm. (B) CT scan with contrast enhancement obtained 24 hours later demonstrates multiple nonenhancing abscesses *(arrows)*.

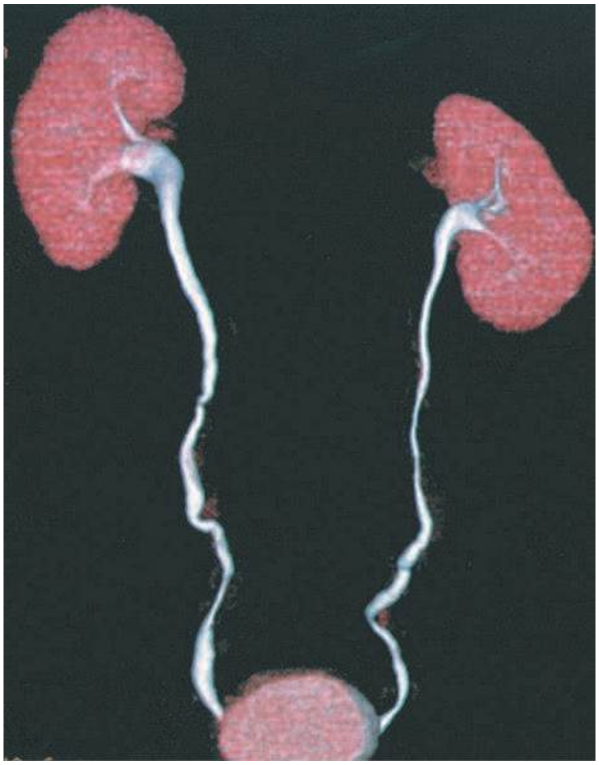

Fig. 5.20 **Noncontrast CT of bladder and kidney.** Computer-reformatted, volume-rendered CT urogram obtained from axial CT acquisition.

TABLE 5.4 Computed Tomography Determination of Density of Common Substances

Substance	Hounsfield Units*
Air	−1000
Fat	−120
Water	0
Muscle	+40
Bone	+400 or more

*Hounsfield unit (HU) scale is a measurement of relative densities compared with distilled water.

allows the kidneys to be evaluated for the presence of calcium deposition and hemorrhage, which are obscured after contrast administration.

Noncontrast CT is the examination of choice in patients with suspected nephrolithiasis and has replaced the KUB and IVU in most situations. The study consists of unenhanced images from the kidneys through the bladder for detection of calculi. CT has the advantage of being both highly sensitive (97% to 100%) and specific (94% to 96%) for diagnosis of urinary calculi.[15,16] Noncontrast CT can identify a possible obstructing calculus and the extent of parenchymal and perinephric involvement.

In cases other than stone evaluation, the kidneys are imaged after contrast administration (CT urography [CTU]). The kidneys are imaged in the corticomedullary phase for evaluation of the renal vasculature and in the nephrographic phase for evaluation of the renal parenchyma. The degree of enhancement can be assessed in both solid masses and complex cysts.

A compression device can be used as in IVU, but is very uncommonly used. Delayed images through the kidneys and bladder are performed for evaluation of the opacified and distended collecting system, ureters, and bladder.[17,18] After acquisition, the axial images can be reformatted into coronal or sagittal planes to optimize visualization of the entire collecting system (Fig. 5.20). The CT study can be tailored to the individual clinical scenario. For example, the corticomedullary phase can be eliminated to decrease the radiation dose if there is no concern about a vascular abnormality or no need for presurgical planning. A diuretic or saline bolus can be administered after contrast to better distend the collecting system and ureters during the excretory phase.

The kidneys should be similar in size and show equivalent enhancement and excretion. During the corticomedullary phase, there is brisk enhancement of the cortex. The cortical mantle should be intact. Any disruption of the cortical enhancement requires further evaluation; it may be caused by acute pyelonephritis (see Fig. 5.19), scarring, mass lesions, or infarction (Fig. 5.21). During the excretory phase, the entire kidney and renal pelvis enhance. Delayed excretion and delay in pelvicalyceal appearance of contrast material may be found in obstruction (Fig. 5.22), but also in renal parenchymal disease such as acute tubular necrosis (ATN).

Computed Tomographic Angiography

Helical scanning facilitates CTA, which can produce images similar to conventional angiograms, but is less invasive. A bolus of contrast material is administered, and the images are reconstructed at 0.5- to 3-mm

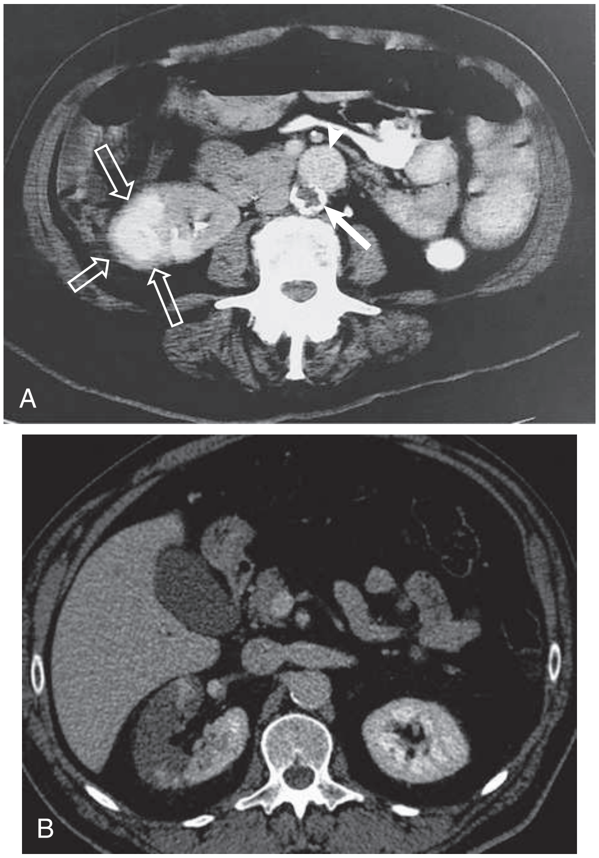

Fig. 5.21 Renal infarction. (A) CT scan showing a chronic calcified infarct *(open arrows)* involving half of the right kidney after aortic bypass surgery. The native aorta has a densely calcified wall *(arrow)*. The aortic graft is anterior to the native aorta *(arrowhead)*. (B) CT scan showing acute infarct in the right kidney with decreased parenchymal enhancement *(arrows)*.

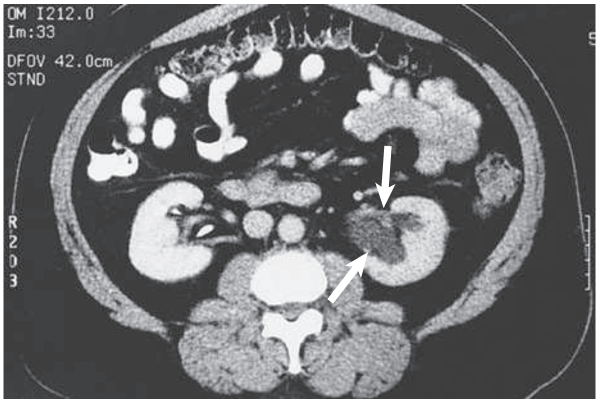

Fig. 5.22 Delayed excretion in left kidney secondary to distal calculus. Contrast-enhanced CT scan shows dilated left renal pelvis *(arrows)*.

consecutive intervals. The contrast bolus is timed for optimal enhancement of the aorta. The tightly focused and narrow CT beam allows higher resolution and better subsequent multiplanar reconstructions. The aorta and branch vessels are well demonstrated (Fig. 5.23). This technique is now widely used in living transplant donor evaluation (see Fig. 104.2), providing information not only on arterial and venous anatomy but also on size, number, and location of the kidneys and any ureteral anomalies of number or position.

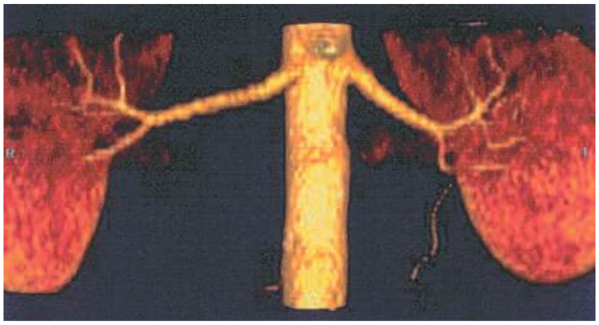

Fig. 5.23 Normal renal arteries. 3D reformatted CT angiogram.

In addition, CTA can be used to evaluate for atheromatous renal artery stenosis, with sensitivity of 96% and specificity of 99% for the detection of hemodynamically significant stenosis compared with digital subtraction angiography (DSA).[19] Furthermore, CTA allows visualization of both the arterial wall and lumen, which helps in planning renal artery revascularization procedures. Another advantage of CTA is the depiction of accessory renal arteries as well as nonrenal causes of hypertension, such as adrenal masses. CTA can be used to diagnose fibromuscular dysplasia but has a lower sensitivity (87%) than DSA.[20]

Dual-Energy Computed Tomography

In dual-energy CT (DECT), two CT datasets are acquired using different tube potentials, usually 140 and 80 kilovolts (kV), with different x-ray spectra. The density values at both acquired spectra differentiate materials on the basis of the photoelectric effect. Among other uses of DECT, using mathematical algorithms, the density values allow kidney stone differentiation (i.e., differentiation of uric acid from magnesium or calcium), allowing tailored treatment strategies.[21,22]

Limitations of Computed Tomography

CT does have some limitations. The cradle that the patient lies on usually has an upper weight limit of 100 to 200 kg (300 to 400 lb), but newer scanners can now accommodate up to 270 kg (600 lb). Obese patients often have suboptimal scans because of weight artifact and need higher radiation exposures to adjust for x-ray attenuation. Contrast-enhanced CT studies may be contraindicated in patients with an allergy to radiographic contrast and in patients with impaired renal function. If contrast is administered, subjects should be hydrated with intravenous saline and/or sodium bicarbonate. For further discussion on contrast use in patients with impaired renal function, see Radiologic Contrast Agents.

CT is very sensitive to metal artifact and patient motion. Retroperitoneal clips and intramedullary rods will cause extensive streak artifact, which severely degrades the images. Patients who are unable to remain motionless will also have suboptimal or even nondiagnostic studies, and sometimes sedation or general anesthesia may be needed to obtain diagnostic scans, particularly in children. Critically ill patients may not be stable enough for transport to the CT suite, and ultrasound can be considered as an alternative to CT in that setting.

MAGNETIC RESONANCE IMAGING

Although it only rarely should be the first examination used to evaluate the kidneys, MRI is typically an adjunct to other imaging. The major advantage of MRI over other modalities is direct multiplanar imaging. CT is limited to slice acquisition in the axial plane of the abdomen, and coronal and sagittal planes are acquired only by reconstruction, which can lead to loss of information.

Tissues contain an abundance of hydrogen, the nuclei of which are positively charged protons. These protons spin on their axis, producing a magnetic field (magnetic moment). When a patient is placed in a strong magnetic field in an MRI scanner, some of the protons align themselves with the field. When a radiofrequency pulse is applied, some of the protons aligned with the field will absorb energy and reverse direction. This absorbed energy is given off as a radiofrequency pulse as the protons relax (return to their original alignment), producing a voltage in the receiver coil. The coil is the hardware that covers the region of interest. For renal imaging, a body coil or torso coil is used. Relaxation is a 3D event giving rise to two parameters: T1 relaxation results in the recovery of magnetization in the longitudinal (spin-lattice) plane, whereas T2 results from the loss of transverse (spin-spin) magnetization. A rapid-sequence variant of T2 in common use is fast spin echo (FSE). Hydrogen ions move at slightly different rates in the different tissues. This difference is used to select imaging parameters that can suppress or aid in the detection of fat and water. Fluid, such as urine, is dark or low in signal on T1-weighted sequences and bright or high in signal on FSE sequences. Fat is bright on T1 and not as bright on FSE sequences (Fig. 5.24). The sequences and imaging planes selected must be tailored to the individual MR study. Diffusion-weighted imaging (DWI) evaluates the freedom of water molecules to diffuse in tissues; restriction of diffusion is imaged as bright areas on the DWI image set. Using the DWI data, regional apparent diffusion coefficients of the tissue can be calculated and an image of the distribution of the coefficients of the tissue can be produced. Dark areas on what is known as an apparent diffusion coefficient map are seen in infection, neoplasia, inflammation, and ischemia (Fig. 5.25).

Standard MR images usually include T1, T2, or FSE sequences and often additional contrast-enhanced T1 images. The imaging plane varies according to the clinical concerns. Usually, at least one sequence is performed in the axial plane. Sagittal and coronal images cover the entire length of the kidney and can make some subtle renal parenchymal abnormalities more conspicuous (Fig. 5.26).

On T1-weighted sequences, the normal renal cortex is higher in signal than the medulla, producing a distinct corticomedullary differentiation, which becomes indistinct in parenchymal renal disease. It is analogous to the echogenic kidney seen on ultrasound. On FSE sequences, the corticomedullary distinction is not as sharp but should still be present.

Contrast-Enhanced Magnetic Resonance Imaging

As with CT, intravenous contrast material can be administered to allow further characterization of renal lesions. Gadolinium is a *paramagnetic* contrast agent frequently used in MRI. Nephrotoxicity to gadolinium agents appears to be very uncommon and likely insignificant.[23] Adverse reactions to gadolinium are discussed later (see Magnetic Resonance Contrast Agents). Paramagnetic contrast agents are being evaluated for measurement of glomerular function.

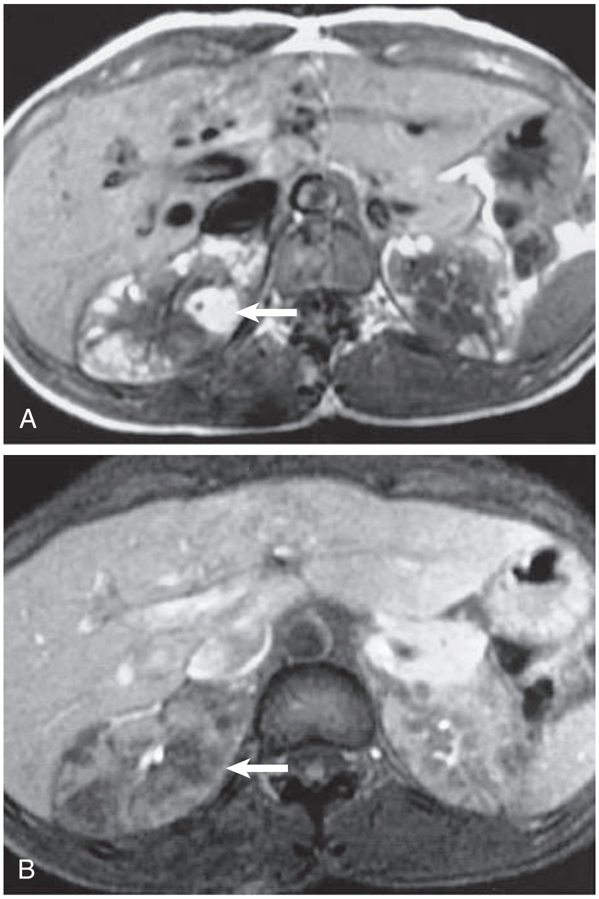

Fig. 5.24 Tuberous sclerosis on MRI. Multiple renal angiomyolipomas are seen. (A) T1-weighted MR image. The tumors are high in signal on T1 because of their fat; *arrow* shows the largest tumor. (B) T1-weighted MR image with fat suppression. The fat within the tumors is now low in signal *(arrow)*.

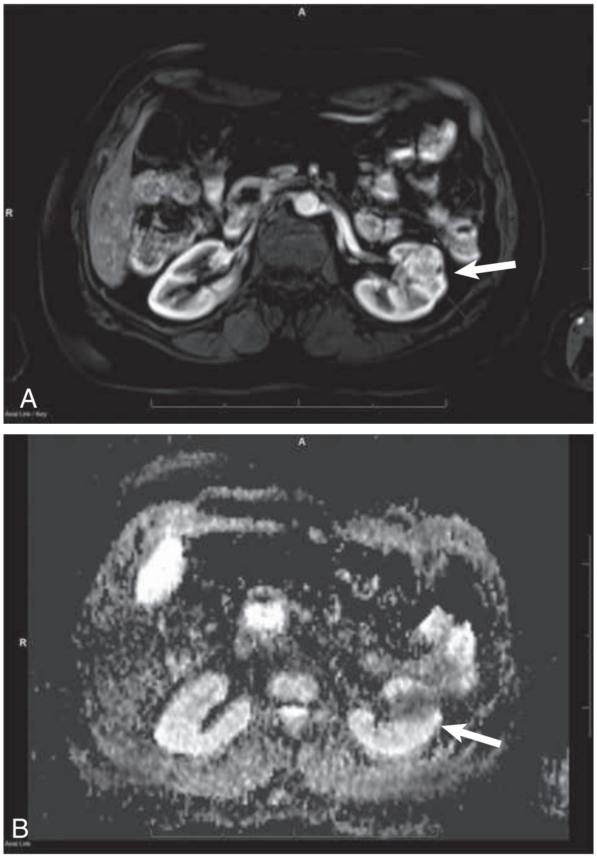

Fig. 5.25 MRI of renal tumor. T1-weighted contrast enhanced image showing enhancing left renal tumor.

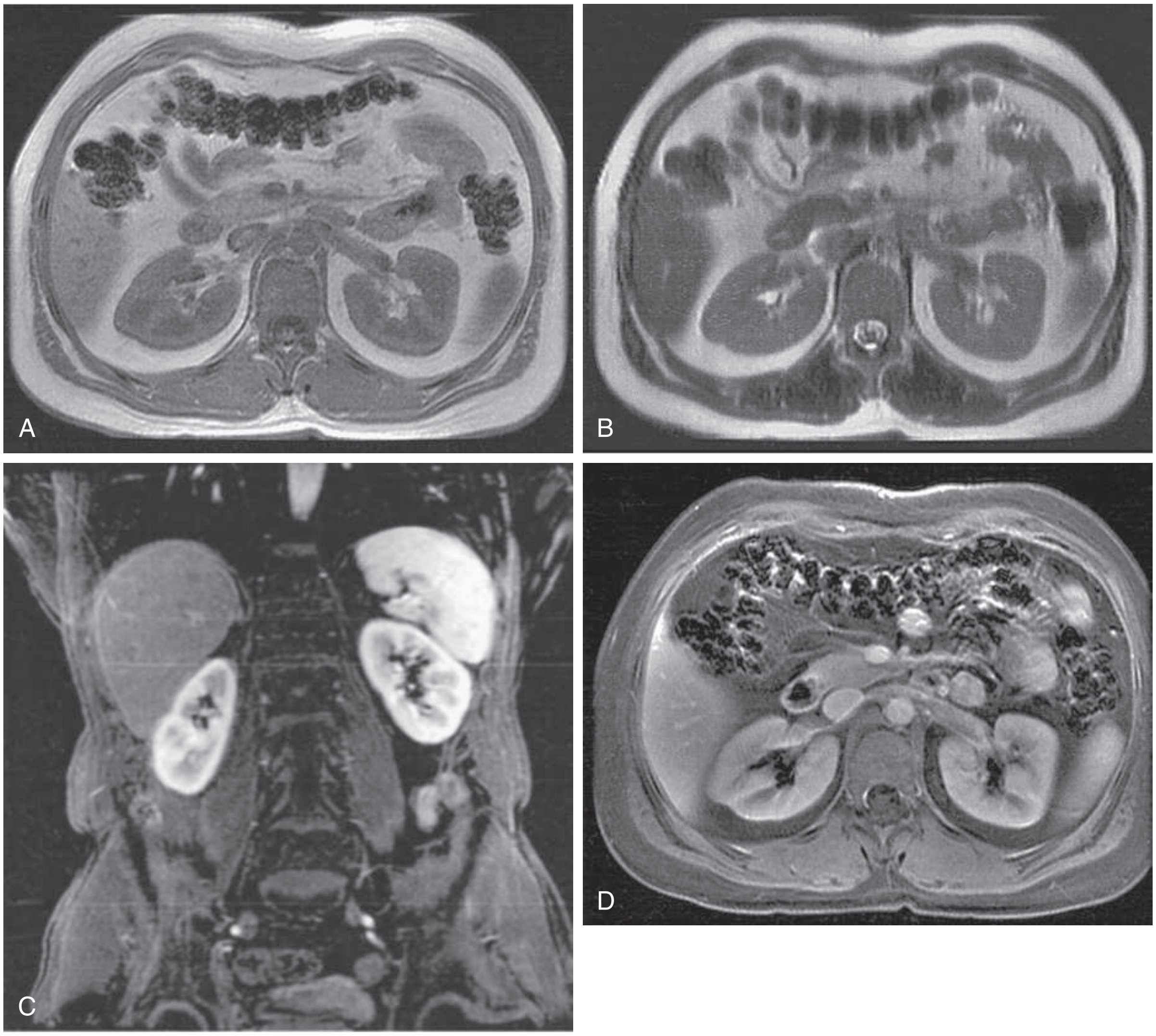

Fig. 5.26 **Normal MR images through kidneys.** (A) T1-weighted MR image. Note the distinct corticomedullary differentiation. (B) Fast spin echo MR image. Urine in the collecting tubules causes the high signal within the renal pelvis on this sequence. (C) Coronal T1-weighted, fat-suppressed MR image after contrast administration. (D) Axial T1-weighted, fat-suppressed image after contrast administration.

After injection of gadolinium, the vessels appear high in signal, or white, on T1-weighted sequences. Multiple images can be obtained in a single breath-held acquisition. This technique is useful for lesion characterization in patients who cannot receive iodinated contrast material. As with contrast-enhanced CT, the kidneys initially show symmetric cortical enhancement, which progresses to excretion. A delay in enhancement can be seen with renal artery stenosis.

Magnetic Resonance Urography

There are two techniques for performing magnetic resonance urography (MRU).[24] The first technique is sometimes called *static* MRU. Because urine contains abundant water, it will demonstrate high signal on a T2-weighted image. Therefore a heavily T2-weighted sequence accentuates the static fluid in the collecting system and ureters, which stands out against the darker background soft tissues. Static MRU can be performed rapidly, which is a benefit in imaging of children. A disadvantage is that any fluid in the abdomen or pelvis, such as fluid collections or fluid in the small bowel, will demonstrate a similar bright signal that can obscure superimposed structures. Also, the collecting system and ureters need to be distended for acquisition of good MR images.

The second technique, often referred to as *excretory* MRU, is similar to CTU. Intravenous administration of gadolinium is followed by T1-weighted imaging. This technique allows some assessment of renal function because the contrast is filtered by the kidney and excreted into the urine (see Fig. 58.10). The opacified collecting system and ureters are well seen, and a diuretic can be administered to further dilate the renal pelvis and ureters if necessary. MRU has limited capacity to detect calculi because calcification is poorly visualized by MRI.

Because CTU and MRU are comparable examinations in identifying the cause and anatomic location of urinary obstruction, the choice of modality is a matter of local preference. CTU is the better choice in the evaluation of urinary tract calculi. In patients with renal impairment caused by obstruction, MRU is superior to CTU in identifying noncalculous causes of obstruction, whereas CTU is superior in identifying calculi as a cause of obstruction.[25] CTU is also more widely available, faster, and less expensive than MRU. MRU is better suited in patients with allergy to iodinated contrast agents and

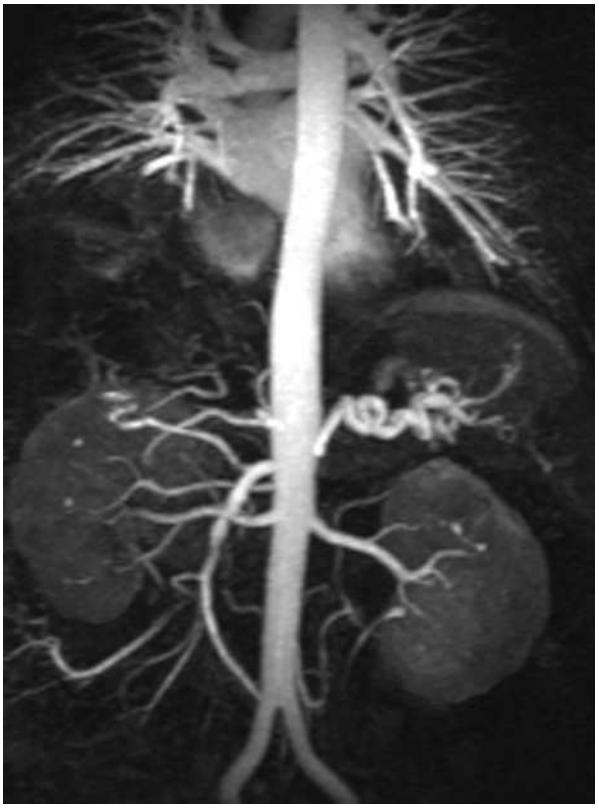

Fig. 5.27 **Magnetic resonance angiography.** Coronal 3D MR angiogram after contrast administration shows normal renal arteries.

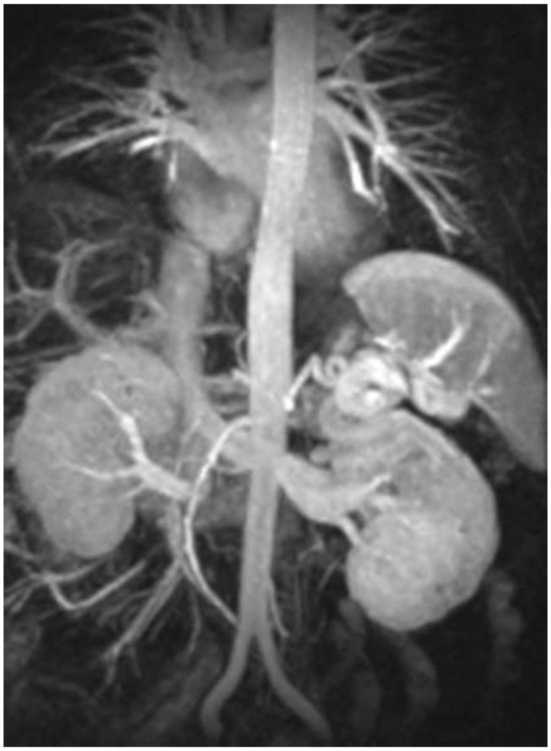

Fig. 5.28 MR venography.

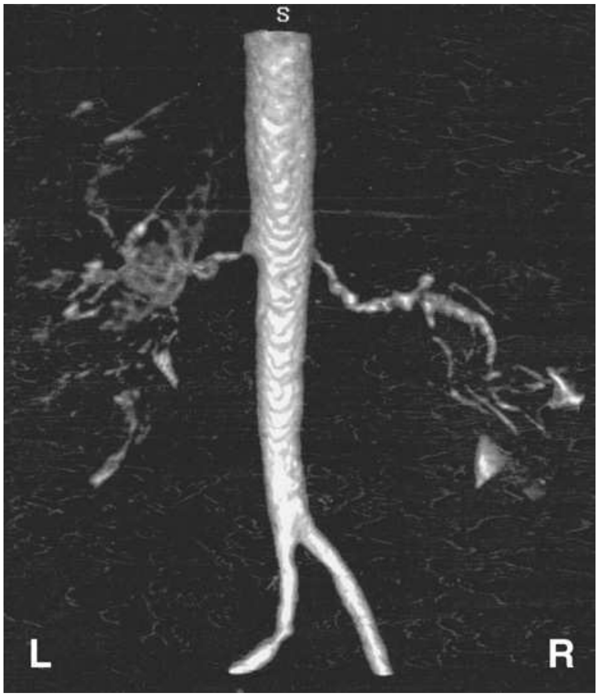

Fig. 5.29 **Dysplasia on MR angiography.** Coronal 3D MR angiogram shows fibromuscular dysplasia of the proximal right renal artery.

sometimes in children when radiation is an issue. MRU is also useful in depicting the anatomy in patients with urinary diversion to bowel conduits.

Magnetic Resonance Angiography

Although MRA can be performed with or without intravenous contrast, contrast provides better images. The aorta and branch vessels are beautifully demonstrated (Fig. 5.27). By adjustment of timing and type of sequences, the abdominal venous structures can be visualized (Fig. 5.28). MRA is performed to evaluate the renal arteries for stenosis and is less invasive than catheter angiography (Fig. 5.29). Technical advances, including faster sequences, now give sensitivity of 97% and specificity of 93% compared with DSA for contrast-enhanced MRA in the detection of renal artery stenosis.[26] MRA without gadolinium has a lower sensitivity (53% to 100%) and specificity (65% to 97%) for detection of renal artery stenosis.[27] MRA has limited ability to assess accessory renal arteries and therefore is not an ideal study to evaluate fibromuscular dysplasia. It has become the most commonly used modality in patients with hypertension, declining renal function, or allergy to iodinated contrast agents.[28] Where MRA is unavailable, Doppler ultrasound can be used.

Disadvantages of Magnetic Resonance Imaging

As with CT, MRI has some disadvantages. The table and gantry are confining, so claustrophobic patients may be unable to cooperate. Patients with some types of internal metallic hardware cannot undergo MRI. MRI safety guidelines have been developed with an extensive list of devices that are or are not MRI approved, and any devices in the patient need to be checked against this list. Examples of contraindications include neural stimulator devices and cerebral aneurysm clips. Many cardiac pacemakers are now compatible with MRI, but if the patient is pacemaker-dependent, they cannot be scanned.

Determination of in-stent stenosis is impossible as metallic artifact from renal artery stents completely obscures the lumen. Even with the new, fast imaging techniques, patients need to be able to cooperate with breath-holding instructions to minimize motion-related artifacts. MRI with gadolinium had been contraindicated in patients with GFR below 30 ml/min/1.73 m^2 in older linear contrast agents because of the risk for nephrogenic systemic fibrosis (see Magnetic Resonance Contrast Agents).

MRI can be used in the intensive care unit and in critically ill patients only if they are stable enough to be transported to the MRI suite and have no implanted metallic devices. Ventilated patients can undergo MRI; however, specific MRI-compatible, nonferromagnetic ventilators and other life support devices must be used. Because of the confined nature of the MRI gantry, visualization and monitoring of the patient during the scan are compromised.

Incidental Findings

With the growth of cross-sectional imaging, incidental renal lesions are being found with increasing frequency. Almost 70% of renal cell carcinomas are discovered incidentally on imaging studies performed for other reasons. There is an age-dependent incidence of renal cysts, from about 5% in patients younger than 30 to almost one third of those older than 60.[29] The differentiation of solid and cystic lesions is the first mandate because as many as two thirds of solid lesions are found to be malignant.[30] MRI is ideally suited for lesion evaluation and is often better than ultrasound, particularly for complex cystic lesions. Parameters being characterized include solid versus cystic, overall lesion complexity, lesion enhancement, involvement of renal vasculature and collecting system, and extension into perirenal tissues and organs. Diffusion-weighted MRI sequences are often useful as a means of further differentiating benign and malignant solid lesions.

MEASUREMENT OF GLOMERULAR FILTRATION RATE

Renal blood flow and split renal function can be evaluated by CT and MRI.[31-33] The attenuation of the accumulated contrast material within the kidney is directly proportional to the GFR. Taking into account the renal volume, the function of each kidney can be determined. Although both modalities yield similar information, MRI is used more in children and in patients with allergy to contrast agents. This technique has not yet gained full acceptance, and renal scintigraphy remains a widely used method for determination of renal function, as discussed later.

ANGIOGRAPHY

Angiography is now most often performed for therapeutic intervention, such as embolotherapy or angioplasty and stenting, preceded by diagnostic angiography to evaluate the renal arteries for possible stenosis (Fig. 5.30). With improved resolution and scanning techniques, CTA and MRA have replaced conventional angiography, even for detection of accessory renal arteries, which are often small and bilateral but a possible cause of hypertension. However, angiography remains the gold standard (reference) test for the diagnosis of renal artery stenosis and fibromuscular dysplasia. There also remains a role for diagnostic angiography in the evaluation of medium- and large-vessel vasculitis and detection of renal infarction.

The conventional angiogram is performed through arterial puncture, followed by catheter placement in the aorta. An abdominal aortogram is obtained to identify the renal arteries. Selective renal artery catheterization can be performed as necessary. Contrast is administered intra-arterially, and the images are obtained with conventional film or more often with DSA. Conventional angiography images are superior but require higher doses of contrast material and more radiation exposure. DSA uses computer reconstruction and manipulation to generate the images, with the advantage that previously administered and excreted contrast material and bones can be digitally removed to better visualize the renal vasculature. Angiography can cause contrast-induced nephropathy and cholesterol embolization (see Chapter 41). Pathologic evidence of cholesterol embolization is common, but clinically significant symptoms occur infrequently (1% to 2%).[34]

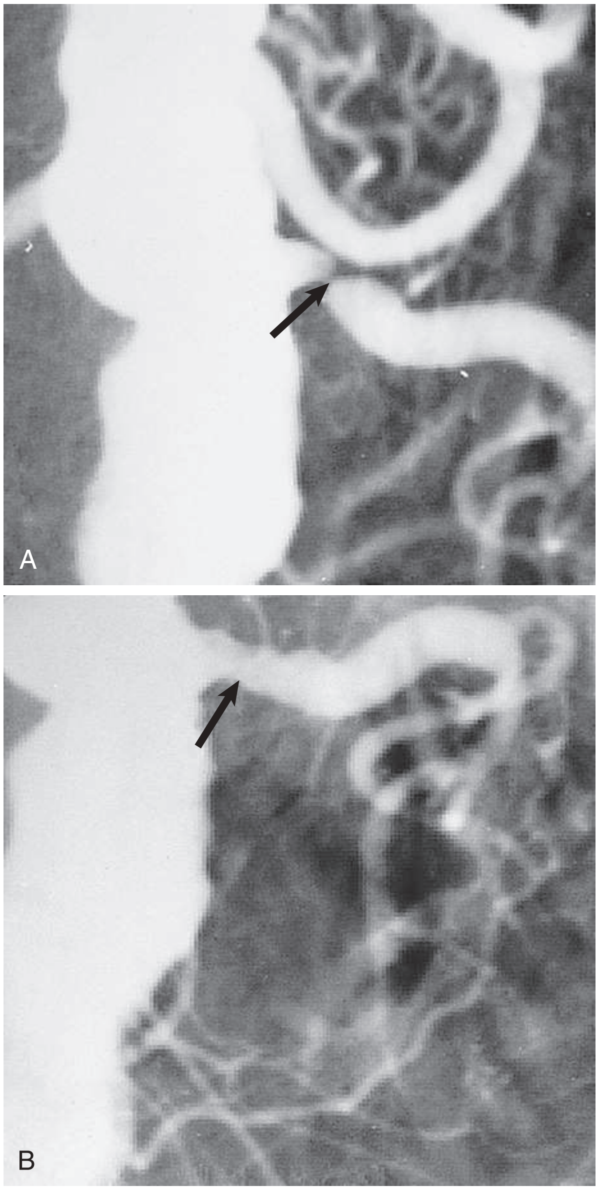

Fig. 5.30 **Left renal artery stenosis and angioplasty.** (A) Aortogram demonstrating a tight left renal artery stenosis *(arrow)*. (B) Postangioplasty image with marked improvement of the stenosis *(arrow)*. (Courtesy Dr. Harold Mitty.)

RENAL VENOGRAPHY

Catheter venography was once used for evaluation of renal vein and gonadal vein thrombosis and for renal vein sampling to measure renin, but has largely been replaced with Doppler ultrasound, followed by contrast-enhanced CT or MRI (see Fig. 5.28).

NUCLEAR SCINTIGRAPHY

Nuclear scintigraphy evaluates function and anatomy seen with other diagnostic imaging modalities. Radiotracers are designed to accumulate

TABLE 5.5 Choice of Radionuclide in Renal Imaging

Imaging Target	Radiotracer
Glomerular filtration rate	^{99m}Tc-DTPA
Glomerular filtration rate with renal impairment	^{99m}Tc-MAG3, ^{131}I-OIH
Effective renal plasma flow	^{99m}Tc-MAG3, ^{131}I-OIH
Renal scarring	^{99m}Tc-DMSA, ^{99}Tc-GH
Renal pseudotumor	^{99m}Tc-DMSA
Upper renal tract obstruction	^{99m}Tc-DTPA
Upper renal tract obstruction with renal impairment	^{99m}Tc-MAG3

^{99m}*Tc-DMSA,* Technetium 99m–labeled dimercaptosuccinate; ^{99m}*Tc-DTPA,* technetium 99m–labeled diethylenetriaminepentaacetic acid; ^{99m}*Tc GH,* technetium-99m glucoheptonate; ^{131}*I-OIH,* 131I orthoiodohippurate.

in tissues or organs on the basis of underlying functions unique to that organ. The gamma camera captures the photons from a radiotracer within the patient and generates an image. Single-photon emission computed tomography (SPECT) is a specialized type of imaging in which the emitted photons are measured at multiple angles, similar to CT, and multiplanar or even 3D images can be created. Three categories of radiotracers that differ in mode of renal clearance are used in renal imaging: glomerular filtration, tubular secretion, and tubular retention agents (Table 5.5).

Scintigraphy remains superior to the other imaging modalities in the evaluation of renal flow. It is the study of choice in the evaluation of renal transplants and functional obstruction, especially when ultrasound evidence is equivocal. Scintigraphy is also widely used to measure GFR, although CT or MRI are preferred in some centers.

Nuclear scintigraphy also provides an accurate assessment of renal function, used, for example, in estimating the reduction in renal function after nephron-sparing surgery. Although CT, MRI, and contrast-enhanced ultrasound are being assessed for the evaluation of renal function, scintigraphy remains the preferred modality. Both CTA and MRA have replaced nuclear scintigraphy in the evaluation of renal artery stenosis and benign renal masses, such as a column of Bertin. Nuclear medicine is still used to assess the functional significance of renal artery stenosis independent of anatomy.

Glomerular Filtration Agents

Glomerular filtration agents can be used to measure GFR. Technetium-99m–labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) is the most common glomerular agent used for imaging and also can be used for GFR calculation. In patients with poor renal function, renal imaging with tubular secretion agents such as mercaptoacetyltriglycine (^{99m}Tc-labeled MAG3) is superior to DTPA.[35,36]

Tubular Secretion Agents

^{99m}Tc-labeled MAG3 is handled primarily by tubular secretion and can be used to estimate effective renal plasma flow. The clearance rate for ^{99m}Tc-MAG3 is 340 ml/min.[37]

Tubular Retention Agents

Tubular retention agents include ^{99m}Tc-labeled dimercaptosuccinate (DMSA) and less often ^{99m}Tc-labeled glucoheptonate (GH). These agents provide excellent cortical imaging and can be used in suspected renal scarring or infarction, in pyelonephritis, and for clarification of renal pseudotumors. These agents bind with high affinity to sulfhydryl groups on the surface of proximal tubular cells.

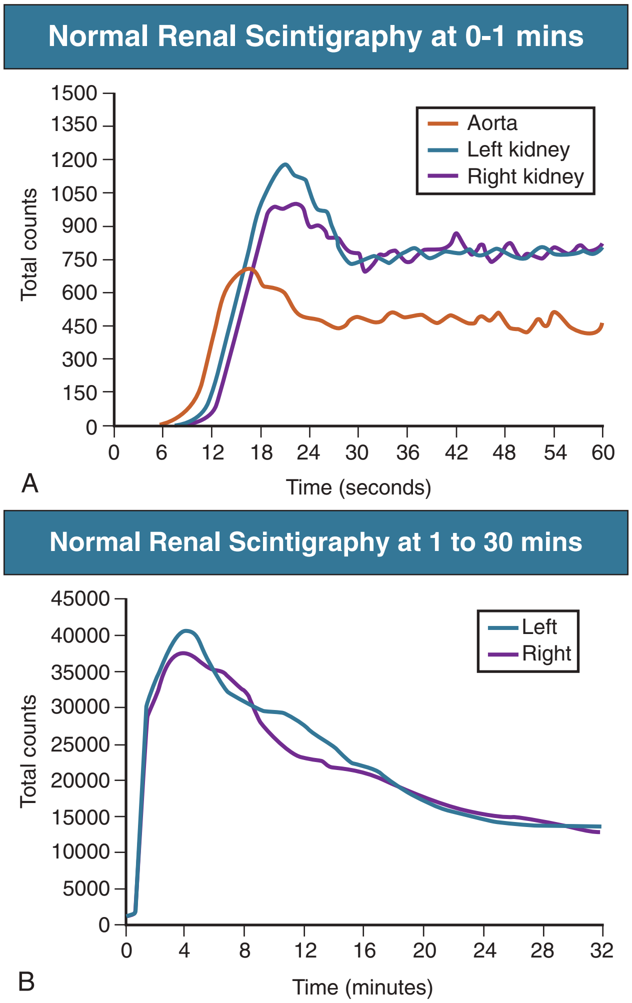

Fig. 5.31 Normal ^{99m}Tc-labeled DTPA study: time-activity curves. (A) Early (0 to 1 minute), showing renal blood flow. (B) Later (1 to 30 minutes), showing renal uptake and excretion of tracer. (Courtesy Dr. Chun Kim.)

Renogram

A renogram (or renal scintigram) is generated by scintigraphy and provides information about blood flow, renal uptake, and excretion. Time-activity graphs are produced that plot blood flow of the radiotracer into each kidney relative to the aorta. Peak cortical enhancement and pelvicalyceal clearance of the tracer are also plotted. DTPA or MAG3 can be used to generate the renogram. The relative radiotracer uptake can be measured and can provide split or differential information about renal function (Fig. 5.31).

The blood pool or flow images are obtained after bolus injection of the radiotracers. Images are obtained with the gamma camera every few seconds for the first minute. The second component of the renogram evaluates renal function by measuring radiotracer uptake and excretion by the kidney. In health, the peak renal cortical concentration occurs between 3 and 5 minutes after injection of tracer. Delayed transit of the isotope secondary to renal dysfunction (e.g., ATN or rejection) or obstructive uropathy will alter the curve of the renogram.

In cases of suspected obstructive uropathy, a diuresis renogram can be obtained. A loop diuretic is injected intravenously when radiotracer activity is present in the renal pelvis; a computer-generated washout curve is obtained. In patients with true obstruction, activity will remain

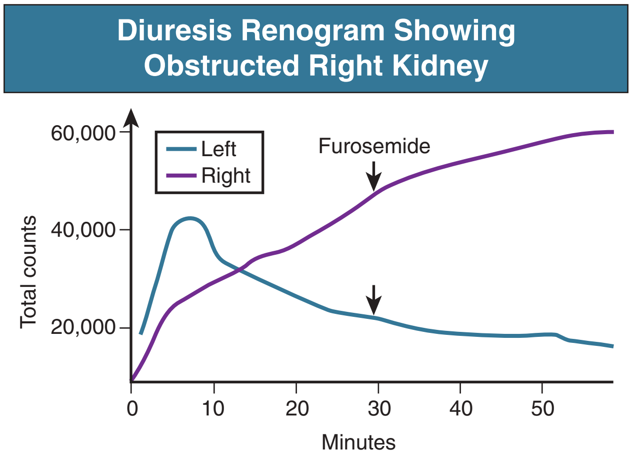

Fig. 5.32 Diuresis renogram showing obstructed right kidney. Isotope continues to accumulate in the right kidney despite intravenous furosemide (given at 30 minutes). Isotope excretion in the left kidney is normal.

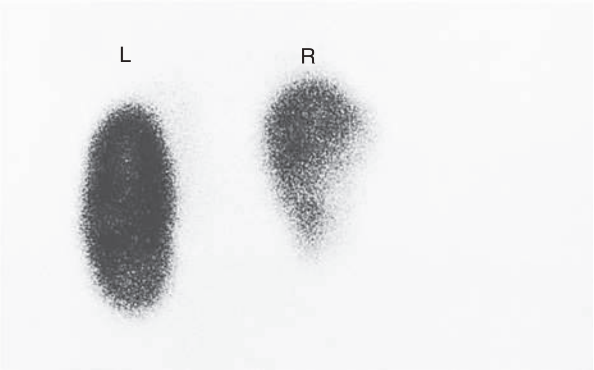

Fig. 5.33 Renal infarct. ^{99m}Tc-DMSA scan in a newborn with an infarct of the right lower pole *(R)* secondary to embolus from umbilical catheter. (Courtesy Dr. Chun Kim.)

in the renal pelvis, whereas it will quickly wash out in patients without an obstruction (Fig. 5.32; see also Fig. 58.12).

Cortical Imaging

Renal cortex imaging is performed with tubular retention agents, usually ^{99m}Tc-DMSA. Information about renal size, location, and contour can be obtained (Fig. 5.33). The cortical study is used most frequently for evaluation of renal scarring, particularly in children with reflux or chronic infections (see Chapter 61). It was formerly used for clarification of renal pseudotumors, such as a suspected column of Bertin, but this is now done with CT and MRI. Split renal function also can be determined from cortical imaging. Pinhole imaging (pinhole collimator magnifies the kidney to provide more anatomic detail than with planar imaging) and more recently SPECT have been found useful for detection of cortical defects caused by inflammation or scarring. Cortical imaging may be better than ultrasound in the evaluation of the young patient with urinary tract infection.[38] An infection, scar, or space-occupying lesion (tumor or cyst) will create a cortical defect, and correlation of the cortical defect site with other cross-sectional imaging should be performed to differentiate these entities.

Vesicoureteral Reflux

In children with suspected vesicoureteral reflux, a standard cystogram is obtained. If reflux is shown, follow-up is subsequently performed with radioisotope cystography, which exposes the child to a lower radiation dose and can be used to quantitate the bladder capacity when reflux occurs. The study is performed after instillation of technetium pertechnetate through a catheter into the bladder. Images are obtained during voiding.

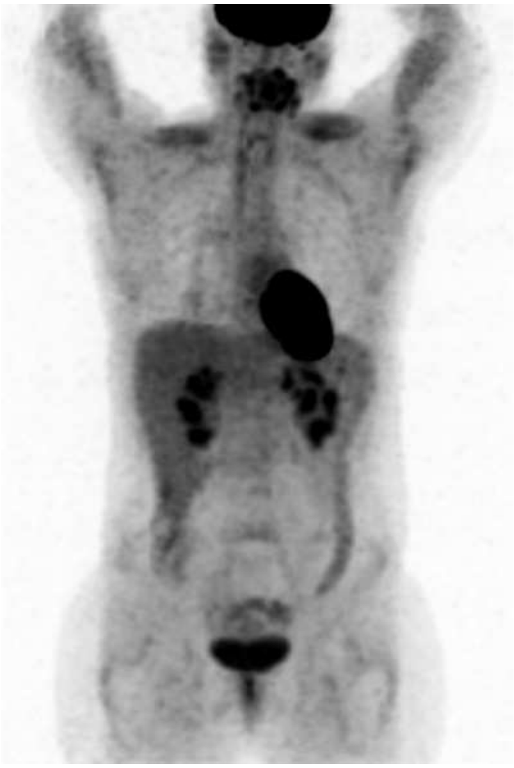

Fig. 5.34 Normal PET scan. Note normal radiotracer uptake in brain, heart, intestines, and liver, with normal excretion in kidneys.

Renal Transplant

Renal transplants are easily evaluated with scintigraphy. ^{99m}Tc-MAG3 is cleared through tubular secretion, which is maintained in most kidneys to a better degree than glomerular filtration in renal failure. Because many transplant recipients have declining renal function, ^{99m}Tc-MAG3 is the first-choice nuclide.

As with the normal kidneys, information about blood flow and function can be determined. Postoperative complications involving the artery, vein, or ureter are also well delineated. Nuclear imaging can help define ATN versus rejection in transplant patients with declining renal function. Ultrasound with Doppler evaluation of resistive index is often a complementary investigation, and choice of imaging modality in part depends on local expertise and preference.

POSITRON EMISSION TOMOGRAPHY

PET scanning uses radioactive positron emitters, most often fluorine-18–labeled fluorodeoxyglucose (FDG). The FDG is intravenously injected and distributes in the body according to metabolic activity. Any process, such as a tumor or infection, that causes increased metabolic activity will result in an area of increased uptake on the scan. These areas of abnormality need to be differentiated from normally hypermetabolic tissues, such as brain, liver, bone marrow, and to some extent heart and bowel (Fig. 5.34). Because FDG is cleared through the kidneys and excreted in the urine, which can obscure renal masses or infection, PET scanning has a limited role in renal imaging but is useful in the staging and follow-up of metastatic renal cancer.[39,40]

MOLECULAR IMAGING

With molecular imaging, radiology is moving from the identification of generic anatomy and nonspecific enhancement patterns to assessment of specific molecular differences in tissues and disease processes. Nuclear imaging presently is molecular based but still nonspecific (e.g., FDG-PET, renal DTPA). The newer focus of molecular imaging studies is dynamic processes such as metabolic activity, cell proliferation, apoptosis, receptor status, and antigen modulation. Typically, this involves imaging of biochemical and physiologic processes. Techniques are being developed with optical scanning, MRI, and ultrasound as well as with radionuclides.

Applications are established in clinical practice, particularly in oncology (e.g., CD20 imaging in lymphoma), and work is under way for renal-specific molecular imaging. For example, MR renal cell imaging may be available soon to help differentiate ATN from renal rejection and renal cell cancer from benign tumors.

RADIOLOGIC CONTRAST AGENTS

X-ray Contrast Agents

Contrast agents continue to have a role in many imaging techniques. A triiodinated benzene ring forms the chemical basis for CT intravascular contrast agents. Conventional contrast agents have high osmolality, about five times greater than plasma osmolality. Modifications to the benzene ring have led to newer contrast agents, including low-osmolar (which is still hyperosmolar compared with normal plasma) and more recently iso-osmolar nonionic agents, which are less nephrotoxic.

Intravascular iodinated contrast material rapidly passes through the capillary pores into the interstitial, extracellular space and into the renal tubules through glomerular filtration.[41] In patients with normal renal function, the kidneys eliminate almost all the contrast agent. Extrarenal routes of excretion include the liver and bowel wall and account for less than 1% of elimination, but this can increase when renal function is compromised. The half-time in patients with normal renal function is 1 to 2 hours, compared with 2 to 4 hours in dialysis patients.[42]

The overall incidence of contrast reactions for iodinated agents is 3.1% to 4.7%.[43-45] Of patients who have a contrast reaction, 20% will experience a reaction on reexposure that may be similar or worse. Contrast reactions can be anaphylactoid or chemotoxic reactions. The anaphylactoid reactions mimic an allergic response, whereas the chemotoxic reactions are believed to be mediated by direct toxic effects of the contrast material. The exact mechanism of contrast reaction is not known but is likely to be multifactorial. Formation of antigen-antibody complexes, complement activation, protein binding, and histamine release have been cited as possible mechanisms.

Reactions may be minor, intermediate, or severe. Minor reactions include heat sensation, nausea, and mild urticaria. Intermediate reactions include vasovagal reaction, bronchospasm, and generalized urticaria. Severe reactions include profound hypotension, pulmonary edema, and cardiac arrest. The use of low-osmolar or iso-osmolar contrast agents reduces the incidence of minor and intermediate contrast reactions. The reported incidence of death related to high-osmolar contrast agents is 1 in 40,000. Immediate treatment of reactions should be directed toward the symptoms. In patients with a history of contrast allergy, pretreatment on reexposure is usually recommended. Various protocols are used but typically include antihistamines and corticosteroids.

Contrast-Induced Nephropathy

Although acute kidney injury (AKI) associated with the administration of contrast material has been reported as the third most common cause of in-hospital AKI, recent data indicate this risk has been markedly overestimated.[45] The original studies and reports came from cardiac catheterization, and most follow-up studies have failed to provide adequate control groups. Patients with normal renal function rarely develop contrast-induced AKI. Even in patients with GFR less than 45 ml/min, this should not preclude the use of intravenous contrast if clinically necessary. Despite the concern for long-term complications, there is evidence suggesting that intravenous contrast carries little risk for dialysis dependence or mortality.[46] Although low risk, some caution should be taken in patients with preexisting renal impairment, and possible risk factors include preexisting renal impairment, diabetes, cardiovascular disease, use of diuretics, advanced age (>75 years), multiple myeloma in dehydrated patients, hypertension, uricosuria, and high-dose contrast. In end-stage renal disease, contrast administration may result in fluid overload because of thirst induced by the osmotic load.

Historically, there have been several theories for the pathogenesis of contrast-induced nephropathy, including renal vasoconstriction, perhaps mediated by alterations in nitric oxide, direct nephrotoxicity of the contrast agent, and possibly the effects of uricosuria (induced by the contrast agent). Most underlying cellular events were thought to occur within the first 60 minutes after administration of the contrast agent, with the greatest risk in the first 10 minutes.

There is some evidence that suggests that patients with diabetes and heart failure have altered nitric oxide metabolism, which may account for their reported increased risk for nephrotoxicity. Tubular injury produces oxygen free radicals, possibly from the vasoconstriction. In animal studies, reduction in antioxidant enzymes associated with hypovolemia contributes to the injury.[47] Hydration with normal saline or sodium bicarbonate is the mainstay of prevention; there is no substantial evidence that sodium bicarbonate offers any advantage over saline.[48] Oral *N*-acetylcysteine, a thiol-containing antioxidant, is often given in conjunction with hydration but has not proved consistently to be protective.[49]

An important differential diagnosis for contrast-induced nephropathy in patients with vascular disease undergoing catheter angiography is cholesterol embolization (see Chapter 41).

In patients with estimated GFR less than 60 ml/min/1.73 m^2, low-osmolar or iso-osmolar contrast agents can be used and the doses reduced. Repetitive, closely performed contrast studies should be avoided. In high-risk patients, alternative imaging studies—ultrasound, MRI, or noncontrast CT— always should be considered. Issues related to contrast-induced nephropathy is further discussed in Chapter 70.

Magnetic Resonance Contrast Agents

The two classes of MRI contrast agents are diffusion and nondiffusion agents. Diffusion agents, with appropriate timing of imaging sequences, can delineate vessels as well as parenchymal tissues. Nondiffusion agents remain in the bloodstream and are primarily useful for MRA. All the contrast agents are based on the paramagnetic properties of gadolinium. Gadolinium itself is highly toxic and is given only when it is tightly chelated (e.g., Gd-tetraazacyclododecane-1,4,7,10-tetraacetic acid [Gd-DOTA], Gd-diethylenetriamine penta-acetic acid [Gd-DTPA]).

Minor reactions such as headache and nausea occur in 3% to 5% of patients; but life-threatening reactions and nephrotoxic reactions are rare. In patients with renal impairment, a rare severe reaction, nephrogenic systemic fibrosis (NSF), has been described (see Chapter 87). The most recent guidelines confirm that MRI using high-risk gadolinium-containing contrast agents is contraindicated in patients with AKI and in those with chronic kidney disease stages 4 and 5 (i.e., GFR <30 ml/min/1.73 m^2),[27] because use of some agents has been linked to NSF. Cases of NSF are particularly associated with the linear structure chelates (such as gadodiamide, gadopentetate, and gadoversetamide). However, some linear chelates have a higher dissociation constant and to date have not been associated with NSF (such as gadobenate).[50] The newer macrocyclic gadolinium–containing contrast agents (e.g., gadoterate and gadoteridol) also have not been associated with NSF, even in patients with significantly impaired renal function (GFR <30 ml/min/1.73 m^2). Recently, studies have shown gadolinium deposition and retention in tissues, especially the brain, and especially after multiple injections of the contrast material. To date there are no documented adverse events associated with this retention. The choice of gadolinium agent in each case should be determined by discussion between the nephrologist and radiologist.

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SELF-ASSESSMENT QUESTIONS

1. On ultrasound, compared with the liver, the normal adult renal cortex is:
   - **A.** Isoechoic
   - **B.** Hyperechoic
   - **C.** Hypoechoic
   - **D.** Anechoic
2. Which of the following imaging modalities has the *least* chance of inducing contrast nephropathy?
   - **A.** CO_2 angiography
   - **B.** Contrast-enhanced CT
   - **C.** Contrast-enhanced MRI
   - **D.** Intravenous urography
3. The imaging modality that exposes the patient to the *least* radiation risk is:
   - **A.** CT urography
   - **B.** Dual-energy CT with virtual noncontrast imaging
   - **C.** Intravenous urography
   - **D.** Diffusion-weighted MRI
4. Which of the following is a mandatory reason that a renal MRI *cannot* be performed?
   - **A.** Cardiac pacemaker in a patient who is not pacemaker-dependent
   - **B.** Titanium total hip replacement less than 6 weeks old
   - **C.** When eGFR is 35 ml/min
   - **D.** History of cerebral aneurysm clip
5. Which of the following is usually the recommended *best* modality to evaluate for renal stones?
   - **A.** Noncontrast CT scan
   - **B.** MRI
   - **C.** Ultrasound
   - **D.** Nuclear medicine renogram

6

Renal Biopsy

Peter S. Topham, Yipu Chen

Percutaneous renal biopsy was first described in the early 1950s by Iversen and Brun[1] and Alwall.[2] These early biopsies were performed with the patient in the sitting position by use of a suction needle and intravenous urography for guidance. An adequate tissue diagnosis was achieved in less than 40% of these early cases. In 1954, Kark and Muehrcke[3] described a modified technique using the Franklin-modified Vim-Silverman needle, with the patient in a prone position and an exploring needle used to localize the kidney before insertion of the biopsy needle. These modifications yielded a tissue diagnosis in 96% of cases, and no major complications were reported. Since then, the renal biopsy procedure has remained largely unchanged, although the use of real-time ultrasound and refinement of biopsy needle design have offered significant improvements. Renal biopsy now provides a tissue diagnosis in more than 95% of patients, with a life-threatening complication rate of less than 0.1%.

INDICATIONS FOR RENAL BIOPSY

Ideally, analysis of a renal biopsy sample should identify a specific diagnosis, reflect the level of disease activity, and provide information to allow informed decisions about treatment. Although not always able to fulfill these criteria, the renal biopsy remains a valuable clinical tool and is particularly beneficial in the clinical situations discussed in Box 6.1.

Nephrotic Syndrome

Routine clinical and serologic examination of patients with nephrotic syndrome usually allows the clinician to determine whether a systemic disorder is present. In adults and in adolescents beyond puberty without systemic disease, the glomerular pathologic process cannot be predicted with confidence by noninvasive criteria alone; therefore a renal biopsy should be performed. In children age 1 year up to puberty, a presumptive diagnosis of minimal change disease (MCD) usually can be made. Renal biopsy is reserved for nephrotic children with atypical features, including microhematuria, reduced serum complement levels, renal impairment, and failure to respond to corticosteroids.

Acute Kidney Injury

In most patients with acute kidney injury (AKI) on a background of chronic kidney disease (CKD), the cause can be determined without a renal biopsy. Obstruction, reduced renal perfusion, and acute tubular necrosis (ATN) usually can be identified from other lines of investigation. In a minority of patients, however, a confident diagnosis cannot be made, and a renal biopsy should be urgently performed so appropriate treatment can be started before irreversible renal injury develops. This is particularly true in patients with AKI accompanied by an active urine sediment or with suspected drug-induced or infection-induced acute interstitial nephritis.

Systemic Disease Associated With Renal Dysfunction

Patients with diabetes mellitus and renal dysfunction do not usually require biopsy if the clinical setting is associated with diabetic nephropathy, as in isolated proteinuria, diabetes of long duration, or evidence of other microvascular complications. However, renal biopsy should be performed if the presentation is atypical, such as proteinuria associated with glomerular hematuria (acanthocytes), absence of retinopathy or neuropathy (in patients with type 1 diabetes), onset of proteinuria less than 5 years from documented onset of diabetes, uncharacteristically rapid change in renal function or renal disease of acute onset, or immunologic abnormalities.

Serologic testing for antineutrophil cytoplasmic antibody (ANCA) and for anti–glomerular basement membrane (anti-GBM) antibodies has allowed a confident diagnosis of renal small-vessel vasculitis or Goodpasture disease without invasive measures in most patients. Nonetheless, a renal biopsy still should be performed to confirm the diagnosis and clarify the extent of active inflammation versus chronic fibrosis and thus the potential for recovery. This information may be important in helping decide whether to initiate or continue immunosuppressive therapy, particularly when complications of immunosuppression are observed or expected.

Lupus nephritis usually can be diagnosed by noninvasive criteria such as autoantibodies, urine protein excretion, renal function, and urine sediment abnormalities. Some argue that this information can be used to gauge the severity of renal involvement and inform decisions about initial immunosuppressive treatment. However, a renal biopsy will clarify the underlying pathologic lesion, level of active inflammation, and extent of chronic fibrosis, thereby providing robust guidance for therapy.

The diagnosis of viral infection–related nephropathy (e.g., hepatitis B virus–associated membranous nephropathy) is suggested by the presence of the expected glomerular lesion in association with evidence of active viral infection. However, the identification of virus-specific protein or DNA or RNA in the renal biopsy tissue by immunopathologic and molecular pathologic techniques (e.g., in situ hybridization) can ensure the diagnosis.

Other systemic diseases, such as amyloidosis, sarcoidosis, and myeloma, can be diagnosed with renal biopsy. However, because these diagnoses often can be made by other investigative approaches, a renal biopsy is indicated only if the diagnosis remains uncertain or if knowledge of renal involvement would change management.

BOX 6.1 Indications for Renal Biopsy

Nephrotic Syndrome

- Routinely indicated in adults
- In prepubertal children, indicated only if clinical features atypical of minimal change disease present

Acute Kidney Injury

- Indicated if obstruction, reduced renal perfusion, and acute tubular necrosis have been ruled out

Systemic Disease With Renal Dysfunction

- Indicated in patients with small-vessel vasculitis, anti–glomerular basement membrane disease, and systemic lupus
- Indicated in patients with diabetes only if atypical features present

Non-Nephrotic Proteinuria

- May be indicated if proteinuria is greater than 1 g/24 h

Isolated Microscopic Hematuria

- Indicated only in unusual circumstances

Unexplained Chronic Kidney Disease

- May be diagnostic (e.g., identify immunoglobulin A nephropathy even in "end-stage kidney")

Familial Renal Disease

- Biopsy of one affected member may give diagnosis and minimize further investigation of family members

Renal Transplant Dysfunction

- Indicated if ureteral obstruction, urinary sepsis, renal artery stenosis, and toxic calcineurin inhibitor levels are not present

Renal Transplant Dysfunction

Renal allograft dysfunction in the absence of ureteral obstruction, urinary sepsis, renal artery stenosis, or toxic levels of calcineurin inhibitors requires a renal biopsy to determine the cause. In the early post-transplantation period, this is most useful in differentiating acute rejection from ATN and the increasingly prevalent BK virus nephropathy. Later, renal biopsy can differentiate acute rejection from chronic allograft nephropathy, recurrent or de novo glomerulonephritis (GN), and calcineurin inhibitor toxicity. The accessible location of the renal transplant in the iliac fossa facilitates biopsy of the allograft and allows repeated biopsies when indicated. This has encouraged many units to adopt a policy of *protocol* (surveillance) biopsies to detect subclinical acute rejection and renal scarring and to guide the choice of immunosuppressive therapy (see Chapter 104).

Non-Nephrotic Proteinuria

The value of renal biopsy in patients with non-nephrotic proteinuria is debatable. All conditions that result in nephrotic syndrome can cause non-nephrotic proteinuria, except for MCD. However, the benefit of specific treatment with corticosteroids and other immunosuppressive agents in these patients probably does not justify the risk for significant drug-related side effects. In patients with proteinuria of more than 1 g/day, generic treatment with strict blood pressure control and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) reduces proteinuria and reduces the risk for development of progressive renal dysfunction (see Chapter 79). Nonetheless, although the renal biopsy may not lead to an immediate change in management, it can be justified in these circumstances if it will provide prognostic information, identify a disease for which a different therapeutic approach is indicated, or provide clinically important information about the future risk for disease recurrence after renal transplantation.

Isolated Microhematuria

Patients with microhematuria initially should be evaluated to identify structural lesions such as renal stones or renal and urothelial malignant neoplasms if they are older than 40 years. The absence of a structural lesion suggests that the hematuria may have a glomerular source. Biopsy studies have identified glomerular lesions in up to 75% of biopsies.[4] In all series, immunoglobulin A (IgA) nephropathy is the most common lesion, followed by thin basement membrane nephropathy and normal kidney morphology. In the absence of nephrotic proteinuria, renal impairment, or hypertension, the prognosis for patients with these conditions is excellent, and because specific therapies are not available, renal biopsy is not necessary and patients require only follow-up. Biopsy should be performed only if the result would reassure the patient, avoid repeated urologic investigations, or provide specific information, as in the evaluation of potential living kidney donors, in familial hematuria, or for life insurance and employment purposes.

Unexplained Chronic Kidney Disease

Renal biopsy can be informative in the patient with unexplained chronic renal impairment and normal-sized kidneys, because in contrast to AKI, it is often difficult to determine the underlying cause with clinical criteria alone. Studies have shown that in these patients, the biopsy will demonstrate disease that was not predicted in almost half.[5] However, if both kidneys are small (<9 cm on ultrasound), the risks of biopsy are increased and the diagnostic information may be limited by extensive glomerulosclerosis and tubulointerstitial fibrosis. In this setting, however, immunofluorescence studies still may be informative. For example, glomerular IgA deposition may be identified despite advanced structural damage.

Familial Renal Disease

A renal biopsy can be helpful in the investigation of patients with a family history of renal disease. A biopsy performed in one affected family member may secure the diagnosis for the whole family and avoid the need for repeat investigation. Conversely, a renal biopsy may unexpectedly identify inherited disease, thereby stimulating evaluation of other family members.

Role of Repeat Renal Biopsy

In some patients, a repeat biopsy may be indicated. For example, the pathologic changes in lupus nephritis may evolve, necessitating treatment adjustment. In addition, corticosteroid-resistant, corticosteroid-dependent, or frequently relapsing MCD may represent a missed diagnosis of focal segmental glomerulosclerosis (FSGS), which may be detected on repeat biopsy. Some nephrologists think repeat biopsy in patients who have had aggressive immunosuppressive therapy of crescentic GN can help determine the most appropriate next line of therapy.

VALUE OF RENAL BIOPSY

Biopsy Adequacy

In the assessment of a renal biopsy, the number of glomeruli in the sample is the major determinant of whether the biopsy will be diagnostically informative.

For a focal entity such as FSGS, the diagnosis could be made on a biopsy specimen containing a single glomerulus that contains a typical sclerosing lesion. However, the probability that FSGS is not present in a patient with nephrotic syndrome and minimal changes on the biopsy specimen depends on the actual proportion of abnormal glomeruli in the kidney and the number of glomeruli obtained in the biopsy specimen. For example, if 20% of glomeruli in the kidney have sclerosing lesions and five glomeruli are sampled, there is a 35% chance that all the glomeruli in the biopsy specimen will be normal and the biopsy will miss the diagnosis. By contrast, in the same kidney, if 10 or 20 glomeruli are sampled, the chance of obtaining all normal glomeruli is reduced to 10% and less than 1%, respectively, and the biopsy is more discriminating. This argument assumes that any segmental lesions present in the biopsy specimen are actually identified; this requires the biopsy specimen to be sectioned at multiple levels.

Unless all glomeruli are affected equally, the probability that the observed involvement in the biopsy specimen accurately reflects true involvement in the kidney depends not only on the number of glomeruli sampled but also on the proportion of affected glomeruli (Fig. 6.1). For example, in a biopsy specimen containing 10 glomeruli, of which 3 are abnormal (30%), there is a 95% probability that the actual glomerular involvement is between 7% and 65%. In the same kidney, if the biopsy specimen contained 30 glomeruli with 30% being abnormal, the 95% confidence intervals are narrowed to 15% and 50%.

Therefore the interpretation of the biopsy needs to take into account the number of glomeruli obtained. A typical biopsy sample will contain 10 to 15 glomeruli and will be diagnostically useful. Nonetheless, it must be appreciated that because of the sampling issue, a biopsy sample of this size will occasionally be unable to diagnose focal diseases and at best will provide imprecise guidance on the extent of glomerular involvement.

An adequate biopsy also should provide samples for immunohistologic examination and electron microscopy (EM). Immunohistologic examination is performed by either immunofluorescence on frozen material or immunoperoxidase on fixed tissue, according to local protocols and expertise. It is helpful for the biopsy cores to be viewed under an operating microscope immediately after being taken to ensure that they contain cortex and that when the cores are divided, the immunohistologic and EM samples both contain glomeruli.

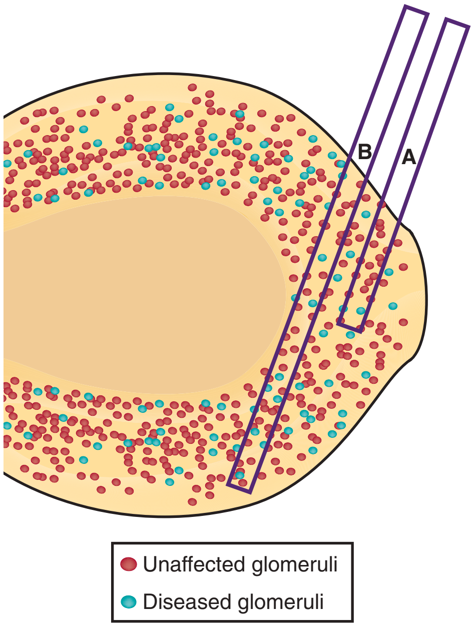

Fig. 6.1 Effect of sampling on renal biopsy interpretation. Red dots represent unaffected glomeruli. Blue dots represent diseased glomeruli. The size of the biopsy core affects the probability that the observed glomerular involvement is a true reflection of involvement in the whole kidney. In a biopsy specimen containing 10 glomeruli (core A), of which three are abnormal (30%), there is a 95% probability that the actual glomerular involvement is between 7% and 65%. In the same kidney, if the biopsy specimen contained 30 glomeruli with 30% being abnormal *(core B),* the 95% confidence intervals are narrowed to 15% and 50%.

If the material obtained for a complete pathologic evaluation is insufficient, a discussion with the pathologist should address how best to proceed before the tissue is placed in fixative, so the material can be processed in a way that will provide maximum information for the specific clinical scenario. For example, if the patient has heavy proteinuria, most information will be gained from EM because it can demonstrate podocyte foot process effacement, focal sclerosis, electron-dense deposits of immune complexes, and the organized deposits of amyloid.

If a sample is supplied for immunofluorescence microscopy but contains no glomeruli, it may be possible to reprocess the paraffin-embedded sample to identify immune deposits by immunoperoxidase or immunofluorescence techniques.

Is Renal Biopsy a Necessary Investigation?

The role of the renal biopsy has been much debated. Early studies suggested that renal biopsy provided diagnostic clarity in most patients, but that this information did not alter management, except for those with heavy proteinuria or systemic disease. More recent prospective studies have suggested that the renal biopsy identifies a diagnosis different from that predicted on clinical grounds in 50% to 60% of patients and leads to a treatment change in 20% to 50%.[6] This is particularly apparent in patients with heavy proteinuria or AKI, more than 80% of whom have biopsy findings that alter their management.[7]

PREBIOPSY EVALUATION

The prebiopsy evaluation identifies issues that may compromise the safety and success of the procedure (Fig. 6.2). It will determine whether the patient has two normal-sized unobstructed kidneys, sterile urine, controlled blood pressure, and no bleeding diathesis. A thorough history should be taken to identify evidence of a bleeding diathesis, such as previous prolonged surgical bleeding, spontaneous bleeding, family history of bleeding, and ingestion of medication that increases bleeding risk, including antiplatelet agents and warfarin.

An ultrasound scan should be performed to assess kidney size and identify significant anatomic abnormalities, such as solitary kidney, polycystic or simple cystic kidneys, malpositioned kidneys, horseshoe kidneys, small kidneys, and hydronephrosis.

The value of the *bleeding time* in patients undergoing renal biopsy is controversial. The predictive value of the bleeding time for postrenal biopsy bleeding has never been prospectively tested. Retrospective studies, however, demonstrated a threefold to fivefold increase in bleeding complications after renal biopsy in patients with prolonged bleeding time. Prospective studies of percutaneous liver biopsy patients showed a fivefold increase in bleeding complications in those with uncorrected bleeding times.[8] A consensus document concluded that the bleeding time is a poor predictor of postsurgical bleeding, but it does correlate with clinical bleeding episodes in uremic patients.[9]

Several approaches to the management of bleeding risk have been adopted. First, all subjects undergoing biopsy should discontinue any agent that can prolong bleeding, including aspirin (7 days before biopsy), clopidogrel (7 days), warfarin (7 days), nonsteroidal antiinflammatory drugs (NSAIDs; 24 hours), and subcutaneous heparin (24 hours). Many centers measure the prebiopsy bleeding time and administer 1-desamino-8-D-arginine vasopressin (desmopressin, DDAVP; 0.4 µg/kg intravenously 2 to 3 hours before biopsy) if the bleeding time is prolonged

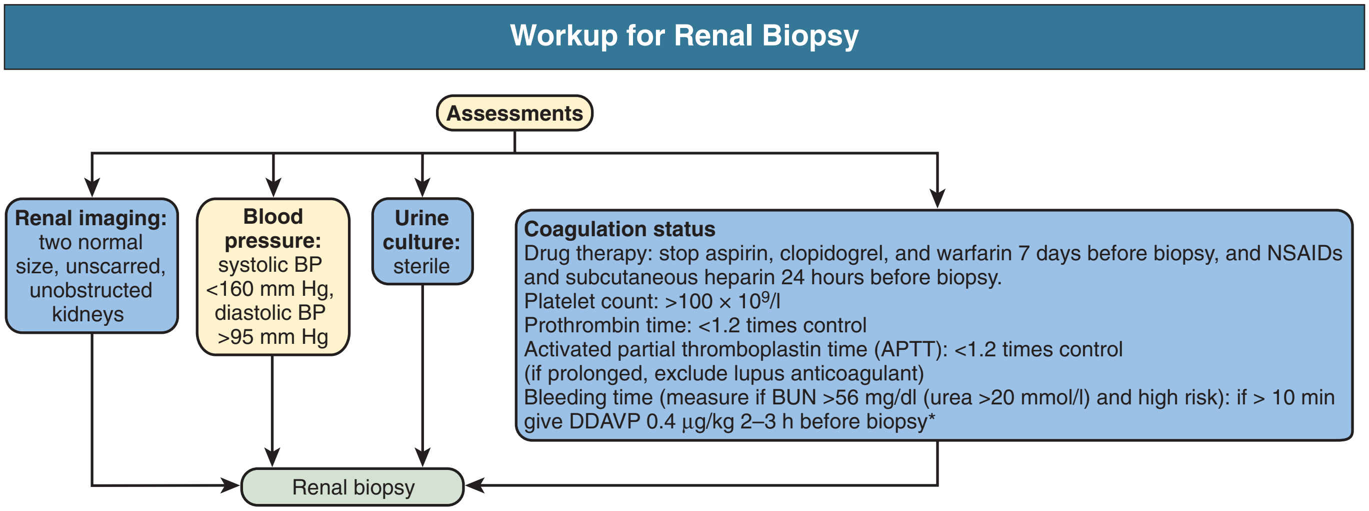
Workup for Renal Biopsy
Assessments
Renal imaging: two normal size, unscarred, unobstructed kidneys
Blood pressure: systolic BP <160 mm Hg, diastolic BP >95 mm Hg
Urine culture: sterile
Coagulation status
Drug therapy: stop aspirin, clopidogrel, and warfarin 7 days before biopsy, and NSAIDs and subcutaneous heparin 24 hours before biopsy.
Platelet count: >100 × 10⁹/l
Prothrombin time: <1.2 times control
Activated partial thromboplastin time (APTT): <1.2 times control (if prolonged, exclude lupus anticoagulant)
Bleeding time (measure if BUN >56 mg/dl (urea >20 mmol/l) and high risk): if > 10 min give DDAVP 0.4 µg/kg 2–3 h before biopsy*
Renal biopsy

Fig. 6.2 Workup for renal biopsy. *BUN,* Blood urea nitrogen; *DDAVP,* desmopressin; *NSAID,* nonsteroidal antiinflammatory drug. *Some centers administer DDAVP in high risk cases without measuring bleeding time (see text).

beyond 10 minutes. Another approach is not to measure the bleeding time but routinely administer DDAVP to patients with significant renal impairment (blood urea nitrogen level >56 mg/dl [urea >20 mmol/l] or serum creatinine >3 mg/dl [250 µmol/l]). Platelet transfusion also can be used to reverse clopidogrel-induced platelet dysfunction when the renal biopsy is urgent.

The routine use of desmopressin in low-risk patients (estimated GFR >60 ml/min; blood pressure <140/90 mm Hg; normal coagulation parameters) has been shown to reduce the risk for hematoma formation after biopsy compared with placebo (13.7% vs. 30.5%, respectively).[10] The hematomas were clinically silent, however, and no patient in either group had macrohematuria or required a transfusion. The study was also unable to determine the risks related to DDAVP (thrombosis or hyponatremia). Therefore use of DDAVP prophylaxis in all patients undergoing renal biopsy cannot be recommended.

The use of thromboelastography (TEG) has been described in the patient undergoing renal transplant biopsy.[11] TEG provides an overall measure of the coagulation, platelet, and fibrinolytic systems in one assay and thus may be more predictive of clinical bleeding. In this study, most bleeding episodes were associated with normal clotting test results, but TEG was the only assay associated with an increased risk for post-biopsy bleeding. The role of TEG in the patient undergoing native kidney biopsy requires further evaluation.

Contraindications to Renal Biopsy

The contraindications to percutaneous renal biopsy are listed in Table 6.1. The major contraindication is a bleeding diathesis. If the disorder cannot be corrected and the biopsy is deemed indispensable, alternative approaches can be used, such as open biopsy, laparoscopic biopsy, or transvenous (usually transjugular) biopsy. Inability of the patient to comply with instructions during renal biopsy is another major contraindication. Sedation or, in extreme cases, general anesthesia may be necessary.

Hypertension (>160/95 mm Hg), hypotension, perinephric abscess, pyelonephritis, hydronephrosis, severe anemia, large renal tumors, and cysts are relative contraindications to renal biopsy. When possible, these should be corrected before the biopsy is undertaken.

TABLE 6.1 Contraindications to Renal Biopsy

Kidney Status	Patient Status
Multiple cysts	Uncontrolled bleeding diathesis
Solitary kidney	Uncontrolled blood pressure
Acute pyelonephritis	Uremia
Perinephric abscess	Obesity
Renal neoplasm	Uncooperative patient

Most contraindications are relative rather than absolute. Clinical circumstances that necessitate urgent renal biopsy may be overridden, except for uncontrolled bleeding diathesis.

The presence of a solitary functioning kidney has been considered a contraindication to percutaneous biopsy, and some argue that the risk of biopsy is reduced by direct visualization at open biopsy. However, the postbiopsy nephrectomy rate of 1/2000 to 1/5000 is comparable to the mortality rate associated with the general anesthetic required for an open procedure. Therefore, in the absence of risk factors for bleeding, percutaneous biopsy of a solitary functioning kidney can be justified.

RENAL BIOPSY TECHNIQUE

Percutaneous Renal Biopsy

Native Renal Biopsy

At our centers, the kidney biopsy is performed by nephrologists with continuous (real-time) ultrasound guidance and disposable automated biopsy needles. We use 16-gauge needles as a compromise between the greater tissue yield of larger needles and the trend toward fewer bleeding complications of smaller needles. For most patients, premedication or sedation is not required. The patient is prone, and a pillow is placed under the abdomen at the level of the umbilicus to straighten the lumbar spine and splint the kidneys. Fig. 6.3 shows the anatomic relationships of the left kidney. Ultrasound is used to localize the lower pole of the kidney where the biopsy will be performed (usually the left kidney). An indelible pen mark is used to indicate the point of entry of the biopsy needle. The skin is sterilized with povidone-iodine (Betadine) or chlorhexidine solution. A sterile fenestrated sheet is placed over the area to maintain a sterile field. Local anesthetic (2% lidocaine [lignocaine]) is infiltrated into the skin at the point previously marked.

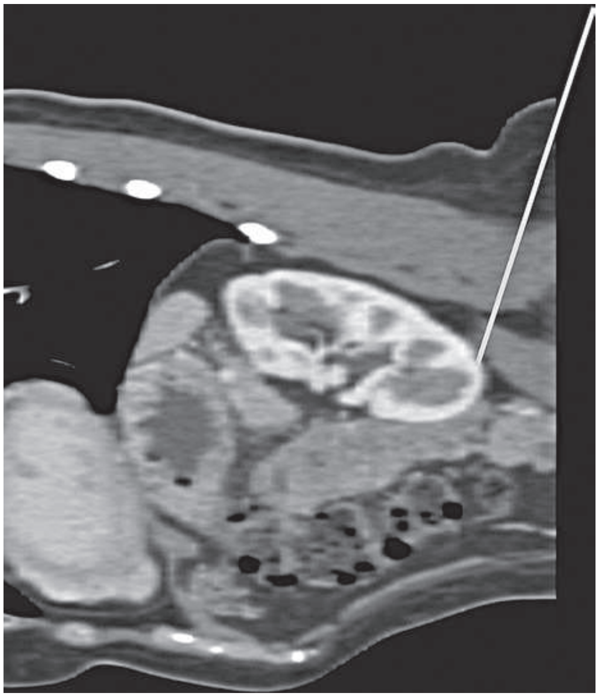

Fig. 6.3 Computed tomography through the left kidney. The angle of approach of the needle is demonstrated. Note the relative adjacency of the lower pole of the kidney to other structures, particularly the large bowel.

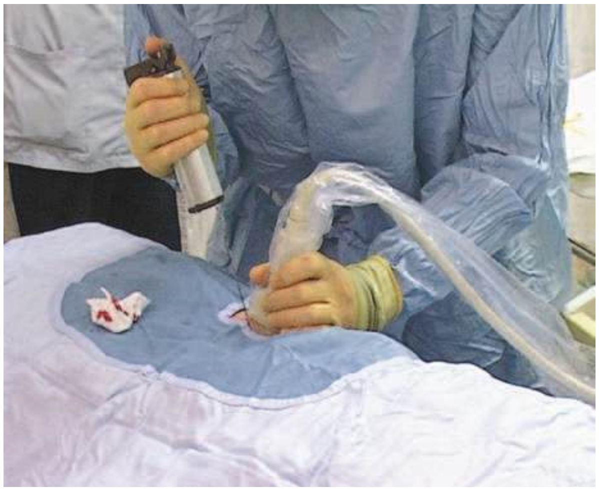

Fig. 6.4 Renal biopsy procedure. The biopsy needle is introduced at an angle of approximately 70 degrees to the skin and is guided by continuous ultrasound. The operator is shown wearing a surgical gown. This is not strictly necessary; sterile gloves and maintenance of a sterile field are sufficient.

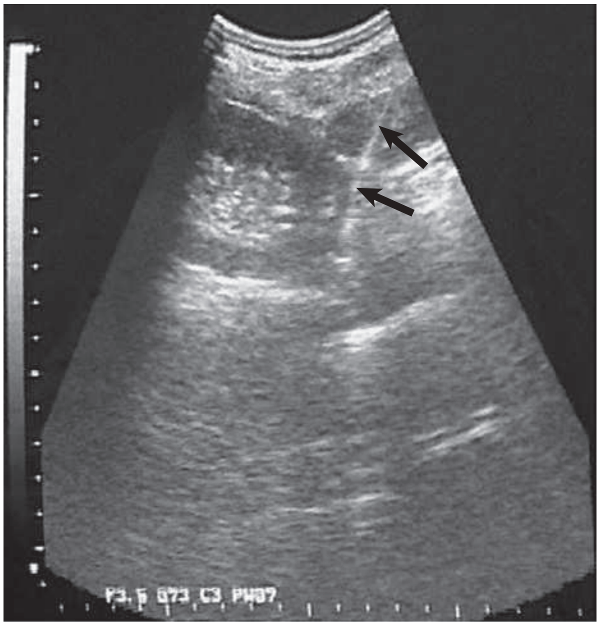

Fig. 6.5 Renal biopsy imaging. Ultrasound scan shows the needle entering the lower pole of the left kidney. *Arrows* indicate the needle track, which appears as a fuzzy white line.

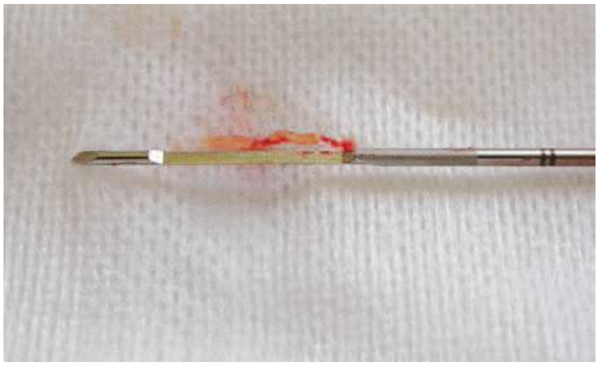

Fig. 6.6 Renal biopsy sample. A core of renal tissue is demonstrated in the sampling notch of the biopsy needle.

While the anesthetic takes effect, the ultrasound probe is covered in a sterile sheath. Sterile ultrasound jelly is applied to the skin, and, under ultrasound guidance, a 10-cm, 21-gauge needle is guided to the renal capsule and further local anesthetic infiltrated into the perirenal tissues, then along the track of the needle on withdrawal. A stab incision is made through the dermis to ease passage of the biopsy needle. This is passed under ultrasound guidance to the kidney capsule (Fig. 6.4). As the needle approaches the capsule, the patient is instructed to take a breath until the kidney is moved to a position such that the lower pole rests just under the biopsy needle, and then to stop breathing. The biopsy needle tip is advanced to the renal capsule, and the trigger mechanism is released, firing the needle into the kidney (Fig. 6.5). The needle is immediately withdrawn, the patient is asked to resume breathing, and the contents of the needle are examined (Fig. 6.6). We examined the tissue core under an operating microscope to ensure that renal cortex has been obtained (Fig. 6.7). A second pass of the needle is usually necessary to obtain additional tissue for immunohistologic examination and EM. If insufficient tissue is obtained, further passes of the needle are made. In our experience, however, passing the needle more than four times is associated with a modest increase in the postbiopsy complication rate.

Once sufficient renal tissue has been obtained, the skin incision is dressed and the patient rolled directly into bed for observation.

No single fixative has been developed that allows good-quality light microscopy, immunofluorescence, and EM to be performed on the same sample. Therefore the renal tissue is often divided into three samples and placed in formalin for light microscopy, normal saline for subsequent snap-freezing in liquid nitrogen for immunofluorescence, and glutaraldehyde for EM. Some centers can produce satisfactory light

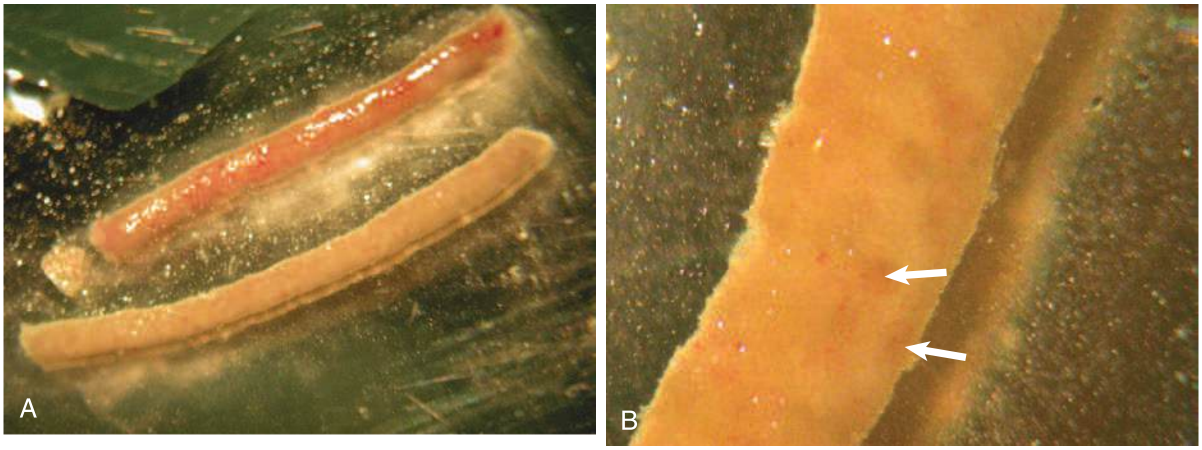

Fig. 6.7 **Renal biopsy micrographs.** Appearance of renal biopsy material under the operating microscope. (A) Low-power view shows two good-sized cores. (B) Higher magnification view shows the typical appearance of glomeruli *(arrows)*.

microscopy, immunohistochemistry, and EM on formalin-fixed biopsy material, although this depends on the expertise of individual laboratories.

The percutaneous renal biopsy technique has several variations. Whereas most biopsies are guided by ultrasound, some operators use ultrasound only to localize the kidney and determine the depth and angle of approach of the needle and perform the biopsy without further ultrasound guidance. The success and complication rates appear to be no different from those seen with continuous ultrasound guidance. For technically challenging biopsies, computed tomography (CT) can be used to guide the biopsy needle.

For obese patients and patients with respiratory conditions who find the prone position difficult, the supine anterolateral approach recently has been described.[12] Patients lie supine with the flank on the side to be sampled elevated by 30 degrees with towels under the shoulder and buttocks. The biopsy needle is inserted through the inferior lumbar triangle, bounded by the latissimus dorsi muscle, 12th rib, and iliac crest. This technique provides good access to the lower pole of the kidney, is better tolerated than the prone position by these patients, and has a diagnostic yield and safety profile comparable to that of the standard technique for native renal biopsy.

Renal Transplant Biopsy

Biopsy of the transplant kidney is facilitated by the proximity of the kidney to the anterior abdominal wall and the lack of movement on respiration. It is performed under real-time ultrasound guidance with use of an automated biopsy needle. It is important to confirm that the transplanted kidney is in the normal extraperitoneal position—occasionally it will be intraperitoneal (simultaneous pancreas and kidney transplants in particular), and bowel injury becomes a potential hazard. In most patients, the renal transplant biopsy is performed to identify the cause of acute allograft dysfunction. In these circumstances, the goal is to identify acute rejection, and therefore the diagnosis can be made on a formalin-fixed sample alone for light microscopy. If vascular rejection is suspected, a snap-frozen sample for C4d immunostaining also should be obtained (although some laboratories can detect C4d on formalin-fixed material). If recurrent or de novo GN is suspected in patients with chronic allograft dysfunction, additional samples for EM and immunohistologic examination should be collected.

Postbiopsy Monitoring

After the biopsy, the patient is placed supine and subjected to strict bed rest for 6 to 8 hours. The blood pressure is monitored frequently, the urine examined for visible hematuria, and the skin puncture site examined for excessive bleeding. If there is no evidence of bleeding after 6 hours, the patient is sat up in bed and subsequently allowed to ambulate. If visible hematuria develops, bed rest is continued until the bleeding settles. We advise minimal activity for 48 hours after biopsy and avoidance of contact sports and activities requiring straining for a total of 2 weeks.

Conventionally, patients have been observed for complications in the hospital for 24 hours after biopsy. However, outpatient (day-case) renal biopsy with same-day discharge after 6 to 8 hours of observation has become increasingly popular for both native and renal transplant biopsies. Largely driven by financial and resource implications of overnight hospital admission, this has been justified by the perception that the significant complications of renal biopsy will become apparent during this shortened period of observation. This view has been challenged by a study of 750 native renal biopsies, which showed that only 67% of major complications, defined as those that required either a blood transfusion or an invasive procedure or resulted in urinary tract obstruction, septicemia, or death, were apparent by 8 hours after biopsy.[13] These authors concluded that the widespread application of an early discharge policy after renal biopsy is not in the patient's best interest and that a 24-hour observation period is preferable.

In the author's UK center, approximately half of renal biopsies are outpatient procedures. The patient population is selected to avoid those with the highest risk for complications, including impaired renal function (estimated GFR <30 ml/min), small kidneys, and uncontrolled hypertension. In addition, we require that the patient not be alone at home for at least one night after the biopsy. This selection policy has proved to be safe. Of 429 outpatient biopsies performed in our unit, 6% developed a self-limited postbiopsy complication within 6 hours that required a short hospital admission. Five patients returned after same-day discharge with biopsy-related complications, one with visible hematuria at 24 hours and four with loin pain between 3 and 5 days after biopsy. All patients recovered with conservative management. We believe that outpatient renal biopsy is acceptably safe when a low-risk patient group is selected.

A study investigated whether ultrasound 1 hour after biopsy is able to predict bleeding complications.[14] The absence of hematoma was predictive of an uncomplicated course, but the identification of hematoma was not reliably predictive of a significant biopsy complication; identification of hematoma at 1 hour had a 95% negative predictive value and 43% positive predictive value. The role of this imaging in the wider clinical setting remains to be determined given the additional expense of routine postbiopsy ultrasound.

Alternatives to the Percutaneous Approach

When the percutaneous approach is contraindicated, other approaches to renal biopsy have been described. The choice of technique depends on the safety, morbidity, recovery period, and adequacy of the technique, but mainly on the local expertise available.

Transvenous (Transjugular or Transfemoral) Renal Biopsy

Transvenous sampling of the kidney is theoretically safer than the percutaneous approach because the needle passes from the venous system into the renal parenchyma and is directed away from large blood vessels. Any bleeding that occurs should be directed back into the venous system, and if capsular perforation develops, significant bleeding points can be immediately identified and controlled by coil embolization. Others argue that coil embolization of the punctured vein is unhelpful because significant bleeding into a perirenal hematoma or the urine indicates an arterial breach that requires selective angiography and arterial embolization.

Transvenous renal biopsy cannot be regarded as routine because it involves specialist skills and additional time and expense compared with the percutaneous approach. The main indication for this approach is an uncontrollable bleeding diathesis. It also has been advocated for patients receiving artificial ventilation in the intensive care unit; the need to obtain tissue from more than one organ, including the kidney, liver, or heart; large-volume ascites that precludes the prone position; uncontrolled hypertension; morbid obesity; severe respiratory insufficiency; solitary kidney; failed percutaneous approach; and coma.

The patient lies supine, and the right internal jugular vein is cannulated. A guidewire is passed into the inferior vena cava (IVC), and a catheter is passed over the guidewire and selectively into the right renal vein, which is shorter and enters the IVC at a more favorable angle than the left renal vein. A sheath is passed over the catheter to a suitable peripheral location in the kidney with the aid of contrast enhancement. Finally, the biopsy device (usually a side-cut biopsy needle system) is passed through the sheath and samples are taken. Contrast is then injected into the biopsy track to identify capsular perforation, and embolization coils are inserted if brisk bleeding is identified.

The quality of renal tissue obtained by transjugular biopsy is variable, although studies report diagnostic yields of more than 90%.[15] The complication rate appears comparable to that seen with percutaneous renal biopsy, which is reassuring given that these are high-risk patients.

Open Renal Biopsy

Open renal biopsy has been established as a safe alternative to percutaneous biopsy when uncorrectable contraindications exist. In a series of 934 patients, tissue adequacy was 100% with no major complications.[16] This is an effective approach with minimal postprocedure complications, but the risk of general anesthesia and the delayed recovery time have prevented its widespread adoption. Open biopsy still may be performed, however, when a renal biopsy is required in patients who are otherwise undergoing abdominal surgery.

Laparoscopic Renal Biopsy

Laparoscopic renal biopsy requires general anesthesia and two laparoscopic ports in the posterior and anterior axillary lines to gain access to the retroperitoneal space. Laparoscopic biopsy forceps are used to obtain cortical biopsy samples, and the biopsy sites are coagulated with laser and packed to prevent hemorrhage. In the largest study of laparoscopic renal biopsy, adequate tissue was obtained in 96% of 74 patients.[17] Significant bleeding occurred in three patients, the colon was injured in one, and a biopsy was performed inadvertently on the spleen and liver, respectively, in two others. Inadvertent biopsy was subsequently averted using intraoperative ultrasound to define the anatomy in difficult cases.

COMPLICATIONS OF RENAL BIOPSY

The complication rates compiled from large series of renal biopsies are shown in Table 6.2.[18]

Pain

Patients should be informed about the inevitable dull ache around the needle entry site when the local anesthetic wears off after renal biopsy. Simple analgesia with acetaminophen (paracetamol) or acetaminophen-codeine combinations usually suffices. More severe pain in the loin or abdomen on the side of the biopsy suggests significant perirenal hemorrhage. Opiates may be necessary for pain relief, with appropriate investigation to clarify the severity of the bleed. Patients with visible hematuria may develop clot colic and describe the typical severe pain associated with ureteral obstruction.

Hemorrhage

A degree of perirenal bleeding accompanies every renal biopsy. The mean decrease in hemoglobin after a biopsy is approximately 1 g/dl.[19] Significant perirenal hematomas are almost invariably associated with severe loin pain. Both visible hematuria and painful hematoma are seen in 3% to 4% of patients after biopsy. The initial management is strict bed rest and maintenance of normal coagulation indices. If bleeding is brisk and associated with hypotension or prolonged and fails to settle with bed rest, renal angiography should be performed to identify the source of bleeding. Coil embolization can be performed during the same procedure, and this has largely eliminated the need for open surgical intervention and nephrectomy.

Arteriovenous Fistula

Most postbiopsy arteriovenous fistulas are detected by Doppler ultrasound or contrast-enhanced CT and, when looked for specifically, can be found in as many as 18% of patients. Because most are clinically silent and more than 95% resolve spontaneously within 2 years, fistulas should not be routinely sought. In a small minority of patients, arteriovenous fistulas can lead to visible hematuria (typically recurrent, dark red, and often with blood clots), hypertension, and renal impairment, which requires embolization.

Other Complications

A variety of rare complications have been reported, including biopsy performed on other organs (liver, spleen, pancreas, bowel, gallbladder), pneumothorax, hemothorax, calyceal-peritoneal fistula, dispersion of carcinoma, and Page kidney (compression of kidney by perirenal hematoma leading to renin-mediated hypertension).

TABLE 6.2 **Complications in 9474 Native Kidney Biopsies**

Complication	Percentage
Visible hematuria	3.5
Need for blood transfusion	0.9
Need for intervention to control bleeding	0.7 (0.6 angiographic; 0.1 surgical)
Death	0.02

Data from reference 18.

Death

Death resulting directly from renal biopsy is much less common in recent biopsy series compared with earlier reports. Most deaths are the result of uncontrolled hemorrhage in high-risk patients, particularly those with severe renal impairment.

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SELF-ASSESSMENT QUESTIONS

1. A 68-year-old woman with non-nephrotic proteinuria of unknown cause attended the outpatient unit for a renal biopsy. She had a background of hypertension, chronic alcohol abuse, and osteoarthritis. Which of the following would be a contraindication to renal biopsy for this patient?
   A. Ingestion of naproxen 24 hours earlier
   B. Blood pressure of 162/94 mm Hg
   C. Dipstick urinalysis positive for nitrites and leukocytes
   D. Presence of simple cysts in both kidneys (four in left, three in right)
   E. Body mass index (BMI) of 36 kg/m^2
2. A 32-year-old woman was referred to the renal-obstetric clinic for evaluation of kidney disease. Which is a recognized indication for renal biopsy during pregnancy?
   A. Isolated proteinuria, ratio of protein to creatinine of 320 mg/mmol
   B. Asymptomatic proteinuria with nonvisible hematuria
   C. Episodic visible hematuria
   D. Symptomatic nephrotic syndrome after 32 weeks of gestation
   E. Unexplained deterioration in renal function before 32 weeks of gestation
3. A 75-year-old man was admitted as an emergency with acute kidney injury (AKI). He had been unwell for 4 months with myalgia, arthralgia, and generalized fatigue. More recently, he had developed epistaxis and a nonblanching leg rash. Six months earlier, he had a myocardial infarction, followed by right coronary artery angioplasty and stenting. He was taking aspirin (75 mg), clopidogrel (75 mg), bisoprolol (5 mg), ramipril (5 mg), and atorvastatin (40 mg). On examination, his blood pressure was 148/86 mm Hg, and he was euvolemic. A purpuric rash was present on both lower legs. Investigations were as follows:
   - Serum creatinine: 523 µmol/l (60-110)
   - Serum C-reactive protein: 25 mg/l (<10)
   - Urine dipstick: 3+ blood, 2+ protein, 0 nitrites, 0 leukocytes
   - Antinuclear antibodies: Negative
   - Anti–neutrophil cytoplasmic antibodies: Negative
   - Anti–glomerular basement membrane antibodies: Negative

   An urgent renal biopsy is requested to determine the cause of AKI. What should be done to minimize the risk for postbiopsy bleeding?
   A. Undertake a transjugular renal biopsy
   B. Transfuse platelets before the biopsy
   C. Administer DDAVP
   D. Stop aspirin and clopidogrel and wait 24 hours before performing the biopsy
   E. Administer vitamin K and proceed if international normalized ratio and activated partial thromboplastin time ratio APTTR are normal
4. A 32-year-old man was seen in the nephrology clinic with proteinuria. He has a background of type 1 diabetes mellitus and hypertension. He was treated with lisinopril (10 mg), amlodipine (5 mg), aspirin (75 mg), simvastatin (40 mg), and insulin. On examination, he was overweight (body mass index [BMI]: 30 kg/m^2), blood pressure was 146/84 mm Hg, and edema was present to midcalf level bilaterally. Investigations were as follows:
   - Serum creatinine: 123 µmol/l (60-110)
   - Serum albumin: 28 g/l (37-49)
   - Serum creatinine: 123 µmol/l (60-110)
   - Serum albumin: 28 g/l (37-49)
   - Urinary protein/creatinine ratio: 460 mg/mmol (<15)

   Which additional feature would provide justification for undertaking a renal biopsy?
   A. Presence of diabetic retinopathy
   B. Duration of diabetes of 12 years
   C. Presence of nonselective proteinuria
   D. Negative dipstick urinalysis 4 months earlier
   E. HbA_{1c} of 7.2%

7

Disorders of Extracellular Volume

David H. Ellison, Robert W. Schrier

EXTRACELLULAR FLUID COMPARTMENT

Water comprises 60% of a typical healthy man's body weight and 50% of a woman's body weight. Total body water (TBW) is distributed in two compartments: the intracellular fluid (ICF) compartment (55% to 65% of TBW) and extracellular fluid (ECF) compartment (35% to 45% of TBW). The ECF is further subdivided into two spaces: the *interstitial* space accounts for about 75% of the ECF, and the *intravascular* space represents the remaining 25% (Fig. 7.1).

Water diffuses freely between the intracellular space and the extracellular spaces in response to gradients in effective osmolality, where effective osmolality (tonicity) is the product of the solute concentration and its reflection coefficient (similar to the inverse of permeability). Therefore the amount of water in different compartments depends on the quantity of effective osmoles in that compartment. The major solute in the ECF is sodium ion (Na^+), and the major intracellular solute is potassium ion (K^+); the number of cations always equals the number of anions in fluid. The maintenance of this uneven ion distribution is fulfilled by active transport through the Na^+K^+–adenosine triphosphate (ATP)–dependent pumps on the cell membrane, and this determines the relative volume of different compartments. Because sodium (with anions) is the predominant extracellular solute, the ECF volume is determined primarily by the sodium content of the body. The sodium content largely depends on salt intake and renal excretion, which is tightly regulated.

Fluid movement between the intravascular and interstitial spaces of the ECF occurs across the capillary wall and is governed by Starling forces, namely, the capillary hydrostatic pressure and colloid osmotic pressure. Unlike cell membranes, capillary membranes are traditionally believed to be highly permeable to small solutes, such as Na^+, rendering small molecules incapable of generating transcapillary water movement. In this case, plasma proteins, especially albumin, play special roles in retaining fluid within capillaries, because proteins are poorly permeable across capillary membranes. The outward transcapillary hydrostatic pressure gradient exceeds the corresponding inward oncotic pressure gradient, thereby favoring movement of plasma ultrafiltrate into the interstitial space.

Titze and colleagues[1] proposed revisions to this model. They emphasize that not all fluid compartments are in osmotic equilibrium and not all extracellular sodium is osmotically active. Accordingly, sodium can be stored in compartments such as the skin (whether osmotically silent[2] or osmotically active[3] is not clear) and then released in a rhythmic manner that is independent of ECF volume.[4] One of the contributors to the skin sodium storage is immune cells, and this process may help determine the ability of skin to resist microbial pathogens. Both the traditional and the alternative model of sodium homeostasis rely on the crucial role of the lymphatics in returning sodium to the circulation. Despite these important revisions to the traditional model, treating edema removes fluid primarily from an "interstitial" (nonplasma) compartment, indicating that most extravascular fluid is in osmotic equilibrium with plasma.[5]

The ECF volume determines the adequacy of the circulation and in turn the adequacy of delivery of oxygen, nutrients, and other substances needed for organ functions; it is also necessary for removal of waste products. This is achieved despite day-to-day variations in the intake of sodium and water, with the ECF volume varying by only 1% to 2%.

REGULATION OF EXTRACELLULAR FLUID HOMEOSTASIS

Circulatory stability depends on homeostatic mechanisms that include an *afferent* sensing limb, comprising several volume and stretch detectors distributed throughout the vascular bed, and an *efferent* effector limb (Table 7.1). Adjustments in the effector mechanisms occur in response to afferent stimuli by sensing-limb detectors, to modify circulatory parameters. Disorders of either sensing mechanisms or effector mechanisms can lead to failure of adjustment of sodium handling by the kidney, with resultant hypertension or edema formation in the patient with positive sodium balance or hypotension and hypovolemia in the patient with negative sodium balance.

Afferent (Sensor) Limb

Afferent limb (sensing) sites include low-pressure cardiopulmonary receptors (atrial, ventricular, and pulmonary stretch receptors), high-pressure arterial baroreceptors (carotid, aortic arch, and renal sensors), central nervous system (CNS) receptors, and hepatic receptors. The cardiac atria possess the distensibility and compliance needed to monitor changes in intrathoracic venous volume. Atrial distention and a sodium load cause release of atrial natriuretic peptide (ANP), a polypeptide normally stored in secretory granules within atrial myocytes. The closely related brain natriuretic peptide (BNP) is stored primarily in ventricular

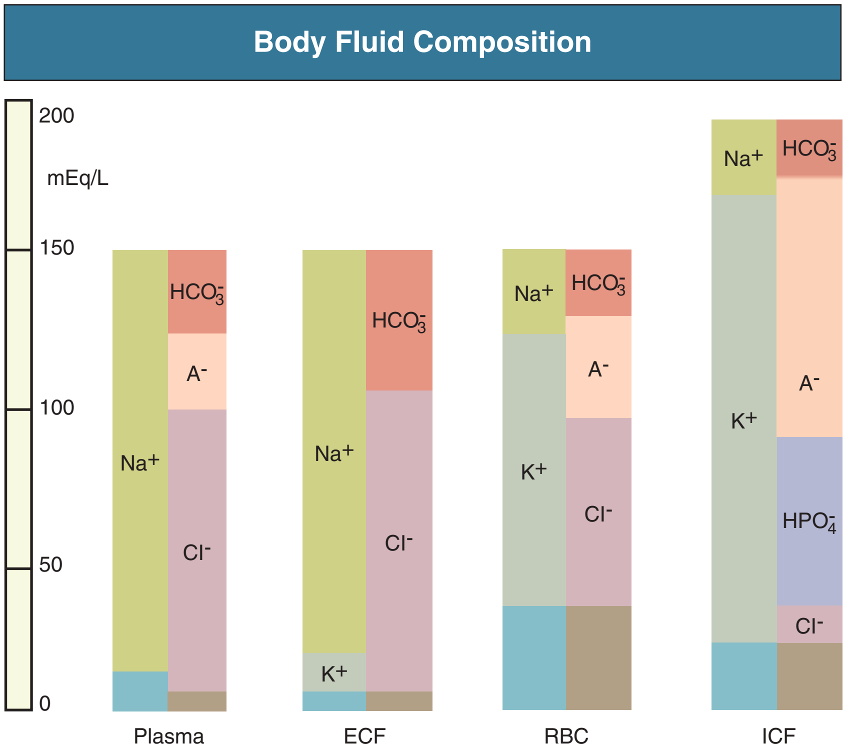

Fig. 7.1 Gamblegram of body composition. A 70-kg man has 42 liters (60%) of water, whereas a 60-kg woman has 36 liters (50%) of water. Of water, two thirds is intracellular *(ICF)* and one third is extracellular (ECF). The osmolality in compartments is similar, even though solute concentrations differ, owing to valence of ions. *RBC,* Red blood cell.

TABLE 7.1 Homeostatic Mechanisms in Extracellular Fluid Volume

Afferent (Sensing)	Efferent (Effector)
Cardiopulmonary receptors Atrial Ventricular Pulmonary High-pressure baroreceptors Carotid Aortic Renal Pressure sensors* Glomerular afferent Juxtaglomerular apparatus Central nervous system receptors Hepatic receptors	Renal-angiotensin-aldosterone system (RAAS) Prostaglandins Arginine vasopressin (AVP) Natriuretic peptides Atrial (ANP) Brain (BNP) C-type (CNP) Other hormones Nitric oxide (NO) Endothelin Kallikrein-kinin system

*Pressure sensors are unspecified receptors contributing to pressure natriuresis.

myocardium and is released when ventricular diastolic pressure rises. An increase in left atrial pressure also sends signals to the hypothalamus that can suppress the release of antidiuretic hormone (ADH), also called arginine vasopressin (AVP). These atrial-renal and atrial-hypothalamic reflexes enhance renal sodium and water excretion on sensing of a distended left atrium.

The sensitive arterial stretch receptors in the carotid artery, aortic arch, and glomerular afferent arteriole respond to a decrease in arterial pressure. Information from these nerve endings is carried by the vagal and glossopharyngeal nerves to vasomotor centers in the medulla and brainstem. In the normal situation, these receptors exert a tonic restraining effect on the heart and circulation by inhibiting the sympathetic outflow and augmenting parasympathetic activity. In addition, changes in transmural pressure across the arterial vessels and the atria also influence the secretion of AVP and renin and the release of ANP. Activation of the arterial receptors signals the kidney to retain sodium and water by increases in sympathetic activity and vasopressin release. Stimulation of the sympathetic nervous system (SNS) also enhances the renin-angiotensin-aldosterone system (RAAS). A rise in arterial pressure elicits the opposite response, resulting in decreased catecholamine release and natriuresis.

Renal sensing mechanisms include the juxtaglomerular apparatus (JGA), which is involved in the generation and release of renin from the kidney and in tubuloglomerular feedback (THF) (see later discussion). Renin secretion is inversely related to perfusion pressure and directly related to intrarenal tissue pressure. Solute delivery to the macula densa is also an important determinant of renin release; an increase in sodium chloride entry into macula densa cells inhibits renin release, whereas a decrease in entry stimulates it. Renal nerve stimulation through activation of β-adrenergic receptors of the JGA directly enhances renin release. Other receptors reside in the CNS and hepatic circulation but have been less well defined.

Glomerulotubular Balance

Increases or decreases in glomerular filtration rate (GFR) lead to parallel changes in NaCl reabsorption (Fig. 7.2), the phenomenon of glomerulotubular balance (GTB), so that GFR is not a major determinant of net solute excretion. A second process, TGF, senses NaCl at the macula densa

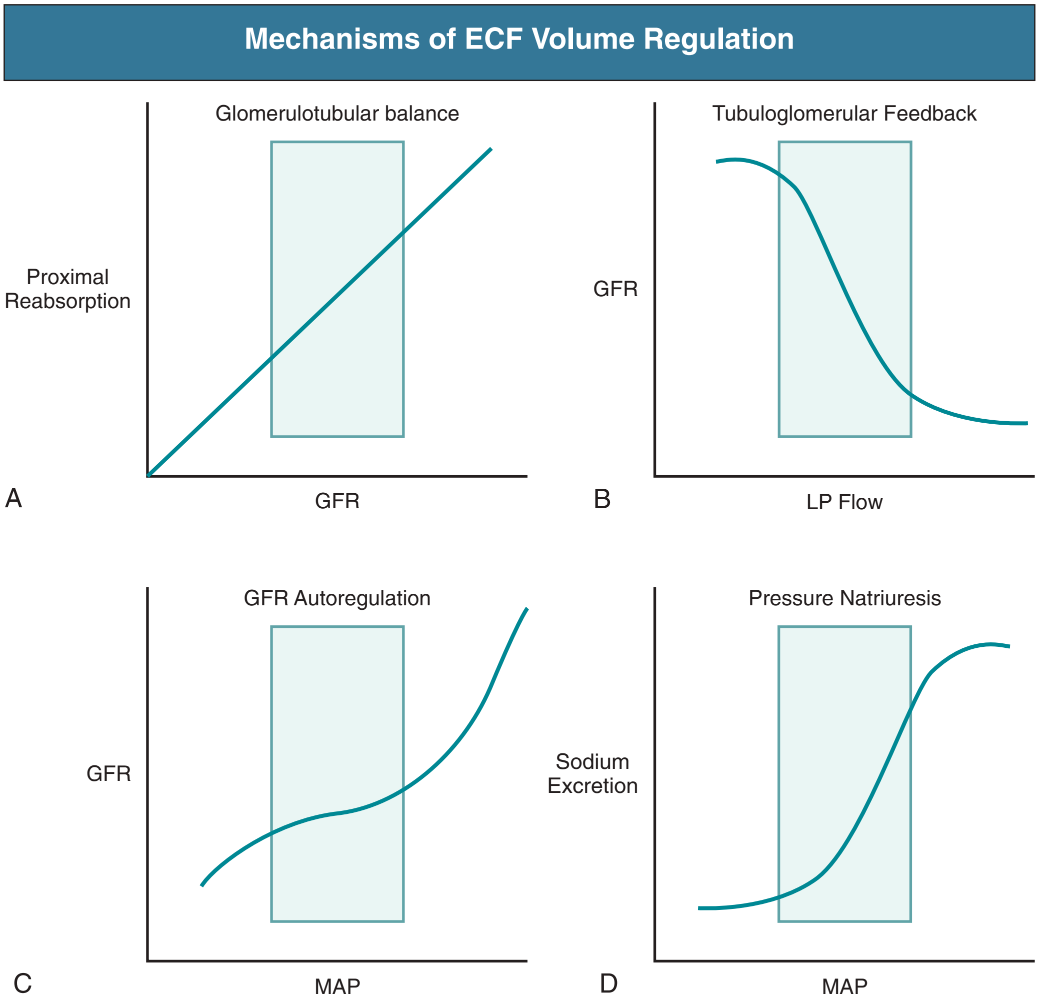

Fig. 7.2 Overall mechanisms of ECF volume regulation. (A) Proximal reabsorption rises with increased glomerular filtration rate (GFR) (glomerulotubular balance). (B) Relationship between late proximal (LP) flow and GFR (tubuloglomerular feedback). (C) GFR is autoregulated across mean arterial pressure (MAP). (D) Sodium excretion increases, as MAP increases, the pressure natriuresis. *Boxes* indicate typical operating ranges.

to adjust GFR. High luminal NaCl concentration at the macula densa, as occurs during high loop segment flow rates and volume expansion, leads to constriction of the nearby afferent arteriole and reduction of GFR (see Fig. 7.2). This process reduces GFR (see Fig. 7.2) and therefore proximal flow, tending to keep solute excretion rates constant. Although functionally independent of GTB, the sequential arrangement of GTB and TGB means they work in concert and are remarkably effective in maintaining NaCl excretion rates in the face of changing GFR.[6]

Pressure Natriuresis

Both renal blood flow and GFR are autoregulated (see Fig. 7.2), meaning they are relatively insensitive to variations in arterial pressure, within a range of typical pressure values. In contrast, urinary Na^+ excretion is strongly affected by even modest variations in pressure, with a rise in pressure increasing renal Na^+ excretion (see Fig. 7.2). This process appears to be intrinsic to the kidney, but the shape of the relationship is strikingly altered by actions of the RAAS. The phenomenon, termed *pressure natriuresis,* likely results from the adjustment of Na^+ reabsorption by several segments of the nephron, via pathways that remain incompletely defined. The dominant importance of pressure natriuresis, at least under sodium retentive conditions, is clear from experimental models. Natriuretic sensitivity to natriuretic peptides can be restored[7] by a rise in renal perfusion pressure (RPP). Conversely, escape from the sodium retentive effects of aldosterone[8] or angiotensin II (Ang II)[9] also requires a rise in RPP.

Efferent (Effector) Limb

The stimulation of the effector limb of the ECF volume homeostasis leads to activation of effector mechanisms (see Table 7.1). These effector mechanisms aim predominantly at modulation of renal sodium and water excretion to preserve circulatory stability.

Renin-Angiotensin-Aldosterone System

Renin secretion from the JGA increases in response to depletion of the ECF volume, as a result of the processes described previously. Renin converts angiotensinogen to Ang I, which is then converted to Ang II by the action of the angiotensin-converting enzyme (ACE); Ang II can subsequently affect circulatory stability and volume homeostasis. It is a vasoconstrictor, it stimulates sodium retention, and it stimulates aldosterone release, all effects that maintain arterial pressure, when ECF volume is low. Ang II has complex effects on GFR and renal plasma flow (RPF), but when the ECF volume is low, it preferentially increases renal efferent arteriolar tone, thus tending to preserve GFR; this is one reason that the RAAS contributes importantly to autoregulation of GFR. Ang II also increases the filtration fraction by altering Starling forces across the glomerulus, which leads to enhanced proximal sodium and water retention.[10]

Ang II also augments sympathetic neurotransmission and enhances the TGF mechanism. In addition to these indirect mechanisms, Ang II directly enhances proximal tubular volume reabsorption by activating apical membrane sodium-hydrogen (Na^+-H^+) exchangers. Ang II also enhances sodium absorption by stimulating secretion of aldosterone, which in turn increases sodium reabsorption in the cortical collecting tubule.

Sympathetic Nervous System

Sympathetic nerves that originate in the prevertebral celiac and paravertebral ganglia innervate cells of the afferent and efferent arterioles, JGA, and renal tubule. Sympathetic nerves alter renal sodium and water handling by direct and indirect mechanisms.[11] Increased nerve stimulation indirectly stimulates proximal tubular sodium reabsorption by altering preglomerular and postglomerular arteriolar tone, thereby influencing filtration fraction. Renal nerves directly stimulate proximal tubular fluid reabsorption through receptors on the basolateral membrane of the proximal convoluted tubule cells. These effects on sodium handling are further amplified by the ability of the sympathetic nerves to stimulate renin release, which leads to the formation of Ang II and aldosterone.

Natriuretic Peptides

Secretion of ANP and BNP was discussed earlier. These peptides augment sodium and water excretion by increasing the GFR, possibly by dilating the afferent arteriole and constricting the efferent arteriole. Furthermore, they inhibit sodium reabsorption in the cortical collecting tubule and inner medullary collecting duct, reduce renin and aldosterone secretion, and oppose the vasoconstrictive effects of Ang I.[12] Circulating levels of ANP and BNP are elevated in congestive heart failure (CHF) and in cirrhosis with ascites, but these levels are not sufficient to overcome the sodium-retaining effects of low RPP.

Prostaglandins

Prostaglandins are derived from arachidonic acid and modulate renal blood flow and sodium handling. Important renal prostaglandins include prostaglandin I_2, which mediates baroreceptor (but not β-adrenergic) stimulation of renin release. Prostaglandin E_2 is stimulated by Ang II and has vasodilatory properties. Increased levels of Ang II, AVP, and catecholamines stimulate synthesis of prostaglandins, which in turn act to dilate the renal vasculature, inhibit sodium and water reabsorption, and stimulate renin release. In situations of ECF volume depletion or depletion of the effective arterial blood volume (EABV), the combination of prostaglandin-mediated afferent arteriolar dilation and Ang II–mediated efferent arteriolar constriction plays a central role in autoregulatory maintenance of GFR. Often, in these situations, interference with efferent vasoconstriction (e.g., ACE inhibition), and with afferent vasodilation (e.g., nonsteroidal antiinflammatory drugs [NSAIDs]) leads to a precipitous decline in GFR, manifested as acute kidney injury (AKI).

Arginine Vasopressin

The polypeptide AVP is synthesized in supraoptic and paraventricular nuclei of the hypothalamus and is secreted by the posterior pituitary gland. The predominant stimulus for AVP release under typical conditions is hypertonicity. Substantial reductions in EABV, however, act as a second, nonosmotic regulatory pathway.[13] AVP release is suppressed in response to ECF volume overload sensed by increased afferent impulses from arterial baroreceptors and atrial receptors, whereas decreased ECF volume has the opposite effect. AVP release leads to antidiuresis and, at higher concentrations, to systemic vasoconstriction through the V_1 receptors.[14] The antidiuretic action of AVP results from the effect on the principal cell of the collecting duct through activation of the V_2 receptor. AVP increases the synthesis and provokes the insertion of aquaporin 2 (AQP2) water channels into the luminal membrane, thereby allowing water to be reabsorbed down the favorable osmotic gradient. AVP also may lead to enhanced Na^+ reabsorption and K^+ secretion. AVP appears to have synergistic effects with aldosterone on sodium transport in the cortical collecting duct.[15] AVP stimulates potassium secretion by the distal nephron, and this preserves potassium balance during ECF depletion, when circulating levels of vasopressin are high and tubular delivery of sodium and fluid is reduced.

Other Hormones

Other hormones that contribute to renal sodium handling and ECF volume homeostasis include nitric oxide (NO), endothelin, and the kallikrein-kinin system. NO is an endothelium-derived mediator that participates in the natriuretic responses to increases in blood pressure or ECF volume expansion. Endothelins, in addition to their potent actions to constrict vascular smooth muscle, are natriuretic factors. Endothelin 1, via the endothelin B (ET_B) receptor, increases NO production, which tends to increase urinary salt excretion. Kinins are potent vasodilator peptides, but their physiologic roles are not yet fully defined.

Terms Useful for Disorders of Extracellular Fluid Volume

In clinical practice it is helpful to view disorders of ECF volume as distinct from disorders of water. The latter reflect gain or loss of electrolyte-free water, typically resulting in changes in plasma osmolality (hyponatremia or hypernatremia); when losses or gains are substantial, detectable changes in ECF volume can occur. But changes in ECF volume, often termed simply *volume contraction* or *volume expansion,* reflect gain or loss of NaCl. Water is often retained or lost secondarily.

Loss of salt and water produces true depletion of ECF volume, but there are many pathologic conditions (e.g., heart failure [HF]; cirrhosis) in which ECF volume is expanded but the kidneys behave as if contracted. To account for this discrepancy, the term *EABV* is used to describe the blood volume detected by the sensitive arterial baroreceptors. The EABV can change independently of the total ECF volume. The state of the EABV is often inferred from the behavior of the kidneys.

EXTRACELLULAR FLUID VOLUME CONTRACTION

Contraction of ECF volume typically results from sodium losses that exceed intake. Losses may be renal or extrarenal through the gastrointestinal tract, skin, and lungs or by sequestration in potential spaces in the body (e.g., abdomen, muscle) that are not in hemodynamic equilibrium with the ECF (Table 7.2). The reduction in ECF volume occurs from both the interstitial and intravascular compartments. The loss of solute-free water (e.g., diabetes insipidus [DI]) has a lesser effect on intravascular volume because water is lost from all aqueous spaces in the body, and the body's solute content remains unchanged. Thus, in this case of disordered water balance, hypertonicity—rather than ECF volume contraction—predominates.

Extrarenal Causes

Gastrointestinal Losses

Approximately 3 to 6 liters of fluids and digestive juices are secreted daily throughout the gastrointestinal tract, and most of this fluid is

TABLE 7.2 Major Causes of Extracellular Fluid Volume Depletion

Renal

- Diuretic use
- Tubular disorders
  - Genetic
    - Bartter and Gitelman syndromes
    - Pseudohypoaldosteronism type 1
  - Acquired tubular disorders
    - Acute kidney injury
    - Recovery phase of oliguric kidney injury
    - Release of urinary tract obstruction
- Hormonal and metabolic disturbances
  - Mineralocorticoid deficiency or resistance
    - Primary adrenal insufficiency
    - Hyporeninemic hypoaldosteronism
      - Diabetes mellitus
      - Chronic interstitial renal diseases
  - Solute diuresis
- Renal water loss
  - Diabetes insipidus

Extrarenal

- Gastrointestinal losses
  - Vomiting
  - Gastrointestinal suctioning
- Diarrhea
  - Ileostomy and colostomy secretions
- Dermal losses
  - Sweat
  - Exudative skin disease
- Third-space sequestration
  - Ascites
  - Pleural effusion, hydrothorax
  - Intestinal obstruction
- Retroperitoneal collection
  - Hemorrhage
    - Internal
    - External

reabsorbed. Vomiting or nasogastric suction may cause volume loss that is usually accompanied by metabolic alkalosis, whereas diarrhea may result in volume depletion that is accompanied by metabolic acidosis.

Dermal Losses

Sweat is typically hypotonic, leading to more water loss than salt loss. Sweat production can be excessive in high ambient temperature or with prolonged exercise in hot, humid climates and may lead to volume depletion. Loss of the skin barrier with superficial burns and exudative skin lesions may lead to significant ECF volume depletion.

Third-Space Sequestration

Body fluid accumulation in potential spaces that are not in hemodynamic equilibrium with the ECF compartment can cause volume depletion. This pathologic accumulation, often called third-space sequestration, includes ascites, hydrothorax, and intestinal obstruction, with fluid collecting in the peritoneal cavity, pleural space, and intestines, respectively, and leading to significant ECF volume loss. Severe pancreatitis may result in retroperitoneal fluid collections.

Hemorrhage

Hemorrhage occurring internally (e.g., from bleeding esophageal varices) or externally (e.g., trauma) may lead to significant volume loss.

Renal Losses

In health, approximately 25,000 mmol of sodium is filtered every day. The small quantities of sodium excreted in urine relative to the filtered load depend on intact tubular reabsorptive mechanisms to adjust urinary sodium excretion to maintain ECF homeostasis. Impairment in the integrity of these mechanisms can result in significant volume depletion.

Diuretic Use

Most of the widely used diuretic medications inhibit sodium transport pathways along the nephron (see later discussion). Diuretics may cause renal sodium wasting, volume contraction, and metabolic acid-base disturbances.

Genetic and Acquired Tubular Disorders

Tubular sodium reabsorption may be disrupted in several genetic disorders that include Bartter syndrome and Gitelman syndrome. These autosomal recessive disorders are caused by mutations of sodium transporters and result in sodium wasting, volume contraction, and hypokalemic metabolic alkalosis. They are discussed in more detail in Chapter 47. Pseudohypoaldosteronism type 1 (PHA1) is another rare inherited disorder, characterized by sodium wasting and hyperkalemic metabolic acidosis and is caused by mutations in the epithelial sodium channel, ENaC.

Acquired tubular disorders that may be accompanied by salt wasting include AKI, during the recovery phase of oliguric AKI or urinary obstruction (see Chapters 58 and 70).

Hormonal and Metabolic Disturbances

Mineralocorticoid deficiency and resistance states often lead to sodium wasting. This may occur in the setting of primary adrenal insufficiency (Addison disease) and PHA1. Salt wasting also can be seen in chronic tubular and interstitial renal diseases. Severe hyperglycemia or high levels of blood urea during release of urinary tract obstruction can lead to obligatory renal sodium and water loss secondary to glycosuria or urea diuresis, respectively.

Renal Water Loss

DI represents a spectrum of diseases resulting from AVP deficiency, (*central* DI), or tubular resistance to AVP (*nephrogenic* DI). The most common causes of polyuria from nephrogenic DI in adults are chronic lithium ingestion, hypercalcemia, and less frequently, hypokalemia (see Chapter 8). In these disorders the tubular reabsorption of solute-free water is impaired. This generally results in a lesser effect on ECF volume because, in contrast to sodium, there is a relatively smaller amount of the TBW in the ECF compartment compared with the ICF compartment.

Clinical Manifestations of Extracellular Fluid Volume Contraction

The spectrum of the clinical manifestations of volume contraction (Box 7.1) depends on the amount and rate of ECF volume loss, as well as on the vascular and renal responses to that loss. An adequate history and physical examination are crucial to elucidate the cause of hypovolemia. Symptoms are usually nonspecific and can range from mild postural symptoms, thirst, muscle cramps, and weakness to drowsiness and disturbed mentation with profound volume loss. Physical examination may reveal tachycardia, cold clammy skin, postural or recumbent hypotension, and reduced urine output, depending on the degree of volume loss. Low jugular venous pressure (JVP; ≤5 cm H_2O) is consistent with volume depletion. However, the JVP may be elevated in patients with pulmonary hypertension or when the EABV is low. The lack of symptoms or discernible physical findings does not preclude volume depletion, and hemodynamic monitoring and administration of a fluid challenge may be necessary.

Laboratory Tests

Hemoconcentration and increased serum albumin concentration may be seen early with hypovolemia, but anemia or hypoalbuminemia caused by a concomitant disease may confound interpretation of these laboratory values. In healthy individuals, the ratio of blood urea nitrogen (BUN) to serum creatinine is approximately 10 to 20:1 (measured in milligrams per deciliter). In volume-contracted states, this ratio may increase because of an associated differential increase in urea reabsorption

BOX 7.1 Clinical Evaluation of Extracellular Fluid Volume Depletion

Mild to Moderate Volume Loss

- Thirst
- Delay in capillary refill
- Postural dizziness, weakness
- Dry mucous membranes and axillae
- Cool, clammy extremities and collapsed peripheral veins
- Tachypnea
- Tachycardia with pulse rate >100 beats/min, or postural pulse increment of 30 beats/min or more
- Postural hypotension (systolic blood pressure decrease >20 mm Hg on standing)
- Low jugular venous pulse
- Oliguria

Severe Volume Loss and Hypovolemic Shock

- Depressed mental status (or loss of consciousness)
- Peripheral cyanosis
- Reduced skin turgor (in young patients)
- Marked tachycardia, low pulse volume
- Supine hypotension (systolic blood pressure <100 mm Hg)

in the collecting duct. Several clinical conditions affect this ratio. Upper gastrointestinal tract hemorrhage and administration of corticosteroids increase urea production, and hence the ratio of BUN to creatinine increases. Malnutrition and liver disease diminish urea production, making the ratio less helpful.

Urine osmolality and specific gravity may be elevated in hypovolemic states, but may be altered by an underlying renal disease that leads to renal sodium wasting, concomitant intake of diuretics, or a solute diuresis. Hypovolemia normally promotes avid renal sodium reabsorption, resulting in low urine sodium concentration and low fractional excretion of sodium. Urine chloride follows a similar pattern because sodium and chloride are generally reabsorbed together. Volume depletion with metabolic alkalosis (e.g., with vomiting) is an exception because of the need to excrete the excess bicarbonate in conjunction with sodium to maintain electroneutrality; in this case, urine chloride concentration is a better index of ECF volume contraction. The fractional excretion of sodium (FE_{Na}) is calculated by the following formula:

$$FE_{Na} = [U_{Na} \times P_{creat} / U_{creat} \times P_{Na}] \times 100$$

where U_{Na} and U_{creat} are urinary sodium and creatinine concentrations, respectively, and P_{Na} and P_{creat} are serum sodium and creatinine concentrations, respectively. In an oliguric patient with AKI, FE_{Na} less than 1% is consistent with volume depletion; FE_{Na} greater than 1% is more consistent with acute tubular necrosis.

Therapy of Extracellular Fluid Volume Contraction

The goal of treatment is to replace the fluid deficit and ongoing losses with a fluid that resembles the lost fluid. The first step is to determine the urgency of the hypovolemic condition. In severe hypovolemia or hypovolemic shock, immediate treatment should be initiated, typically with 1 to 2 liters of isotonic crystalloid. The adequacy of repletion can then be monitored clinically, with central venous pressure monitoring or, in the intensive care unit (ICU), respiratory variation in the arterial pressure tracing. Estimating the magnitude of volume deficit is imprecise; thus a key component of successful treatment is frequent monitoring and adjustment of therapy.

Mild volume contraction usually can be corrected orally. It is important to note, however, that unlike oral rehydration solutions used for childhood diarrhea (50 to 90 mmol/L sodium), sports drinks typically contain very little NaCl (7 to 20 mmol/L) and do not replace ongoing losses, although normal kidneys can typically adjust for the discrepancy when losses are mild.

Crystalloid solutions (isotonic or slightly hypotonic) with sodium as the principal cation are effective because they distribute primarily in the ECF. One third of an infusate of isotonic saline (0.9% NaCl) remains in the intravascular compartment, whereas two thirds distributes into the interstitial compartment. Colloid-containing solutions include human albumin (5% and 25%) and hetastarch (6% hydroxyethyl starch [HES]), which remain within the vascular compartment (provided the transcapillary barrier is intact and not disrupted by capillary leak states such as often occurs with multiorgan failure). The solutions augment the plasma oncotic pressure and thus expand the plasma volume by counteracting the capillary hydraulic pressure.

Colloid-containing solutions have not shown an advantage in the treatment of hypovolemic states. A large, multicenter trial that randomized medical and surgical critical patients to receive fluid resuscitation with 4% albumin or normal saline showed similar mortality, morbidity, and hospitalization rates in the two groups.[16] A recent study randomly assigned ICU patients with severe sepsis to fluid resuscitation with either 6% HES or Ringer acetate solution.[17] Patients who received HES had increased mortality and were more likely to receive renal replacement therapy. Consequently, artificial colloids should be avoided in patients with severe sepsis or at risk for developing AKI.[18]

Isotonic saline or a balanced salt solution (e.g., lactated Ringer solution) is usually the preferred initial choice in volume-depleted patients with normal serum [Na^+] and most of those with low serum [Na^+]. Furthermore, isotonic saline is the preferred fluid to restore ECF volume in hypovolemic patients with hypernatremia. Once euvolemia is established, hypotonic (0.45% NaCl) saline should be delivered to gradually correct tonicity. Administration of large volumes of isotonic saline may result in the development of hyperchloremic metabolic acidosis or AKI. Although a number of smaller studies suggest benefit from buffered crystalloid solutions, such as lactated Ringer solution, a randomized trial could not detect a difference.[19] Any hypokalemia should be corrected by adding potassium chloride to replacement solutions.

Hypovolemic shock may be accompanied by lactic acidosis resulting from tissue hypoperfusion. Fluid resuscitation restores tissue oxygenation and will decrease the production of lactate, but lactated Ringer solution is inappropriate because the infused lactate will not be converted to bicarbonate. Correction of acidosis with sodium bicarbonate ($NaHCO_3$) has the potential for increasing tonicity, expanding volume, worsening intracellular acidosis from increased carbon dioxide production, and not improving hemodynamics compared with isotonic saline. Whether $NaHCO_3$ effectively corrects the impaired cardiac contractility associated with lactic acidosis has not been well documented by clinical studies. Therefore $NaHCO_3$ to manage lactic acidosis in the setting of volume depletion is not recommended (unless arterial pH is <7.1).

EXTRACELLULAR FLUID VOLUME EXPANSION

Expansion of ECF volume usually results from renal sodium and water retention. Generalized edema results from an apparent increase in the interstitial fluid volume, most often in response to HF, cirrhosis with ascites, and nephrotic syndrome. Weight gain of several kilograms usually precedes clinically apparent edema. Localized excess fluid may accumulate in the peritoneal and pleural cavities, leading to ascites and pleural effusion, respectively.

Pathogenesis

Renal sodium and water retention secondary to arterial underfilling leads to an alteration in capillary hemodynamics that favors fluid movement from the intravascular compartment into the interstitium. In general, these two processes account for edema formation.

Capillary Hemodynamic Disturbances

According to the Starling equation, the exchange of fluid between the plasma and the interstitium is determined by the hydrostatic and oncotic pressures in each compartment. Interstitial fluid excess results from a decrease in plasma oncotic pressure or an increase in capillary hydrostatic pressure. In other words, edema is a result of an increase in fluid movement from the intravascular compartment to the interstitial space or a decrease in fluid movement from the interstitial space to the intravascular compartment, or both. Thus the degree of interstitial fluid accumulation as determined by rate of fluid removal by the lymphatic vessels is a determinant of edema.

The capillary hydrostatic pressure is relatively insensitive to alterations in arterial pressure. The stability of the capillary pressure is a result of variations in the precapillary sphincter, which governs how much arterial pressure is transmitted to the capillary, a locally controlled response called *autoregulation*. In contrast, the venous end is not similarly well regulated. Therefore, when the blood volume expands, as in HF and renal disease, capillary hydrostatic pressure increases and edema ensues. Venous obstruction works by the same mechanism to cause edema, as exemplified by ascites formation in liver cirrhosis and by acute pulmonary edema after sudden impairment in cardiac function (e.g., myocardial infarction). In hepatic cirrhosis and nephrotic syndrome, another factor in edema formation is reduction in plasma oncotic pressure, with fluid transudation into the interstitial space. Even normal conditions favor net filtration into the interstitium because capillary hydrostatic pressure exceeds the plasma colloid pressure in several tissues throughout the length of the capillary. In these tissues, a substantial amount of filtered fluid is returned to the circulation through lymphatic channels, which minimizes edema formation.

Renal Sodium Retention

The mechanism for maintenance of ECF volume expansion and edema formation is renal sodium retention, which can be primary or secondary in response to reduction in EABV (Table 7.3).

Primary renal sodium retention. A primary defect in renal sodium excretion can occur with AKI, chronic kidney disease (CKD), or glomerular disease. Patients with AKI have limited ability to excrete sodium and water. Advanced CKD may lead to sodium and water retention by GFR reduction. Primary renal sodium retention characterizes some forms of glomerulonephritis and occurs through incompletely understood mechanisms in the presence of a relatively suppressed renin-angiotensin-aldosterone system (RAAS), but frequently with decreased GFR.

TABLE 7.3 Major Causes of Extracellular Fluid Volume Expansion

Primary Renal Sodium Retention	Secondary Renal Sodium Retention*
Acute kidney injury Advanced chronic kidney disease Glomerular diseases	Cardiac failure Cirrhosis Nephrotic syndrome Idiopathic edema Drug-induced edema Pregnancy

*Secondary to reduced effective arterial blood volume depletion (arterial underfilling).

Mineralocorticoid excess or enhanced mineralocorticoid activity are associated with sodium retention. However, because of mineralocorticoid escape (discussed previously) the clinical manifestation is generally hypertension rather than hypervolemia. In normal individuals, administration of a high-dose mineralocorticoid initially increases renal sodium retention so that ECF volume is increased. However, renal sodium retention then ceases, spontaneous diuresis ensues, sodium balance is reestablished, and there is no detectable edema. This escape from mineralocorticoid-mediated sodium retention explains why edema is not a characteristic feature of primary hyperaldosteronism. The pathophysiologic mechanism of mineralocorticoid escape involves an increase in GFR and reduction of proximal tubular sodium and water reabsorption. This leads to an increase in sodium and water delivery to the distal nephron site of aldosterone action, which overrides the sodium reabsorption of aldosterone. Other contributing mechanisms include decreased expression of distal tubular thiazide-sensitive NaCl cotransporters,[20] increased secretion of ANP induced by hypervolemia,[21] and pressure natriuresis. Regardless of the mechanisms involved, RPP must rise to enable the escape process[8]; because this can occur during primary renal salt retention, these states are typically characterized by hypertension and not edema.

Secondary renal sodium retention. An estimated 85% of blood circulates on the low-pressure venous side of the circulation, and 15% in the high-pressure arterial circulation. Thus an increase in total blood volume could occur, even when there is underfilling of the arterial circulation, if the increase in total blood volume is primarily caused by expansion of the venous compartment. Underfilling of the arterial circulation could result from a decrease in cardiac output, as occurs in low-output cardiac failure, or from systemic arterial vasodilation, which occurs early in cirrhosis as a result of decreased systemic vascular resistance (SVR) in the splanchnic circulation.[22] As arterial pressure is determined by the product of cardiac output and SVR, both states would be characterized by a decline in arterial pressure below the kidney's set point. This model proposes that renal sodium retention triggered by arterial underfilling (arterial pressure less than pressure set point) is a compensatory response necessary to restore arterial circulatory integrity.

If there is arterial underfilling from decreased cardiac output or systemic arterial vasodilation, the hypotension is sensed by the arterial stretch receptors. This leads to activation of the efferent limb of body fluid volume homeostasis. Specifically, a decrease in glossopharyngeal and vagal tone from the carotid and aortic receptors to the CNS leads to a rapid increase in sympathetic activity with associated activation of the RAAS axis and nonosmotic release of vasopressin. Additionally, a decrease in pressure at the renal baroreceptors and decreased NaCl delivery to the macula densa increase renin secretion and thereby Ang II and aldosterone. The resultant increase in SVR and renal sodium and water retention attenuates the arterial underfilling, through the Frank-Starling mechanism, and tends to restore arterial perfusion. Together, these actions maintain the arterial circulatory integrity and restore perfusion to vital organs at the expense of expanded ECF volume and edema.

Sodium and Water Retention in Heart Failure

HF can occur with reduced or preserved ejection fraction (HF$_R$EF and HF$_P$EF, respectively), but the mechanisms involved in renal sodium and water retention appear to involve similar mediators.[23] Decreased cardiac output with arterial underfilling leads to reduced stretch of arterial baroreceptors and reduced perfusion pressure in the kidney. In the case of HF$_{P}$EF, this often involves a decrease below a hypertensive baseline or below a baseline raised by CKD. This results in increased sympathetic discharge from the CNS and activation of the RAAS. Adrenergic stimulation and increased Ang II activate receptors on the proximal tubular epithelium that enhance sodium reabsorption. The renal vasoconstriction of the glomerular efferent arteriole by Ang II in CHF also alters net Starling forces in the peritubular capillary in a direction to enhance sodium reabsorption.[24] Thus Ang and α-adrenergic stimulation increase sodium reabsorption in the proximal tubule by a direct effect on the proximal tubule epithelium and secondarily by renal vasoconstriction. This subsequently leads to decreased sodium delivery to the collecting duct, which impairs escape from both aldosterone and natriuretic peptides.[7,25] This failure of escape explains why sodium retention and ECF volume expansion occur in HF (Fig. 7.3). Accordingly, patients with HF may have substantial natriuresis when spironolactone, a competitive mineralocorticoid receptor antagonist (MRA), is given in adequate doses to compete with increased endogenous aldosterone levels.[26]

The atrial-renal reflexes, which normally enhance renal sodium excretion, are also impaired because plasma levels of ANP do not increase further when patients with dilated cardiomyopathy and mild HF receive a saline load, and the natriuretic response is also blunted. Autonomic dysfunction and blunted arterial baroreceptor sensitivity in HF are associated with increased circulating catecholamines and increased renal sympathetic activity. There is also evidence for parasympathetic withdrawal in HF, in addition to the increase in sympathetic drive.

Another outcome of the neurohumoral activation that occurs in HF is the baroreceptor-mediated nonosmotic release of AVP.[27] This nonosmotic AVP stimulation overrides the osmotic regulation of AVP and is the major factor leading to the hyponatremia associated with end-stage HF.[28] AVP causes antidiuresis by activating V_2 receptors on the basolateral surface of the principal cells in the collecting duct.[29] Activation of these receptors initiates a cascade of intracellular signaling events by means of the adenylyl cyclase–cyclic adenosine monophosphate (cAMP) pathway, leading to an increase in AQP2 water channel protein expression and its trafficking to the apical membrane of the collecting duct. This sequence of events leads to increased water reabsorption and can cause hyponatremia, which is an ominous prognostic indicator in patients with HF.[30] Concurrently, increased nonosmotic AVP release stimulates V_1 receptors on vascular smooth muscle cells and thereby may increase SVR. This adaptive vasoconstrictive response may become maladaptive and contribute to cardiac dysfunction in patients with severe HF.

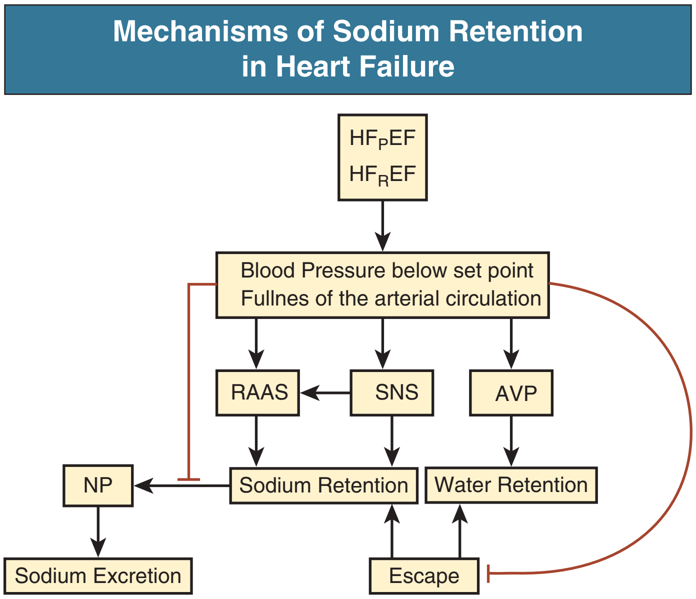
Mechanisms of Sodium Retention in Heart Failure
HF$_{P}$EF
HF$_{R}$EF
Blood Pressure below set point
Fullnes of the arterial circulation
RAAS
SNS
AVP
NP
Sodium Retention
Water Retention
Sodium Excretion
Escape

Fig. 7.3 Mechanisms of sodium retention in heart failure. Heart failure, from reduced ejection fraction *(HF$_{R}$EF)* or preserved ejection fraction *(HF$_{P}$EF),* activates neurohormonal systems, which lead to sodium and water retention, including the renin-angiotensin-aldosterone system *(RAAS),* the sympathetic nervous system *(SNS),* and arginine vasopressin *(AVP).* Ensuing ECF volume expansion increases natriuretic peptide *(NP)* secretion. Low renal perfusion pressure (blood pressure below set point) causes resistance to NP and prevents escape from sodium and water retention from aldosterone, angiotensin II, and AVP.

Sodium and Water Retention in Cirrhosis

Many pathogenetic aspects of sodium and water retention are similar in cirrhosis and HF (Fig. 7.4). However, arterial underfilling in cirrhosis occurs secondary to splanchnic arterial vasodilation, with resultant water and sodium retention. Ascites formation in cirrhosis is likely initiated by sinusoidal and portal hypertension[31] from distortion of hepatic architecture, increased hepatic vascular tone, or increased splenohepatic flow. Decreased intrahepatic bioavailability of NO and increased production of vasoconstrictors (Ang, endothelin) also are responsible for increased resistance in the hepatic vasculature.[32] Portal hypertension caused by increased sinusoidal pressure activates vasodilatory mechanisms in the splanchnic circulation.[33] These mechanisms, mediated at least partly by NO and carbon monoxide (CO) overproduction, lead to splanchnic and peripheral arteriolar vasodilation. In advanced stages of cirrhosis, arteriolar vasodilation causes underfilling of the systemic arterial vascular space. This event, through a decrease in EABV, leads to a fall in arterial pressure. Consequently, baroreceptor-mediated activation of the RAAS, SNS stimulation, and nonosmotic release of ADH occur to restore the blood volume homeostasis.[34] This involves compensatory vasoconstriction as well as renal sodium and water retention. However, splanchnic vasodilation also increases splanchnic lymph production, which exceeds the lymph transporting capacity, and thus lymph leakage into the peritoneal cavity occurs with ascites development.[35] Persistent renal sodium and water retention (along with lymph leakage into the peritoneal cavity from increased splanchnic vascular permeability) play the major role in sustained ascites formation.

Sodium and Water Retention in Nephrotic Syndrome

Unlike HF and liver cirrhosis, in which the kidneys are structurally normal, the nephrotic syndrome is characterized by diseased kidneys. Many nephrotic patients have a higher arterial blood pressure, higher GFR, and less impairment of sodium and water excretion than patients with HF and cirrhosis. Two mechanisms, underfill and overfill, may account for nephrotic edema; components of each mechanism may exist in different edematous conditions (Fig. 7.5). The underfill theory suggests that reduced plasma oncotic pressure from proteinuria increases fluid movement from the vascular to interstitial compartment. The resultant arterial underfilling culminates in activation of homeostatic mechanisms involving the SNS and the RAAS. The overfill theory implicates primary renal sodium and water retention that translates into elevated total plasma volume, hypertension, and suppressed RAAS. Distinguishing between the two mechanisms is important because it influences the approach to diuretic use in nephrotic patients.

The following observations support the underfill theory for edema formation. Plasma volume, systemic arterial blood pressure, and cardiac output are diminished in some nephrotic patients, especially in children with minimal change disease (MCD) (see Chapter 17). The Starling forces governing the fluid movement across the capillary wall equal the difference of the hydrostatic pressure and the oncotic pressure gradients. The gradual decrease in the plasma albumin concentration and the plasma oncotic pressure is mitigated by the reduced entry of albumin

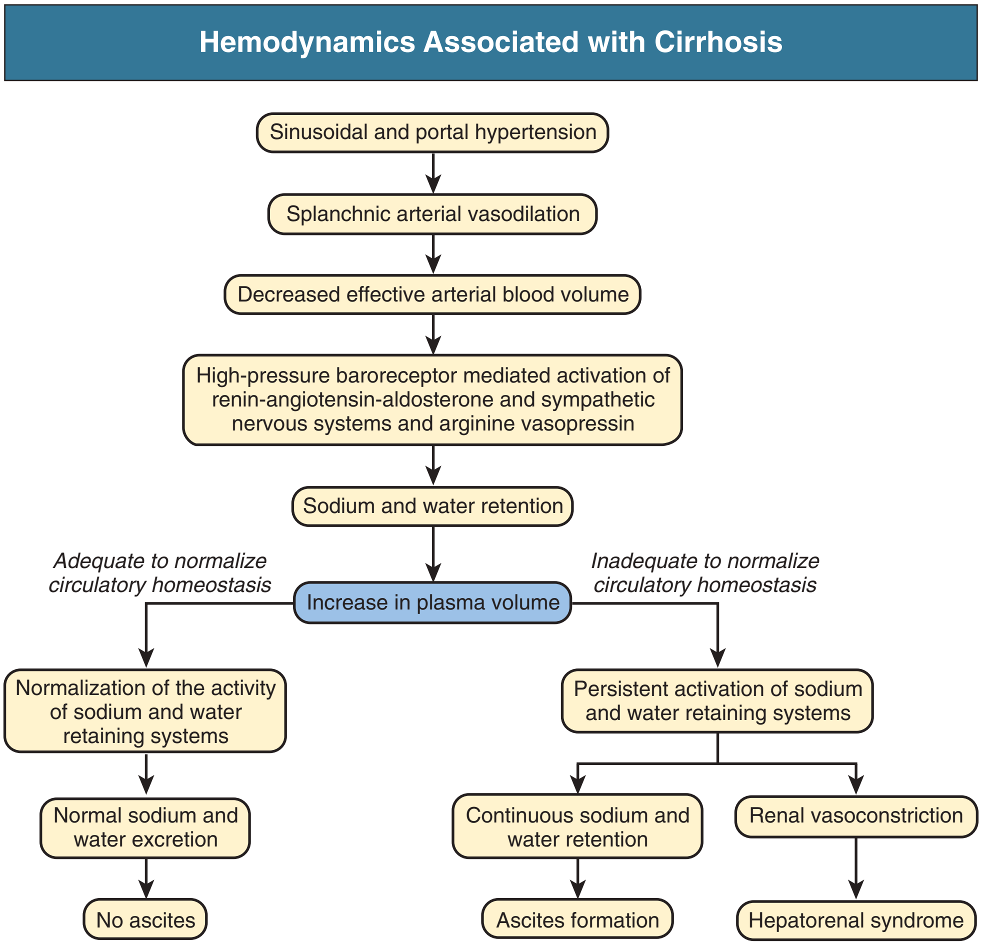
Hemodynamics Associated with Cirrhosis
Sinusoidal and portal hypertension
Splanchnic arterial vasodilation
Decreased effective arterial blood volume
High-pressure baroreceptor mediated activation of renin-angiotensin-aldosterone and sympathetic nervous systems and arginine vasopressin
Sodium and water retention
Adequate to normalize circulatory homeostasis
Increase in plasma volume
Inadequate to normalize circulatory homeostasis
Normalization of the activity of sodium and water retaining systems
Persistent activation of sodium and water retaining systems
Normal sodium and water excretion
Continuous sodium and water retention
Renal vasoconstriction
No ascites
Ascites formation
Hepatorenal syndrome

Fig. 7.4 Pathogenesis of functional renal abnormalities and ascites formation in cirrhosis. (Modified from reference 61.)

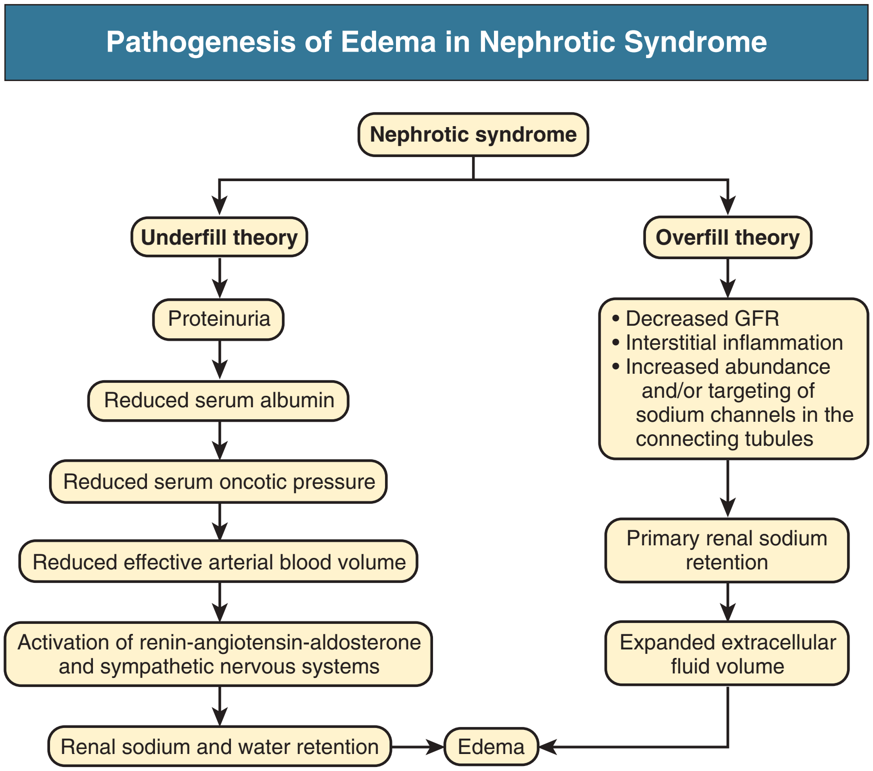
Pathogenesis of Edema in Nephrotic Syndrome
Nephrotic syndrome
Underfill theory
Overfill theory
Proteinuria
• Decreased GFR
• Interstitial inflammation
• Increased abundance and/or targeting of sodium channels in the connecting tubules
Reduced serum albumin
Reduced serum oncotic pressure
Primary renal sodium retention
Reduced effective arterial blood volume
Activation of renin-angiotensin-aldosterone and sympathetic nervous systems
Expanded extracellular fluid volume
Renal sodium and water retention
Edema

Fig. 7.5 Underfill and overfill mechanisms in pathogenesis of edema in nephrotic syndrome. The ratio of underfill and overflow likely varies, depending on the cause of the nephrotic syndrome. *GFR,* Glomerular filtration rate.

into the interstitial space and a concurrent decline in interstitial oncotic pressure. Consequently, less ECF volume expansion and edema formation is noted unless hypoalbuminemia is severe.[36] Thus nephrotic patients who are underfilled and are predisposed to AKI despite generalized edema generally have serum albumin concentration of less than 2 g/dl (20 g/l). However, serum albumin concentration may not be the primary driver of ECF volume expansion, because either spontaneous or steroid-induced remission of minimal change leads to natriuresis before albumin rises[37]; this suggests other mechanisms, in addition to low oncotic pressure, must be involved.

Observations supporting the overfill theory include studies of adults with MCD who have increased blood volume and blood pressure. After remission induced by corticosteroids, plasma volume and blood pressure decline, with an increase in plasma renin activity. However, evaluation of intravascular volume is somewhat unreliable because the afferent stimulus for edema formation appears to be a dynamic process, with different results at different phases of edema formation.[36] Also supporting primary renal sodium retention, experimental studies in animals with unilateral nephrotic syndrome demonstrate that sodium retention occurs secondary to increased reabsorption in the collecting tubules.[38] Increased abundance and apical targeting of ENaC subunits may be mediated, in part, by proteolytic cleavage of the channel by filtered proteases.[39-41]

In summary, nephrotic patients with arterial underfilling are more likely to have MCD with severe hypoalbuminemia, preserved GFR, and low blood pressure or postural hypotension. Other glomerular diseases, especially those involving renal inflammation, are more often associated with an overfill picture with volume expansion, raised blood pressure, and a decline in GFR. It has been postulated that interstitial inflammatory cells, a feature of some glomerular diseases other than MCD, may facilitate an increase in sodium retention and hypertension by releasing mediators that cause vasoconstriction.[42]

Drug-Induced Edema

Systemic vasodilators such as minoxidil and diazoxide induce arterial underfilling and subsequent retention of sodium with water (causing edema) through mechanisms similar to those in HF or cirrhosis. Dihydropyridine calcium channel blockers may cause peripheral edema, which is related to redistribution of fluid from the vascular space into the interstitium, possibly induced by preferential dilation of resistance arterioles in the absence of an appropriate microcirculatory myogenic reflex. This facilitates transmission of the systemic pressure to the capillary circulation.[43] Fluid retention and HF exacerbation may be seen with thiazolidinedione therapy in patients with type 2 diabetes mellitus, involving activation of peroxisome proliferator–activated receptor γ (PPARγ). Although this leads to stimulation of sodium reabsorption by the sodium channels in collecting tubule cells,[44] primary renal sodium retention alone should cause hypertension, not edema (see earlier discussion). Thus the effects of PPARγ agonists on vascular smooth muscle, which reduce arterial pressure,[45] likely play a central role. NSAIDs can exacerbate volume expansion in HF and cirrhotic patients by decreasing vasodilatory prostaglandins in the afferent arteriole of the glomerulus.[46]

Idiopathic Edema

This poorly defined syndrome occurs most often in premenopausal women and is characterized by intermittent edema secondary to sodium and water retention. Patients often complain of face and hand edema, leg swelling, and variable weight gain[47] and often misuse diuretics or laxatives, which may chronically stimulate the RAAS. The diagnosis of idiopathic edema is usually made by exclusion of other causes after history, physical examination, and sometimes diuretic screening.

Sodium and Water Retention in Pregnancy

In the first trimester of normal pregnancy, systemic arterial vasodilation and a decrease in blood pressure occur in association with a compensatory increase in cardiac output.[48] The lower arterial pressure activates the RAAS, contributing to the renal sodium and water retention and expanding the plasma volume (10%-30%).[49] Decreased plasma osmolality, stimulated thirst, and persistent nonosmotic vasopressin release are other features of normal pregnancy. In contrast to diseases such as HF and cirrhosis, pregnancy is associated with an increase in GFR and renal blood flow. The increased GFR leads to higher filtered load and increased distal sodium delivery in pregnancy, which contributes to the better escape from the sodium-retaining effect of aldosterone and attenuates edema formation. See Chapter 42 for more details.

Clinical Manifestations of Extracellular Fluid Volume Expansion

A history of an underlying disease, such as coronary artery disease, hypertension, or liver cirrhosis, can pinpoint the underlying mechanism of edema formation. Patients with left HF may present with exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Patients with right-sided HF or biventricular failure may exhibit weight gain and lower limb swelling. Physical examination reveals increased JVP, pulmonary crackles, a third heart sound, or dependent peripheral edema that may be elicited in the ankles or sacrum.

Nephrotic patients classically present with periorbital edema because of their ability to lie flat during sleep. However, those with severe disease may exhibit marked generalized edema with anasarca. Patients with cirrhosis present with ascites and lower limb edema caused by portal hypertension and hypoalbuminemia. Physical examination may reveal stigmata of chronic liver disease and splenomegaly.

Diagnostic and Therapeutic Approach to Extracellular Volume Expansion

Management of ECF volume expansion consists of recognizing and treating the underlying cause and attempting to achieve negative sodium balance by dietary sodium restriction and administration of diuretics. Before embarking on diuretic therapy, it is imperative to appreciate that ECF volume expansion may have occurred to compensate for arterial underfilling, as in HF and cirrhosis. A judicious approach is therefore necessary to avoid a precipitous fall in cardiac output and tissue perfusion. Rapid removal of excess fluid is generally necessary only in life-threatening situations, such as pulmonary edema and hypervolemia-induced hypertension.

Moderate dietary sodium restriction (2 to 3 g Na^+/day; 86 to 130 mmol/day) should be encouraged. Salt substitutes contain potassium chloride and should not be used in patients with advanced renal impairment or those taking potassium-sparing diuretics. Restriction of total fluid intake is usually necessary only for patients with hyponatremia. Medications that promote sodium retention (e.g., NSAIDs) should be discontinued. Diuretics are the cornerstone of therapy to remove excess volume. Other measures can be used in patients with inadequate response or lack of response to diuretics. In those with liver cirrhosis, large-volume paracentesis with albumin infusion provide symptomatic relief. Although extracorporeal fluid removal by ultrafiltration can be used in patients with acute decompensated HF accompanied by renal impairment or diuretic resistance, a randomized controlled trial did not indicate benefit.[50] ACE inhibitors and angiotensin receptor blockers (ARBs) are effective treatments for HF or nephrotic syndrome. Additional therapies for HF include antiarrhythmic agents, positive inotropes, and left ventricular assist devices.

Sites of Salt and Water Transport and Actions of Diuretics

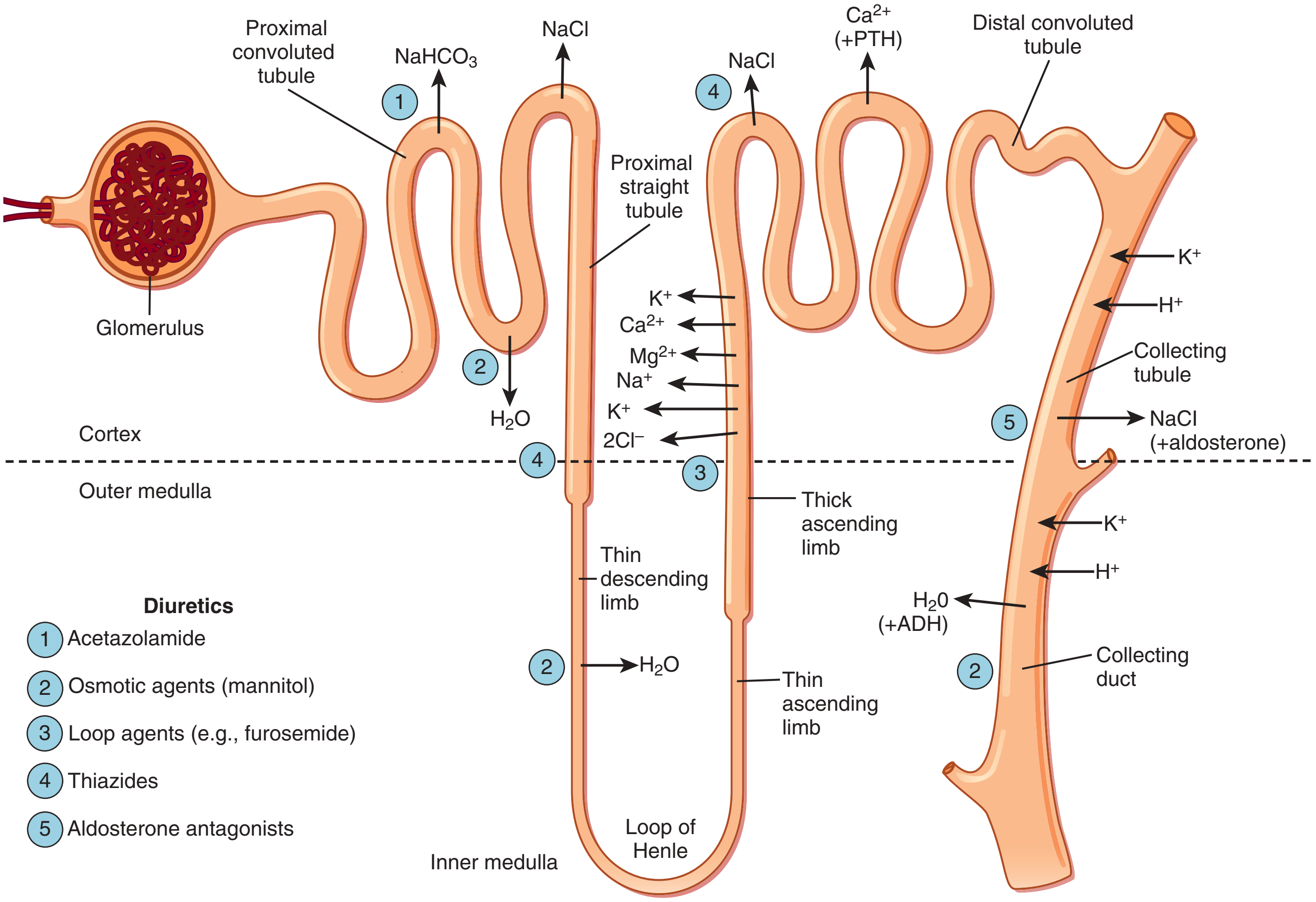
Proximal convoluted tubule
$NaHCO_3$
1
NaCl
Glomerulus
Proximal straight tubule
2
H_2O
NaCl
4
Ca^{2+} (+PTH)
Distal convoluted tubule
K^+
Ca^{2+}
Mg^{2+}
Na^+
K^+
$2Cl^-$
K^+
H^+
Collecting tubule
5
NaCl (+aldosterone)
Cortex
4
3
Outer medulla
Thick ascending limb
K^+
H^+
Thin descending limb
H_2O (+ADH)
Diuretics
1 Acetazolamide
2 Osmotic agents (mannitol)
3 Loop agents (e.g., furosemide)
4 Thiazides
5 Aldosterone antagonists
2
H_2O
Thin ascending limb
2
Collecting duct
Inner medulla
Loop of Henle

Fig. 7.6 **Sites of salt and water transport and actions of diuretics.** Specific sites are indicated by numbers. (Modified from reference 62.)

Diuretics

Principles of Action

Diuretics are the mainstay of therapy for edematous states, with five classes based on the predominant sites of diuretic action along the nephron (Fig. 7.6). Most diuretics reach their luminal transport sites by secretion across the proximal tubule epithelium. All diuretics except osmotic agents have a high degree of protein binding, which limits glomerular filtration, traps the drug in the vascular spaces, and allows it to be delivered to the proximal convoluted tubule for secretion.[51] Diuretics act by inhibiting sodium reabsorption with an accompanying anion, usually chloride. The resultant natriuresis decreases the ECF volume. At least two types of adaptation to diuretics are recognized. Loop diuretics have relatively short half-lives, and each dose is followed by a phase of natriuresis and a phase of antinatriuresis (often referred to as postdiuretic Na^+ retention). A low-salt diet can ensure that postdiuretic Na^+ retention does not overcome effective diuresis. A second type of adaptation occurs during chronic treatment. During continued administration of a diuretic, the magnitude of each natriuretic response declines, so daily salt excretion once again equals daily salt intake. This is known as the *braking phenomenon;* mechanisms include activation of the SNS and RAAS, decreased systemic and renal arterial blood pressure, hypertrophy of the distal nephron cells with increased expression of epithelial transporters, and perhaps alterations in natriuretic hormones (e.g., ANP).[51]

Classes of Diuretics

Loop diuretics. Loop diuretics such as furosemide, bumetanide, and torsemide act by blocking the Na^+-K^+-Cl^- cotransporters at the apical surface of the thick ascending limb (TAL) cells, thereby diminishing net reabsorption.[52] These agents are the most potent of all diuretics, inhibiting the reabsorption of 25% of filtered sodium, which normally occurs along the TAL. Moreover, the nephron segments past the TAL typically do not possess the capacity to reabsorb completely the volume of fluid exiting the TAL. Thus a substantial percentage of the solute rejected from the TAL is excreted.

The oral bioavailability of furosemide averages 50%, but varies between 10% and 100%; that of bumetanide and torsemide are higher (~80%). Loop diuretics have a short elimination half-life, so the dosing interval needs to be short to maintain adequate levels in the lumen. Excessive prolongation of dosing interval provides more time for postdiuretic sodium retention to overcome natriuresis. This is the reason that loop diuretics are typically given twice daily.

The intrinsic potency of a diuretic is defined by its dose-response curve, which is generally sigmoidal. The steep dose-response is the reason that loop diuretics are often referred to as "threshold drugs." This is exemplified by furosemide, which can initiate diuresis in a person with normal renal function with an intravenous dose of 10 mg, and a maximal effect is seen with 40 mg. A larger dose provides minimal or no extra benefit, and side effects may increase. However, the effective diuretic dose is higher in patients with HF, advanced cirrhosis, and renal failure. Patients who respond poorly to intermittent doses of a loop diuretic may receive continuous intravenous infusion, which might enhance the response by virtue of maintaining an effective amount of drug at the site of action.[53] A Cochrane review suggested that continuous infusions led to greater diuresis and a better safety profile, but the quality of the evidence was poor.[54] A randomized trial in acute decompensated HF found no difference in the primary end points—the global assessment of symptoms over the course of 72 hours and the change in serum creatinine from baseline to 72 hours—for continuous versus bolus infusion of furosemide. A higher dose of diuretic was more effective without clinically important negative effects on renal function.[55] This study did not include diuretic-resistant patients or those with significant renal dysfunction, in whom there may be a benefit of continuous infusion.

Although pharmacologically similar to other loop diuretics, ethacrynic acid has greater ototoxic potential and therefore is reserved for patients allergic to other agents.

Distal convoluted tubule diuretics. Thiazide and thiazide-like diuretics (chlorothiazide, hydrochlorothiazide, chlorthalidone, metolazone, and indapamide) inhibit NaCl absorption in the distal tubule, where up to 5% of filtered sodium and chloride is reabsorbed, and are therefore less potent than loop diuretics. Thiazides have a relatively longer half-life and can be administered once or twice daily. Metolazone has pharmacologic characteristics similar to those of thiazide diuretics and is more often used in conjunction with other classes of diuretics.

Thiazides are used commonly to treat hypertension (see Chapter 36). For edema, they are occasionally used alone in patients with mild HF, but more often are used in combination to synergize the effect of loop diuretics by blocking multiple nephron segment sites. Because thiazide diuretics must reach the lumen to be effective, higher doses are required in patients with impaired renal function. Thiazides as sole agents (possibly excluding the thiazide-like diuretics metolazone and indapamide) lose effectiveness at GFR less than 30 ml/min, but can still enhance the diuretic effect of loop diuretics when coadministered in sufficient doses to attain effective nephron lumen concentration. If used, such combination therapy should be closely monitored because of a pronounced risk for hypokalemia and excessive ECF depletion.

Collecting duct diuretics. Amiloride, triamterene, and the aldosterone antagonists spironolactone and eplerenone, act on the collecting duct. Amiloride and triamterene act primarily in the connecting tubule and cortical collecting duct (the aldosterone-sensitive distal nephron) by interfering with sodium reabsorption through the apical ENaC and inhibit potassium secretion by dissipating the electronegative gradient (normally created by sodium reabsorption) that favors potassium secretion. Spironolactone and eplerenone are competitive antagonists of aldosterone and cause natriuresis and potassium retention. Potassium-sparing diuretics are considered weak diuretics because they block only about 3% of the filtered sodium load reaching their site of action and thus are most often used with other diuretics to augment diuresis or preserve potassium. If combination therapy is used, careful monitoring is essential to prevent dangerous hyperkalemia. Vulnerable patients include those with underlying renal dysfunction, those with HF, patients with diabetes, and those concurrently taking ACE inhibitors, ARBs, NSAIDs, or β-blockers. Finerenone is the first of a group of new nonsteroidal MRAs. It is currently in clinical trials and has been suggested to improve albuminuria in the setting of diabetes, perhaps with a lower rate of side effects.[56] A goal is to find a product that will confer the beneficial effects of mineralocorticoid blockade, without the complicating effects on plasma potassium and GFR.

Collecting duct diuretics are considered first-line agents in certain conditions. For example, spironolactone is used in patients with liver cirrhosis with ascites, and amiloride in the treatment of Liddle syndrome, a rare autosomal dominant condition characterized by a primary increase in ENaC function (see Chapter 47).

Proximal tubule diuretics. Acetazolamide indirectly inhibits Na^+-H^+ exchange by reducing the elimination of secreted protons in the proximal tubule lumen, thus increasing sodium bicarbonate excretion. Acetazolamide is a weak diuretic because distal segments reabsorb much of the inhibited Na^+ and proximal inhibition activates the TGF to reduce Na^+ filtration.[6] Acetazolamide generates hyperchloremic metabolic acidosis, particularly with prolonged use. It also may cause hypokalemia because of increased distal sodium delivery; it may cause hypophosphatemia, but the mechanism of this is not well understood. Rarely used as a single agent, acetazolamide is most frequently used with other diuretics, in treatment of metabolic alkalosis accompanied by edematous states, and in chronic obstructive pulmonary disease. It is also used in acute and chronic high altitude sickness because of its ability to stimulate ventilation as a compensatory response to the metabolic acidosis, although unpleasant paresthesias may occur.

Osmotic diuretics. Osmotic diuretics such as mannitol are freely filtered at the glomerulus but are poorly reabsorbed. Mannitol is used intravenously and produces diuresis by increasing the osmotic pressure within the lumen of the proximal tubule and loop of Henle. This causes enhanced water diuresis and to a lesser extent sodium and potassium excretion. Mannitol is not used for edematous states but rather to treat cerebral edema induced by trauma or neoplasms and to reduce intraocular pressure. Mannitol is also used in the treatment of dialysis disequilibrium syndrome, preventing the brisk decline in serum osmolality that would otherwise occur with dialysis. This helps prevent a shift of fluid into the brain that may occur with rapid rate of solute removal by dialysis, which is thought to be responsible for the symptoms.

Adverse Effects

Many common diuretics are derived from sulfanilamide and may therefore induce allergy in susceptible patients, manifested as hypersensitivity reactions, usually as a rash or, rarely, acute interstitial nephritis. The most serious and common adverse effects of diuretics, however, are electrolyte disturbances.

Loop diuretics impair tubular reabsorption by abolishing the transepithelial potential gradient and thus increase excretion of magnesium and calcium. Thiazide diuretics exert the same effect on magnesium. In a recent study of community-dwelling subjects, the use of a thiazide was associated with prevalent hypomagnesemia, whereas loop diuretic use was not.[57] Unlike loop diuretics, thiazide diuretics decrease urinary calcium losses and are therefore preferred in the treatment of hypercalciuric states and in patients with osteoporosis. Thiazide diuretics interfere with urine-diluting mechanisms by blocking sodium reabsorption at the distal convoluted tubule, an effect that may contribute to hyponatremia.[58] Acutely, loop and thiazide diuretics increase the excretion of uric acid, whereas chronic administration results in reduced uric acid excretion. The chronic effect is likely caused by enhanced absorption in the proximal convoluted tubule secondary to volume depletion. Other adverse effects with large doses may include ototoxicity with loop diuretics, particularly with aminoglycoside coadministration, and gynecomastia, which may develop with spironolactone.

Approach to Diuretic Treatment of Extracellular Fluid Volume Expansion

Although the mechanisms underlying expansion of the ECF volume are similar in the different clinical syndromes, some evidence-based differences in diuretic approach are recommended. For HF, either HF_REF or HF_PEF, initial treatment involves loop diuretics. A starting dose of 20 to 40 mg furosemide, or an equivalent, is typical, and may be effective, but it may be necessary to increase, or double, subsequent doses if the initial dose does not elicit a diuresis. Such a diuresis should occur promptly after drug administration and be notable to the patient. This approach is based on the threshold nature of the loop diuretic dose response curve. It is often necessary to use loop diuretics twice daily, but it is always important to ensure that each dose is above the threshold. The pharmacokinetic profile of torsemide is more favorable than that of furosemide; some clinicians prefer this drug, but solid evidence to support this choice is lacking.

For cirrhotic ascites, patients should be started on a combination of spironolactone and furosemide, at a fixed ratio (100 mg spironolactone to 40 mg furosemide).[59] Single-agent spironolactone was used previously, but was shown to cause more potassium imbalance. Doses can be titrated retaining the same ratio of spironolactone and furosemide.

For nephrotic syndrome and CKD, loop diuretics are indicated, but higher doses than used for HF are typically required, because both CKD and nephrotic syndrome are diuretic-resistant conditions.

Diuretic Resistance

Diuretic *resistance* typically refers to edema that has become refractory to maximal doses of loop diuretics. Apparent resistance may be the result of drug interactions. NSAIDs block prostaglandin-mediated increases in renal blood flow and natriuresis and can precipitate HF exacerbations.[46] Arterial underfilling in cirrhosis and HF increases proximal tubular sodium reabsorption, which reduces delivery of sodium to the distal nephron segment sites of diuretic action. Yet, in HF, resistance most commonly results from activation of distal nephron transport.[60] This problem can be addressed by combining loop and thiazide diuretics, because the latter block the distal nephron sites responsible. As loop diuretics stimulate renin secretion at the macula densa, leading to Ang II production and aldosterone secretion, it may be reasonable to initiate aldosterone antagonist therapy before addition of a thiazide diuretic in patients with low or low-normal serum potassium level. In nephrotic syndrome, the filtered protein in tubular fluid may contain serine proteases, which cleave and activate ENaC, thereby promoting excess sodium reabsorption.[41]

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SELF-ASSESSMENT QUESTIONS

1. A 58-year-old woman with a history of alcohol dependence and known chronic liver disease presents to the emergency department with increasing breathlessness and distended abdomen. Vital signs reveal temperature of 36.9° C (98.5° F), respiratory rate of 17 breaths/min, oxygen saturation of 93% on room air, pulse rate of 76/min, and blood pressure of 93/58 mm Hg without significant orthostatic change. Physical examination reveals scleral icterus, and jugular venous pressure (JVP) is flat. Cardiac auscultation is normal; breath sounds are decreased at the bases. Her abdomen is distended with a fluid wave and a positive shifting dullness. The patient has bilateral pitting edema to the midcalves and intact peripheral pulses. The primary mechanism responsible for *maintaining* volume excess in this patient is:
   - **A.** Reduction in plasma oncotic pressure resulting from synthetic hypoalbuminemia causing an increase in fluid movement from the vascular to the interstitial compartment
   - **B.** Underfilling of the arterial circulation resulting from splanchnic venous dilation causing neurally and hormonally mediated renal sodium retention
   - **C.** Primary renal sodium and water retention that results in elevated total plasma volume
   - **D.** Decrease in plasma osmolality with stimulation of thirst and persistent release of antidiuretic hormone
2. Laboratory investigations of the patient described in question 1 reveal serum sodium of 128 mmol/L, potassium 3.7 mmol/L, chloride 101 mmol/L, bicarbonate 23 mg/dL, blood urea nitrogen (BUN) 56 mg/dL, and creatinine 1.0 mg/dL. Albumin is 3.0 g/dL. Reasonable initial approaches to remove excess volume in this patient include all the following *except:*
   - **A.** Prescribe a diet restricted to 2.3 g (100 mmol) of sodium daily to mitigate renal retention of sodium and prevent diuretic resistance
   - **B.** Perform a large-volume paracentesis with albumin infusion to rapidly decompress the abdomen
   - **C.** Administer spironolactone up to 400 mg/day, with a loop diuretic to increase sodium excretion
   - **D.** Administer intravenous mannitol to increase osmotic pressure within the tubule and thus sodium and water reabsorption
3. Over the next 3 days, the patient previously described becomes febrile, temperature 37.8° C (100° F), and confused. Her pulse rate is 120 beats/min with blood pressure of 88/52 mm Hg. The JVP is now near the angle of the jaw when the patient is sitting at 45 degrees. Hemoglobin is 7.6 g/dL, total WBC count 15,000 (85% polymorphonuclear leukocytes [PMNs]), and platelet count 81,000 $\times 10^9$ cells/l. Analysis of the ascitic fluid reveals 100 RBCs/μl and 450 WBCs/μl, but no organisms on Gram stain. BUN is 48 mg/dL, serum creatinine 1.7 mg/dL, and urine sodium 65 mEq/l, with a fractional sodium excretion of 1.4%. Appropriate immediate measures for the patient at this time would include which of the following?
   - **A.** Administer 50 g of albumin, with the goal of improving her hemodynamic profile
   - **B.** Administer fluid resuscitation with 6% HES to expand extracellular fluid compartment rapidly and restore blood pressure
   - **C.** Treat for presumptive bacterial peritonitis
   - **D.** Insert jugular venous dialysis access for urgent initiation of dialysis

8

Disorders of Water Metabolism

Tomas Berl, Jeff M. Sands

PHYSIOLOGY OF WATER BALANCE

The maintenance of the tonicity of body fluids within a narrow physiologic range is made possible by homeostatic mechanisms that control the intake and excretion of water. Vasopressin, known as arginine vasopressin (AVP) or antidiuretic hormone (ADH), governs the excretion of water by its effect on the renal collecting system. Osmoreceptors located in the hypothalamus control the secretion of AVP in response to changes in tonicity.

In the steady state, water intake matches water loss. Water intake is regulated by the need to maintain a physiologic serum osmolality of 285 to 290 mOsm/kg H_2O. Despite major fluctuations of solute and water intake, the total solute concentration (i.e., the tonicity) of body fluids is maintained virtually constant. The ability to dilute and to concentrate the urine allows wide flexibility in urine flow (see Chapter 2). During water loading, the diluting mechanisms permit excretion of 20 to 25 liters of urine daily, and during water deprivation the urine volume may be as low as 0.5 l/day.[1-3]

VASOPRESSIN

AVP plays a critical role in determining the concentration of urine: it is a 9–amino acid cyclic peptide, synthesized and secreted by the supraoptic and paraventricular magnocellular nuclei in the hypothalamus. AVP has a half-life of 15 to 20 minutes and is rapidly metabolized in the liver and the kidney.

Osmotic Stimuli for Vasopressin Release

Substances restricted to the extracellular fluid (ECF), such as hypertonic saline and mannitol, decrease cell volume by acting as effective osmoles and enhancing osmotic water movement from the cell. This stimulates AVP release; in contrast, urea and glucose readily cross cell membranes and thus do not cause changes in cell volume. The "osmoreceptor" cells, located close to the supraoptic nuclei in the anterior hypothalamus, are sensitive to changes in serum osmolality as small as 1% and bring about the release of AVP by a pathway that involves the activation of transient receptor potential (TRPV4) channels.[4] In humans, the osmotic threshold for AVP release is 280 to 290 mOsm/kg H_2O[2,5] (Fig. 8.1). This system is so efficient that serum osmolality usually does not vary by more than 1% to 2% despite wide fluctuations in water intake.

Nonosmotic Stimuli for Vasopressin Release

Decreased effective circulating volume (e.g., heart failure, cirrhosis, vomiting) causes discharge from parasympathetic afferent nerves in the carotid sinus baroreceptors and increases AVP secretion. Much higher AVP levels can be achieved with hypovolemia than with hyperosmolality, although a large (7%) decrease in blood volume is required before this response is elicited. Other nonosmotic stimuli include nausea, pain, pregnancy, and fructose. AVP levels (as reflected by elevation of serum copeptin, a surrogate marker) are also elevated in patients with metabolic syndrome and in patients with chronic kidney disease (CKD) compared to healthy individuals.

Mechanism of Vasopressin Action

AVP binds three types of receptors coupled to G proteins: the V_{1a} (vascular and hepatic), V_{1b} (anterior pituitary and pancreatic islet), and V_2 (renal) receptors. The V_2 receptor is primarily localized in the collecting duct and leads to an increase in water permeability through aquaporin 2 (AQP2), a member of a family of cellular water transporters (Fig. 8.2). AQP1 is localized in the apical and basolateral region of the proximal tubule epithelial cells and the descending limb of the loop of Henle and accounts for the high water permeability of these nephron segments. AQP1 is constitutively expressed and not subject to regulation by AVP.[6] AQP2 is localized primarily in apical plasma membranes and intracellular vesicles in the collecting duct principal cells. AVP affects both the short-term and the long-term regulation of AQP2. The short-term regulation, also described as the "shuttle hypothesis," explains the rapid and reversible increase (within minutes) in collecting duct water permeability after AVP administration. This involves the insertion of water channels from subapical vesicles into the luminal membrane. Long-term regulation relates to AVP-mediated increases in the transcription of genes involved in AQP2 production and occurs if AVP levels are elevated for 24 hours or more. An increased number of AQP2 channels per cell elevates the maximal water permeability of the collecting duct epithelium.[6]

AQPs 3 and 4 are located on the basolateral membranes of the collecting duct (see Fig. 8.2) and are involved in water exit from the cell. AQP3 is expressed along the entire collecting duct, and AQP4 is found in the inner medullary collecting duct. AQP4 is also found in the hypothalamus and is a candidate osmoreceptor for the control of AVP release.[6]

AVP also stimulates urea transporters in the inner medullary collecting duct. UT-A1 is found primarily in apical plasma membranes and intracellularly in inner medullary collecting ducts. UT-A3 is found predominantly in the basolateral plasma membrane in inner medullary collecting ducts. Urea reabsorption into the inner medullary interstitium is important for increasing inner medullary tonicity and the driving force for water reabsorption.[7]

Thirst and Water Balance

Hypertonicity is the most potent stimulus for thirst, with a change of only 2% to 3% in serum osmolality producing a strong desire to drink. The osmotic threshold for thirst usually occurs at 290 to 295 mOsm/

kg H_2O and is above the threshold for AVP release (see Fig. 8.1). This osmolality closely approximates the level at which maximal concentration of urine is achieved. Hypovolemia, hypotension, and angiotensin II (Ang II) are also stimuli for thirst. Between the limits imposed by the osmotic thresholds for thirst and AVP release, serum osmolality may be regulated more precisely by small, osmoregulated adjustments in urine flow and water intake. The exact level at which balance occurs depends on insensible losses, water intake, and water generated from metabolism.

QUANTITATION OF RENAL WATER EXCRETION

Urine volume can be considered as having two components. The osmolar clearance (C_{osm}) is the volume needed to excrete solutes at the concentration of solutes in serum. The free water clearance (C_{water}) is the volume of water that has been added to (positive C_{water}) or subtracted from (negative C_{water}) isotonic urine (C_{osm}) to create either hypotonic or hypertonic urine.

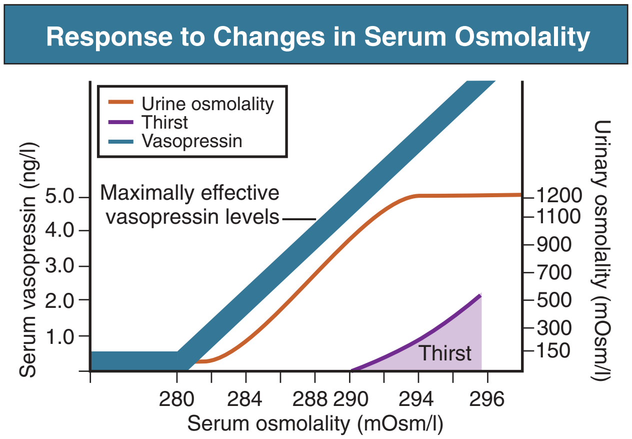

Fig. 8.1 Mechanisms maintaining serum osmolality. Thirst, vasopressin levels, and urinary osmolality in response to changes in serum osmolality. (Modified from reference 2.)

Urine volume flow (V) comprises the isotonic portion of urine (C_{osm}) plus the free water clearance (C_{water}).

$$V = C_{osm} + C_{water}$$

Therefore:

$$C_{water} = V - C_{osm}$$

The C_{osm}, solute clearance is determined by urine flow, urine osmolality, and serum osmolality P_{osm} as follows:

$$C_{osm} = \left(\frac{U_{osm} \times V}{P_{osm}}\right)$$

Therefore:

$$C_{water} = V - \left(\frac{U_{osm} \times V}{P_{osm}}\right)$$

$$= V\left(1 - \frac{U_{osm}}{P_{osm}}\right)$$

This relationship reflects the following:

1. In hypotonic urine ($U_{osm} < P_{osm}$), C_{water} is positive.
2. In isotonic urine ($U_{osm} = P_{osm}$), C_{water} is zero.
3. In hypertonic urine ($U_{osm} > P_{osm}$), C_{water} is negative (i.e., water is retained).

If excretion of free water in a polyuric patient is unaccompanied by water intake, the patient becomes hypernatremic. Conversely, failure to excrete free water with increased water intake can cause hyponatremia.

A limitation of the previous equation is that it fails to predict clinically important alterations in serum tonicity and serum sodium concentration (serum [Na^+]) because urea is included in the calculation of urine osmolality. Urea is an important component of urinary osmolality; however, because it crosses cell membranes readily, urea does not establish a transcellular osmotic gradient and does not cause water movement between fluid compartments. Therefore urea does not influence serum Na^+ concentration or the release of AVP and changes in serum [Na^+] are better predicted by electrolyte free water clearance

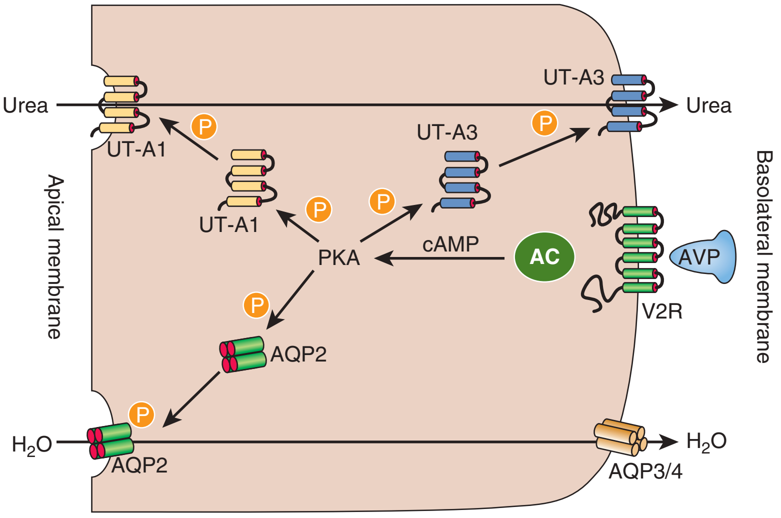

Fig. 8.2 Cellular mechanism of vasopressin action. Vasopressin *(AVP)* binds to V_2 receptors *(V2R)* on the basolateral membrane and activates G proteins that initiate a cascade *(cAMP, PKA)* resulting in aquaporin 2 *(AQP2)* and urea transporter A1 *(UT-A1)* phosphorylation and accumulation in the apical membrane. Water exits the cell through *AQP3* and *AQP4* in the basolateral membrane. Urea exits the cell through *UT-A3* in the basolateral membrane. *AVP,* Arginine vasopressin; *cAMP,* cyclic adenosine monophosphate; *PKA,* protein kinase A.

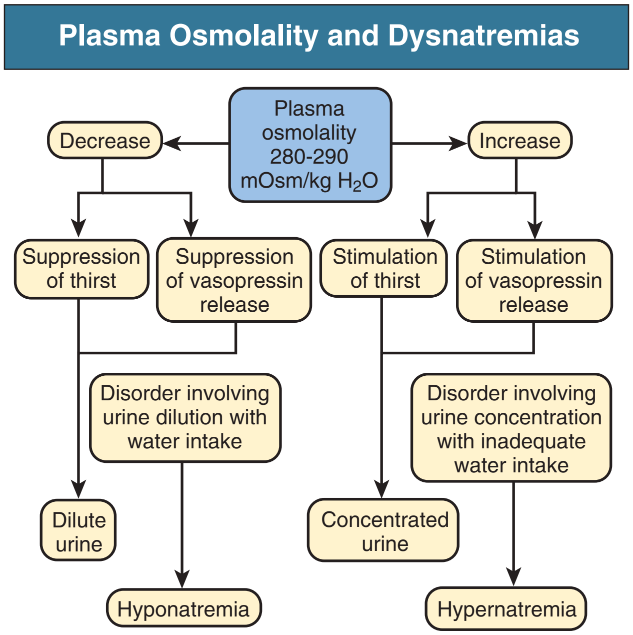
Plasma Osmolality and Dysnatremias
Plasma osmolality 280-290 mOsm/kg H2O
Decrease
Increase
Suppression of thirst
Suppression of vasopressin release
Stimulation of thirst
Stimulation of vasopressin release
Disorder involving urine dilution with water intake
Disorder involving urine concentration with inadequate water intake
Dilute urine
Concentrated urine
Hyponatremia
Hypernatremia

Fig. 8.3 Maintenance of serum osmolality and pathogenesis of dysnatremias. (Modified from reference 8.)

[$C_{water}(e)$]. The equation can be modified, replacing P_{osm} by serum [Na^+] (P_{Na}) and the urine osmolality by urine [Na^+] and urine [K^+], potassium concentration, ($U_{Na} + U_K$):

$$C_{water}(e) = V\left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right)$$

If $U_{Na} + U_K$ is less than P_{Na}, then $C_{water}(e)$ is positive and serum [Na^+] increases. If $U_{Na} + U_K$ is greater than P_{Na}, then $C_{water}(e)$ is negative and serum [Na^+] decreases. In the clinical setting, it is more appropriate to use the equation for electrolyte-free clearance to predict if a patient's serum [Na^+] will increase or decrease in the face of the prevailing water excretion. For example, in a patient with high urea excretion, the original equation would predict negative water excretion and a decrease in serum [Na^+]; but in fact, [Na^+] increases, which is accurately predicted by the latter equation.

SERUM SODIUM CONCENTRATION, OSMOLALITY, AND TONICITY

The kidney's countercurrent mechanism, which allows urinary concentration and dilution, acts in concert with the hypothalamic osmoreceptors through AVP secretion to maintain serum [Na^+] and tonicity within a very narrow range[8] (Fig. 8.3). A defect in the urine-diluting capacity coupled with excess water intake leads to hyponatremia. A defect in urine-concentrating ability with inadequate water intake leads to hypernatremia.

Serum [Na^+], along with its accompanying anions, accounts for nearly all the osmotic activity of the serum. Calculated serum osmolality is given by 2[Na^+] + blood urea nitrogen (BUN) (mg/dl)/2.8 + glucose (mg/dl)/18. The addition of other solutes to ECF results in an increase in measured osmolality (Table 8.1). Solutes that are permeable across cell membranes do not cause water movement and cause hypertonicity without cellular dehydration, as in uremia or ethanol intoxication. By contrast, in diabetic ketoacidosis, when glucose cannot freely cross cell membranes in the absence of insulin, water moves from the cells to the ECF, leading to cellular dehydration and lowering serum [Na^+]. This can be viewed as *translocational* because the decrease in serum [Na^+] does not reflect a change in total body water but rather the movement of water from intracellular to extracellular space. Therefore serum [Na^+] can be corrected by 1.6 mmol/l for every 100 mg/dl (5.6 mmol/l) increase in serum glucose, although this may somewhat underestimate the impact of glucose to decrease serum [Na^+].

TABLE 8.1 Effects of Osmotically Active Substances on Serum Sodium (Na^+) Levels

Substances That Increase Osmolality Without Changing Serum Na^+	Substances That Increase Osmolality and Decrease Serum Na^+ (Translocational Hyponatremia)
Urea	Hyperglycemia
Ethanol	Mannitol
Ethylene glycol	Glycine
Isopropyl alcohol	Maltose
Methanol	

Pseudohyponatremia occurs when the solid phase of serum (usually 6% to 8%) is increased by large increments in either lipids or proteins (e.g., in hypertriglyceridemia and paraproteinemias). Serum osmolality is normal in pseudohyponatremia. This false result occurs because the usual method that measures the concentration of sodium uses whole serum and not just the liquid phase, in which the concentration of sodium is 150 mmol/l. Many laboratories are now moving to direct ion-selective potentiometry, which gives the true aqueous sodium activity. In the absence of a direct-reading potentiometer, an estimate of serum water may be obtained from the following formula[9]:

$$\text{Serum water content (\%)} = 99.1 - (0.1 \times L) - (0.07 \times P)$$

where *L* and *P* refer to the total lipid and protein concentration (in grams per liter), respectively. For example, if the formula reveals that serum water is 90% of the serum sample rather than the normal 93% (which yields a serum sodium concentration of 140 mmol/l as 150 × 0.93 = 140), the concentration of measured sodium would be expected to decrease to 135 mmol/l (150 × 0.90).

ESTIMATION OF TOTAL BODY WATER

In normal individuals, total body water is approximately 60% of body weight (50% in women and obese individuals). With hyponatremia or hypernatremia, the change in total body water can be calculated from the serum [Na^+] by the following formula:

$$\text{Water excess} = 0.6W \times \left(1 - \frac{[Na^+]_{obs}}{140}\right)$$

$$\text{Water deficit} = 0.6W \times \left(\frac{[Na^+]_{obs}}{140} - 1\right)$$

where $[Na^+]_{obs}$ is observed sodium concentration (in millimoles per liter) and *W* is body weight (in kilograms). By use of this formula, a change of 10 mmol/l in the serum [Na^+] in a 70-kg individual is equivalent to a change of 3 liters in free water.

HYPONATREMIC DISORDERS

Hyponatremia is defined as serum [Na^+] of less than 135 mmol/l. If translocational and pseudohyponatremia are not responsible for the

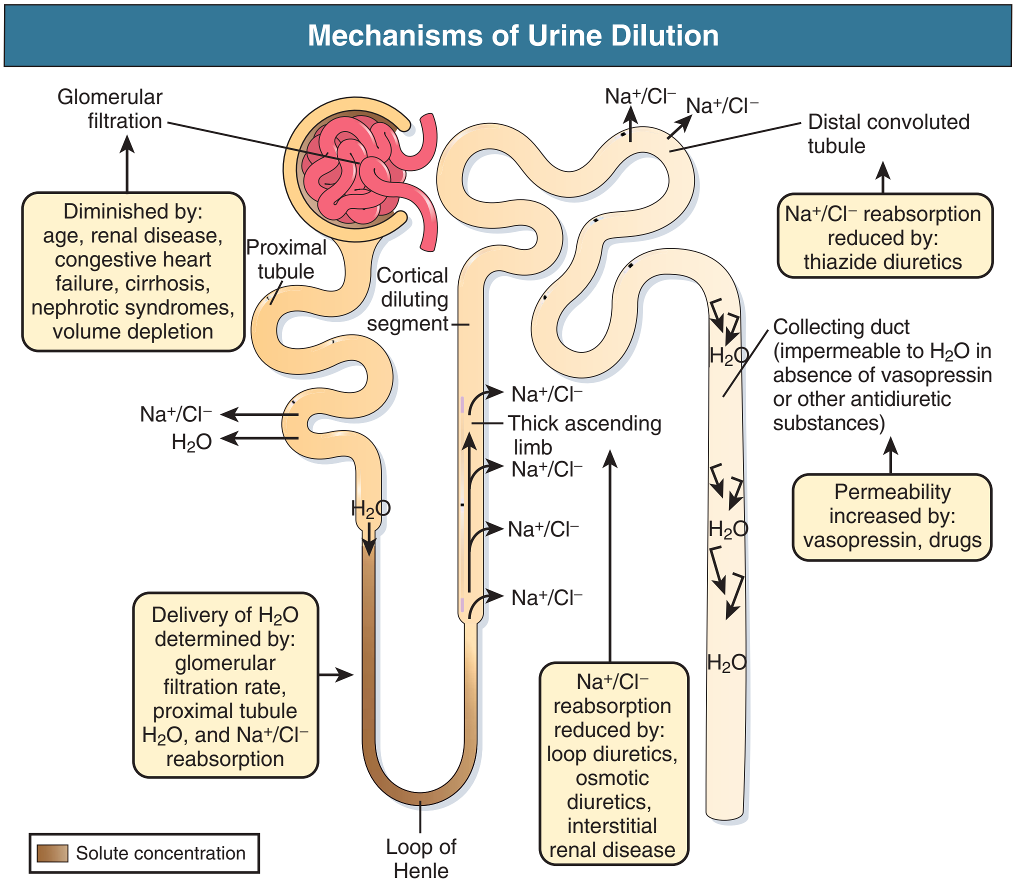
Mechanisms of Urine Dilution
Glomerular filtration
Diminished by: age, renal disease, congestive heart failure, cirrhosis, nephrotic syndromes, volume depletion
Proximal tubule
Cortical diluting segment
Na+/Cl−
Na+/Cl−
Distal convoluted tubule
Na+/Cl− reabsorption reduced by: thiazide diuretics
Collecting duct (impermeable to H2O in absence of vasopressin or other antidiuretic substances)
H2O
Permeability increased by: vasopressin, drugs
Na+/Cl−
H2O
Na+/Cl−
Thick ascending limb
Na+/Cl−
H2O
Na+/Cl−
H2O
Na+/Cl−
Delivery of H2O determined by: glomerular filtration rate, proximal tubule H2O, and Na+/Cl− reabsorption
H2O
Na+/Cl− reabsorption reduced by: loop diuretics, osmotic diuretics, interstitial renal disease
Solute concentration
Loop of Henle

Fig. 8.4 Mechanisms of urine dilution. Normal determinants of urinary dilution and disorders causing hyponatremia. (Modified from reference 10.)

hyponatremia, the decrease in serum sodium concentration reflects a low serum osmolarity, also designated as hypotonicity. The underlying cause of hypotonic hyponatremia is a disturbance in the urinary diluting mechanism.[10] Fig. 8.4 depicts the normal diluting process and the sites at which it can be disrupted so as to impair water excretion, causing its retention and culminating in hyponatremia. A diminished glomerular filtration rate (GFR) and/or an increase in proximal tubular fluid reabsorption decrease distal delivery of filtrate to the diluting segments of the nephron, quantitatively limiting maximal water excretion. In addition, hyponatremia may result from a decrement in Na^+-Cl^- transport from the thick ascending limb of the loop of Henle or distal convoluted tubule, critical processes in the generation of a dilute tubular fluid. Most frequently, hyponatremia results from nonosmotic AVP secretion despite the presence of serum hypo-osmolality. This renders the collecting duct water permeable, thereby not allowing for the excretion of a maximally dilute urine.

Etiology and Classification of Hyponatremia

Once the patient is ascertained as being hypo-osmolar, the next step is to determine whether the individual is hypovolemic, euvolemic, or hypervolemic (Fig. 8.5).

Hypovolemia: Hyponatremia Associated With Decreased Total Body Sodium

A patient with hypovolemic hyponatremia has both a total body Na^+ and a water deficit, with the Na^+ deficit exceeding the water deficit. This occurs in patients with high gastrointestinal and renal losses of water and solute accompanied by free water or hypotonic fluid intake. The underlying mechanism is the nonosmotic release of AVP stimulated by volume contraction, which maintains AVP secretion despite the hypotonic state. Measurement of urine $[Na^+]$ is a useful tool to help diagnose these conditions (see Fig. 8.5).

Gastrointestinal and third-space sequestered losses. The kidney responds to volume contraction by conserving Na^+ and Cl^-. A similar response is observed in burn victims and patients with sequestration of fluids in third spaces, as in the peritoneal cavity with peritonitis or pancreatitis or in the bowel lumen with ileus. In all these, urine $[Na^+]$ is usually less than 10 mmol/l and the urine is hyperosmolar. An exception occurs in patients with vomiting and metabolic alkalosis. Here, increased bicarbonate ion (HCO_3^-) excretion obligates simultaneous cation excretion resulting in a urine $[Na^+]$ that may exceed 20 mmol/l despite severe volume depletion, however the urine $[Cl^-]$ remains less than 10 mmol/l. Sodium conservation is also impaired in CKD that may also result in high urine $[Na^+]$ despite volume depletion.

Diuretics. Diuretic use is one of the most common causes of hypovolemic hyponatremia associated with a high urine $[Na^+]$. Loop diuretics inhibit Na^+-Cl^- reabsorption in the TAL impairing the generation of a hypertonic medullary interstitium. Therefore, despite increased AVP secretion, responsiveness to AVP is diminished and free water is excreted. In contrast, thiazide diuretics act in the distal tubule, where they interfere with urine dilution, limiting free water excretion. Hyponatremia usually occurs within 14 days of initiation of therapy, with manifestation in approximately one third of patients within 5 days. Underweight women and elderly patients are most susceptible. Postulated mechanisms for diuretic-induced hyponatremia include the following:

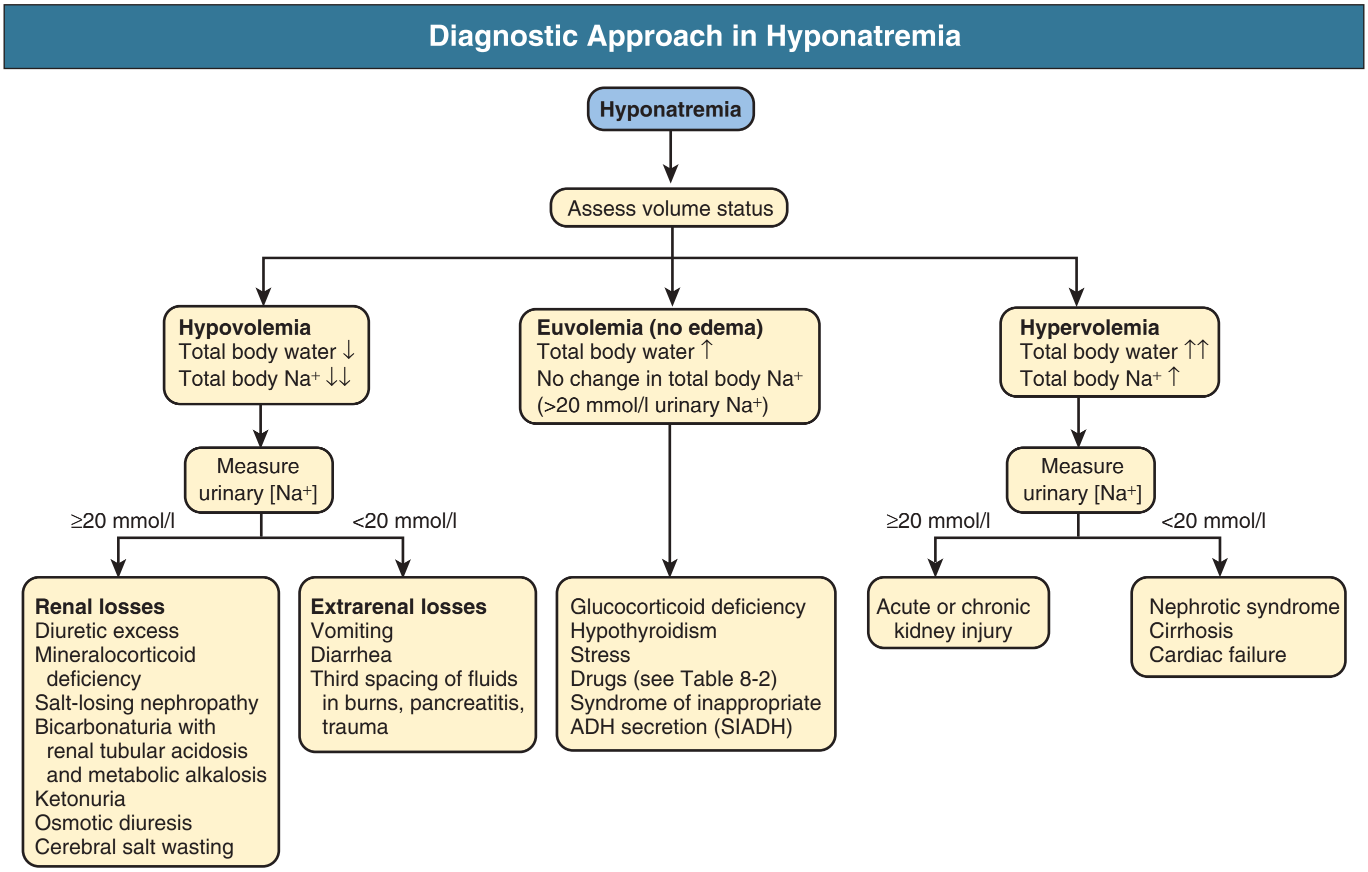
Diagnostic Approach in Hyponatremia
Hyponatremia
Assess volume status
Hypovolemia
Total body water ↓
Total body Na+ ↓↓
Euvolemia (no edema)
Total body water ↑
No change in total body Na+
(>20 mmol/l urinary Na+)
Hypervolemia
Total body water ↑↑
Total body Na+ ↑
Measure urinary [Na+]
≥20 mmol/l
<20 mmol/l
Renal losses
Diuretic excess
Mineralocorticoid deficiency
Salt-losing nephropathy
Bicarbonaturia with renal tubular acidosis and metabolic alkalosis
Ketonuria
Osmotic diuresis
Cerebral salt wasting
Extrarenal losses
Vomiting
Diarrhea
Third spacing of fluids in burns, pancreatitis, trauma
Glucocorticoid deficiency
Hypothyroidism
Stress
Drugs (see Table 8-2)
Syndrome of inappropriate ADH secretion (SIADH)
Measure urinary [Na+]
≥20 mmol/l
<20 mmol/l
Acute or chronic kidney injury
Nephrotic syndrome
Cirrhosis
Cardiac failure

Fig. 8.5 Algorithm for diagnostic assessment of the patient with hyponatremia. (Modified from reference 8.)

- Hypovolemia-stimulated AVP release and decreased fluid delivery to the diluting segment
- Impaired water excretion through interference with maximal urinary dilution in the cortical diluting segment
- K^+ depletion, directly stimulating water intake by alterations in osmoreceptor sensitivity and increasing thirst

Water retention can mask the physical findings of hypovolemia, making the patients with diuretic-induced hyponatremia appear euvolemic.

Salt-losing nephropathy. A salt-losing state may occur in patients with advanced CKD (GFR <15 ml/min), particularly from interstitial disease. It is characterized by hyponatremia and hypovolemia. In proximal (type 2) renal tubular acidosis, there is renal Na^+ and K^+ wasting despite only moderately reduced GFR, and bicarbonaturia further obligates urine Na^+ excretion.

Mineralocorticoid deficiency. Mineralocorticoid deficiency is characterized by hyponatremia with ECF volume contraction, urine $[Na^+]$ above 20 mmol/l, and high serum K^+, urea, and creatinine. Decreased ECF volume provides the nonosmotic stimulus for AVP release.

Osmotic diuresis. An osmotically active, nonreabsorbable solute obligates the renal excretion of Na^+ and results in volume depletion. In the face of continuing water intake, the diabetic patient with severe glycosuria, the patient with a urea diuresis after relief of urinary tract obstruction, and the patient with mannitol diuresis all undergo urinary losses of Na^+ and water, leading to hypovolemia and hyponatremia. Urine $[Na^+]$ is typically above 20 mmol/l. The ketone bodies β-hydroxybutyrate and acetoacetate also obligate urinary electrolyte losses and aggravate the renal Na^+ wasting seen in diabetic ketoacidosis, starvation, and alcoholic ketoacidosis.

Cerebral salt wasting. Cerebral salt wasting is a syndrome described primarily in patients with subarachnoid hemorrhage. The primary defect is salt wasting from the kidneys with subsequent volume contraction, which stimulates AVP release. The exact mechanism is not understood, but it is postulated that brain natriuretic peptide increases urine volume and Na^+ excretion. Serum uric acid is often low, similar to that observed in syndrome of inappropriate anti-diuretic hormone (SIADH, see later). The diagnosis requires evidence of inappropriate sodium losses and reduced effective blood volume. These criteria are rarely fulfilled, suggesting that cerebral salt wasting is overdiagnosed.

Hypervolemia: Hyponatremia Associated With Increased Total Body Sodium

In hypervolemia, if the total body water is increased more than total body Na^+ hyponatremia occurs, as in congestive heart failure (CHF), nephrotic syndrome, and cirrhosis (see Fig. 8.5 and Chapter 7).

Congestive heart failure. Edematous patients with CHF have reduced effective intravascular volume as a result of decreased systemic mean arterial pressure and cardiac output. This reduction is sensed by aortic and carotid baroreceptors activating nonosmotic pathways, resulting in AVP release. In addition, the relative "hypovolemic" state stimulates the renin-angiotensin axis and increases norepinephrine production, which in turn decreases GFR. This causes an increase in proximal tubular reabsorption and a decrease in water delivery to the distal tubule.

The neurohumorally mediated decrease in delivery of tubular fluid to the distal nephron and an increase in AVP secretion mediate hyponatremia by limiting Na^+-Cl^- and water excretion. In addition, low cardiac output and high Ang II levels are potent stimuli of thirst.

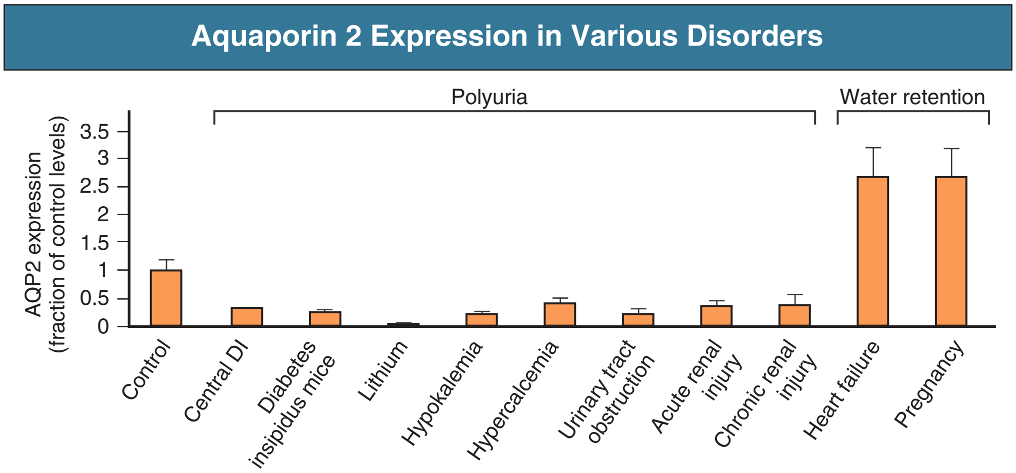

Fig. 8.6 Changes in aquaporin 2 (AQP2) expression seen in association with different water balance disorders. Levels are expressed as a fraction (percentage) of control levels. AQP2 expression is reduced, sometimes dramatically, in a wide range of hereditary and acquired forms of diabetes insipidus *(DI)* characterized by different degrees of polyuria. Conversely, congestive heart failure and pregnancy are conditions associated with increased expression of AQP2 levels and excessive water retention. (Modified from reference 3.)

There is also excessive intracellular targeting of AQP2 to the apical cell membrane of the collecting duct, most likely from high AVP levels (Fig. 8.6).[11]

As cardiac function improves with afterload reduction, plasma AVP decreases, with concomitant improvement in water excretion. The degree of hyponatremia also has been correlated with the severity of cardiac disease and patient survival; serum [Na^+] of less than 125 mmol/l reflects severe CHF.

Hepatic failure. Patients with cirrhosis and hepatic insufficiency also have increased ECF volume (ascites, edema). Because of splanchnic venous dilation, they have increased plasma volume. Cirrhotic patients have an increased cardiac output because of multiple arteriovenous fistulas in their alimentary tract, lungs, and skin. Vasodilation and arteriovenous fistulas cause a decrease in mean arterial blood pressure. As the severity of cirrhosis increases, there are progressive increases in plasma renin, norepinephrine, AVP, and endothelin and an associated decline in mean arterial pressure and serum [Na^+]. In experimental models, expression of AQP2 is upregulated in collecting ducts.[6]

Nephrotic syndrome. In some patients with nephrotic syndrome, especially those with minimal change disease, low plasma oncotic pressure from hypoalbuminemia alters Starling forces, leading to intravascular volume contraction and stimulation of AVP with hyponatremia. In contrast, most nephrotic patients have a renal defect in sodium excretion resulting in increased effective circulating volume. Hyponatremia may still occur in these latter conditions. In experimental models of nephrotic syndrome, expression of AQP2, AQP3, and UT-A1 are downregulated in the collecting duct (which would have countering effects), but so are the sodium transporters, NKCC2, NHE3, and Na^+,K^+-ATPase, in the TAL, resulting in hyponatremia.[6]

Advanced chronic kidney disease. Patients with severely reduced GFR, either acute or chronic, have a profound increase in fractional excretion of Na^+ to maintain normal salt balance given the overall decreased number of functioning nephrons. Edema usually develops when the Na^+ ingested exceeds the capacity of the kidneys to excrete this load. Likewise, if water intake exceeds threshold, there is positive water balance and hyponatremia. At a GFR of 5 ml/min, only 7.2 liters of filtrate is formed daily. Approximately 30%, or 2.2 liters, of this filtered fluid will reach the diluting segment of the nephron, which is therefore the maximum solute-free water that can be excreted daily. As GFR progressively declines, a defect in renal concentration precedes a disorder in urinary dilution. The excretion of free water as a function of remaining glomeruli is well maintained until renal failure is very advanced.[12]

Aging results in 20% reduction in maximum urine osmolality in people over 60 years of age. The concentrating defect is not related to a decrease in GFR or an abnormality in AVP secretion.

Euvolemia: Hyponatremia Associated With Normal Total Body Sodium

Euvolemic hyponatremia is the most common dysnatremia in hospitalized patients. These patients have no physical signs of increased or decreased total body Na^+.

Glucocorticoid deficiency. Glucocorticoid deficiency causes impaired water excretion in patients with primary and secondary adrenal insufficiency. Elevation of AVP accompanies the water excretion defect resulting from anterior pituitary and adrenocorticotropic hormone (ACTH, corticotropin) deficiency. This can be corrected by physiologic doses of corticosteroids, but not by volume expansion. Hyponatremia may be enhanced by reduced renal blood flow and decreased distal fluid delivery to the diluting segments of the nephron.

Hypothyroidism. Hyponatremia occurs in patients with severe hypothyroidism, who usually meet the clinical criteria for myxedema coma. A decrease in cardiac output leads to nonosmotic release of AVP. A reduction in GFR leads to diminished free water excretion through decreased distal delivery to the distal nephron. The exact mechanisms are unclear. In patients with untreated hypothyroidism who have moderately severe disease, an AVP-independent mechanism is suggested by normal suppression of AVP after water loading. However, in patients with more advanced hypothyroidism, elevated AVP levels are reported in the basal state and after a water load. Hyponatremia is readily reversed by hormonal replacement treatment.

Psychosis. Patients with acute psychosis may develop hyponatremia. Psychogenic drugs, particularly selective serotonin reuptake inhibitors (SSRIs), are associated with hyponatremia, but psychosis can cause hyponatremia independently.[13] The pathophysiologic process involves an increased thirst perception, a mild defect in osmoregulation that causes AVP to be secreted at lower osmolality, and an enhanced renal response to AVP. Individuals with self-induced water intoxication also may be more prone to the development of rhabdomyolysis.

Postoperative hyponatremia. Postoperative hyponatremia mainly is a result of excessive infusion of electrolyte-free water (hypotonic saline or 5% dextrose in water) and the presence of AVP, which prevents water excretion. Hyponatremia also can occur despite infusion with near-isotonic (normal) saline within 24 hours of induction of anesthesia.[14] Young premenstrual women are at higher risk for developing acute postoperative hyponatremia accompanied by cerebral edema. The mechanism has not been fully elucidated, and the patients at highest risk cannot be prospectively identified. Nevertheless, hypotonic fluids should be avoided after surgery, isotonic fluids minimized, and serum $[Na^+]$ checked if hyponatremia is suspected (e.g., symptoms of headache or nausea).

Exercise-induced hyponatremia. Hyponatremia is seen in long-distance runners. A study at a marathon race associated increased risk of hyponatremia with body mass index less than 20 kg/m^2, running time exceeding 4 hours, and greatest weight gain.[15] A study in ultramarathon runners showed elevated AVP despite normal or low serum $[Na^+]$. The mechanism may be due to an exuberant AVP response in relation to exercise-induced dehydration.

Drugs causing hyponatremia. Drug-induced hyponatremia is becoming the most common cause of hyponatremia.[13] Thiazide diuretics and SSRIs are the most commonly implicated medications. Hyponatremia can be mediated by AVP analogues such as desmopressin (DDAVP, 1-desamino-D-arginine AVP) that enhance AVP release, and agents potentiating the action of AVP. In other cases, the mechanism is unknown (Table 8.2). Desmopressin for nocturia in elderly patients and enuresis in young persons has caused hyponatremia in some of these subjects, so it is not routinely used to treat these conditions. Desmopressin for nocturia should be used only when the number of voidings is not tolerable and is debilitating (>2/night). On awakening the drug is likely to be still active for several more hours, requiring great attention to water restriction. Hyponatremia also may result from use of intravenous immune globulin (IVIG).[16] The mechanism of IVIG-associated hyponatremia is multifactorial, involving pseudohyponatremia (secondary to increases in serum protein concentration), translocation (as a result of sucrose in the solution), and true dilutional hyponatremia (secondary to the retention of water, particularly when associated with acute kidney injury [AKI]).[16]

TABLE 8.2 **Drugs Associated With Hyponatremia***

Vasopressin Analogues	Drugs That Potentiate Renal Action of Vasopressin
Desmopressin (DDAVP)	Chlorpropamide
Oxytocin	Cyclophosphamide
	Nonsteroidal antiinflammatory drugs (NSAIDs)
	Acetaminophen
Drugs That Enhance Vasopressin Release	**Drugs That Cause Hyponatremia by Unknown Mechanisms**
Chlorpropamide	*Haloperidol*
Clofibrate	Fluphenazine
Carbamazepine-oxcarbazepine	Amitriptyline
Vincristine	Thioridazine
Nicotine	Fluoxetine
Narcotics	*Methamphetamine* (MDMA, "ecstasy")
Antipsychotics/antidepressants (SSRIs)	Intravenous immune globulin (IVIG)
Ifosfamide	

Terms in italics are the most common causes.
From reference 43.
*Not including diuretics.
MDMA, 3,4-Methylenedioxymethamphetamine; *SSRIs,* selective serotonin reuptake inhibitors.

Syndrome of inappropriate antidiuretic hormone secretion. Despite being the most common cause of hyponatremia in hospitalized patients, SIADH is a diagnosis of exclusion. A defect in osmoregulation causes AVP to be inappropriately stimulated, leading to urine concentration (Table 8.3). A few causes deserve special mention. Central nervous system (CNS) disturbances such as hemorrhage, tumors, infections, and trauma cause SIADH by excess AVP secretion. Small cell lung cancer, cancer of the duodenum and pancreas, and olfactory neuroblastoma cause ectopic production of AVP. Idiopathic cases of SIADH are unusual except in elderly patients, in whom hyponatremia is frequently multifactorial,[17] but in whom as many as 10% have abnormal AVP secretion without known cause.

Several patterns of abnormal AVP release have emerged from studies of patients with clinical SIADH,[18] and have now been reproduced employing the simpler, more reliable and stable copeptin assay.[19] In one third of patients with SIADH, AVP release varies appropriately with serum $[Na^+]$ but begins at a lower threshold of serum osmolality, implying a "resetting of the osmostat." Ingestion of free water then leads to water retention to maintain the serum $[Na^+]$ at a new lower level, usually 125 to 130 mmol/l. In two thirds of patients, AVP release does not correlate with serum $[Na^+]$, but a solute-free urine cannot be excreted. Therefore ingested water is retained, giving rise to moderate nonedematous volume expansion and dilutional hyponatremia. In about 10% of patients, AVP levels are not measurable, suggesting that the syndrome of inappropriate antidiuresis (SIAD) is a more accurate term.[18] It was suggested that such patients may have a nephrogenic syndrome of antidiuresis, and a gain-of-function mutation in the AVP receptor. However, none of the six patients who had unmeasurable copeptin (a surrogate marker for AVP) levels had an identifiable gain of function mutation.[19]

The diagnostic criteria for SIADH are summarized in Box 8.1.[1] Plasma AVP may be in the "normal" range (up to 10 ng/l), but this is inappropriate given the hypo-osmolar state. The measurement of plasma AVP is rarely needed because the urinary osmolality provides an excellent surrogate bioassay. Thus a hypertonic urine (>300 mOsm/kg H_2O) provides strong evidence for the presence of AVP in the circulation because such urinary tonicities are unattainable in its absence. Likewise, a urinary osmolality lower than 100 mOsm/kg H_2O reflects the virtual absence of the hormone. Urinary osmolalities in the range of 100 to 300 mOsm/kg H_2O can occur in the presence or absence of AVP. A decrease in serum uric acid concentration associated with a high fractional excretion (>10%) is frequently encountered in the patient with SIADH.

Clinical Manifestations of Hyponatremia

Most patients with a serum $[Na^+]$ above 125 mmol/l are asymptomatic. Below 125 mmol/l, headache, yawning, lethargy, nausea, reversible ataxia, psychosis, seizures, and coma may occur as a result of cerebral edema. Rarely, hypotonicity leads to cerebral edema so severe that there is increased intracerebral pressure, tentorial herniation, respiratory depression, and death. These events occur with rapid development of hyponatremia, typically in hospitalized postoperative patients receiving diuretics

TABLE 8.3 Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion

Carcinomas	Pulmonary Disorders	Nervous System Disorders	Other
Bronchogenic carcinoma	*Viral pneumonia*	*Encephalitis (viral, bacterial)*	*Human immunodeficiency virus (HIV) infection; acquired immunodeficiency syndrome (AIDS)*
Carcinoma of duodenum	*Bacterial pneumonia*	*Meningitis (viral, bacterial, tuberculous, fungal)*	*Idiopathic (elderly)*
Carcinoma of pancreas	*Pulmonary abscess*	*Head trauma*	Prolonged exercise
Thymoma	*Tuberculosis*	*Brain abscess*	
Carcinoma of stomach	Aspergillosis	*Brain tumors*	
Lymphoma	Positive-pressure ventilation	Guillain-Barré syndrome	
Ewing sarcoma	Asthma	Acute intermittent porphyria	
Carcinoma of bladder	Pneumothorax	Subarachnoid hemorrhage or subdural hematoma	
Carcinoma of prostate	Mesothelioma	Cerebellar and cerebral atrophy	
Oropharyngeal tumor	Cystic fibrosis	Cavernous sinus thrombosis	
Carcinoma of ureter		Neonatal hypoxia	
		Hydrocephalus	
		Shy-Drager syndrome	
		Rocky Mountain spotted fever	
		Delirium tremens	
		Cerebrovascular accident (stroke; cerebral thrombosis or hemorrhage)	
		Acute psychosis	
		Peripheral neuropathy	
		Multiple sclerosis	

Terms in italics are the most common causes.
From reference 43.

BOX 8.1 Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion

Essential Diagnostic Criteria

- Decreased extracellular fluid effective osmolality (270 mOsm/kg H_2O)
- Inappropriate urine concentration (>100 mOsm/kg H_2O)
- Clinical euvolemia
- Elevated urine Na^+ concentration under conditions of normal salt and water intake
- Absence of adrenal, thyroid, pituitary, or renal insufficiency or diuretic use

Supplemental Criteria

- Abnormal water-load test result (inability to excrete at least 90% of a 20-ml/kg water load in 4 hours and/or failure to dilute urine osmolality to <100 mOsm/kg)
- Serum vasopressin level inappropriately elevated relative to the serum osmolality
- No significant correction of serum Na^+ level with volume expansion, but improvement after fluid restriction
- Hypouricemia and elevated fractional excretion of uric acid

Modified from reference 1.

or hypotonic fluids. Untreated severe hyponatremia has a mortality rate as high as 50%. Neurologic symptoms in a hyponatremic patient call for immediate attention and treatment.

Cerebral Edema

The development of cerebral edema largely depends on the cerebral adaptation to hypotonicity. Decreases in extracellular osmolality cause movement of water into cells, increasing intracellular volume and causing tissue edema. The water channel AQP4 appears to play a key role in the movement of water across the blood-brain barrier. AQP4 knockout mice are protected from hyponatremic brain swelling, whereas animals overexpressing AQP4 have exaggerated brain swelling.[20] Cellular edema within the fixed confines of the cranium increases intracranial pressure, leading to the neurologic syndrome. In most hyponatremic patients, mechanisms of volume regulation prevent cerebral edema.

Within 1 to 3 hours after hyponatremia develops a decrease in cerebral extracellular volume occurs by movement of fluid into the cerebrospinal fluid, which is then shunted back into the systemic circulation. Loss of extracellular solutes Na^+ and Cl^- occurs as early as 30 minutes after the onset of hyponatremia (Fig. 8.7). If hyponatremia persists for longer than 3 hours, the brain adapts by losing cellular osmolytes, including K^+ and organic solutes, which tends to lower the osmolality of the brain, resulting in water losses. Thereafter, if hyponatremia persists, other organic osmolytes, such as phosphocreatine, myoinositol, and amino acids (e.g., glutamine, taurine), are lost, greatly decreasing cerebral swelling. As a result of these adaptations, some patients may have minimal symptoms despite severe hyponatremia ($[Na^+]$ <125 mmol/l).

Certain patients are at increased risk for development of acute cerebral edema in the course of hyponatremia[21] (Table 8.4). Hospitalized premenstrual women with hyponatremia are more symptomatic and more likely to have complications of therapy than postmenopausal women or men. This increased risk for cerebral edema is independent of the rate of development or the magnitude of hyponatremia. The best management of these patients is to avoid the administration of hypotonic fluids in the postoperative setting. Children are particularly vulnerable to the development of acute cerebral edema, perhaps because of a relatively high ratio of brain to skull volume.

Osmotic Demyelination

Another neurologic syndrome can occur in hyponatremic patients as a complication of correction of hyponatremia. Osmotic demyelination most often affects the central pons and is therefore also termed *central pontine myelinolysis* (CPM). It occurs at all ages; Table 8.4 lists patients most at risk. Osmotic demyelination syndrome is especially common after liver transplantation, with a reported incidence of 13% to 29% at autopsy. The risk for CPM is related to the severity and chronicity of

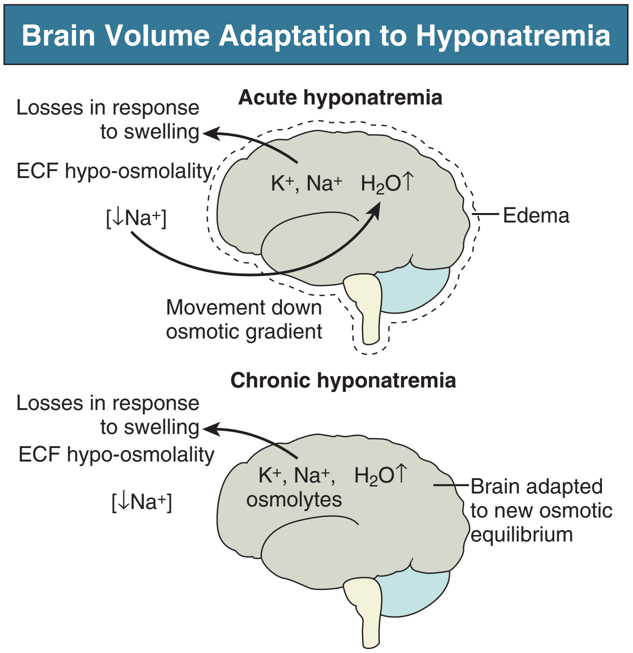
Brain Volume Adaptation to Hyponatremia
Acute hyponatremia
Losses in response to swelling
ECF hypo-osmolality
[↓Na+]
K+, Na+ H2O↑
Edema
Movement down osmotic gradient
Chronic hyponatremia
Losses in response to swelling
ECF hypo-osmolality
[↓Na+]
K+, Na+, H2O↑ osmolytes
Brain adapted to new osmotic equilibrium

Fig. 8.7 Brain volume adaptation to hyponatremia. During acute hyponatremia, water enters the brain to establish osmotic equilibrium with the ECF. As an acute adaptive change, NaCl exits from the brain interstitial space, followed by loss of potassium from cells several hours later. In chronic hyponatremia, the brain loses osmolytes, which lead to further water losses from the brain and an almost full restoration of brain water to levels marginally greater than baseline. (Modified from reference 1.)

TABLE 8.4 Subjects at Risk for Neurological Complications with Hyponatremia

Acute Cerebral Edema	Osmotic Demyelination Syndrome (Central Pontine Myelinolysis)
Postoperative menstruating women	Liver transplant recipients
Elderly women taking thiazides	Alcoholic patients
Children	Malnourished patients
Patients with polydipsia secondary to psychiatric disorders	Hypokalemic patients
Hypoxemic patients	Burn victims
Marathon runners	Elderly women taking thiazides
	Hypoxemic patients
	Severe hyponatremia ([Na^+] <105 mmol/l)

Patient groups at risk for acute cerebral edema and central pontine myelinolysis (osmotic demyelination)
From reference 21.

the hyponatremia. It rarely occurs with serum [Na^+] above 120 mmol/l or a short duration of hyponatremia (<48 hours). The symptoms are biphasic. Initially, there is a generalized encephalopathy associated with rapid correction of serum [Na^+]. At 2 to 3 days after correction, the patient displays behavioral changes, cranial nerve palsies, and progressive weakness, culminating in quadriplegia and a "locked-in" syndrome. T2-weighted magnetic resonance imaging shows nonenhancing and hyperintense pontine and extrapontine lesions. These lesions may not appear until 2 weeks after development, so a diagnosis of myelinolysis should not be excluded if the imaging is initially normal.

The pathogenesis of osmotic demyelination syndrome is uncertain; one suggestion is that sodium-coupled amino acid transporters (e.g., SNAT2) are downregulated by hypotonicity, thereby delaying the return of osmolytes to the brain, rendering it more sensitive to the correction of hyponatremia.[22] Although [Na^+] and [K^+] return to normal in a few hours, osmotically active solutes require several days to return to normal levels. This temporary imbalance causes cerebral dehydration and can lead to a potential breakdown of the blood-brain barrier. Astrocytes appear to be an early target of the disease, activating microglial cells resulting in the expression of proinflammatory cytokines.[23]

Whereas CPM was originally considered to be uniformly fatal, a substantial number of patients can have some neurologic recovery, even with severe symptoms at onset, suggesting there are reversible forms of osmotic demyelination.

Treatment of Hyponatremia

Symptoms and duration of hyponatremia determine treatment. Acutely hyponatremic patients (developing within 48 hours) are at great risk for permanent neurologic sequelae from cerebral edema if the hyponatremia remains uncorrected. Patients with chronic hyponatremia are at risk for osmotic demyelination if the hyponatremia is corrected too rapidly.

Acute Symptomatic Hyponatremia

Acute symptomatic hyponatremia with seizures or other neurologic manifestations almost always develops in hospitalized patients receiving hypotonic fluids (Fig. 8.8). Treatment should be prompt because the risk for acute cerebral edema far exceeds the risk for osmotic demyelination. The cell volume adaptive response whereby the brain decreases its water content in acute hyponatremia may be inhibited by female hormones, possibly explaining the large female predominance. A contribution of hypoxia also may be important, because when hypoxia is combined with hyponatremia in experimental animals; the volume adaptive response is abrogated, resulting in brain edema and increased mortality.[24] Because the neurologic complications associated with acute symptomatic hyponatremia are devastating, patients require prompt treatment with 3% NaCl.[21,25,26] A rapid increment of 4 to 6 mmol/l appears to be sufficient to reverse cerebral edema; correction to normal levels is unnecessary.[27] Initial treatment should entail an infusion of 1 to 2 ml/kg of 3% NaCl over 60 minutes. Administration of a loop diuretic enhances free water excretion and hastens the normalization of serum [Na^+]. If the patient presents with severe neurologic symptoms, such as seizures, obtundation, or coma, 3% NaCl may be infused at higher rates (4 to 6 ml/kg/hr). Patients should be monitored carefully for changes in neurologic and pulmonary status, and serum electrolytes should be checked every 2 hours.

Chronic Symptomatic Hyponatremia

If the hyponatremia has taken more than 48 hours to evolve or if the duration is not known, correction should be undertaken with caution (see Fig. 8.8). Controversy exists as to whether it is the rate of correction or the magnitude of correction of hyponatremia that predisposes to neurologic complications. It is difficult to dissociate these two variables because a rapid correction rate is usually accompanied by a greater absolute magnitude of correction during a given time. The following three important principles guide treatment:

1. Because cerebral water is increased by approximately 10% in severe chronic hyponatremia, the goal is to increase the serum Na^+ level by 10%, or about 10 mmol/l in the first 24 hours.

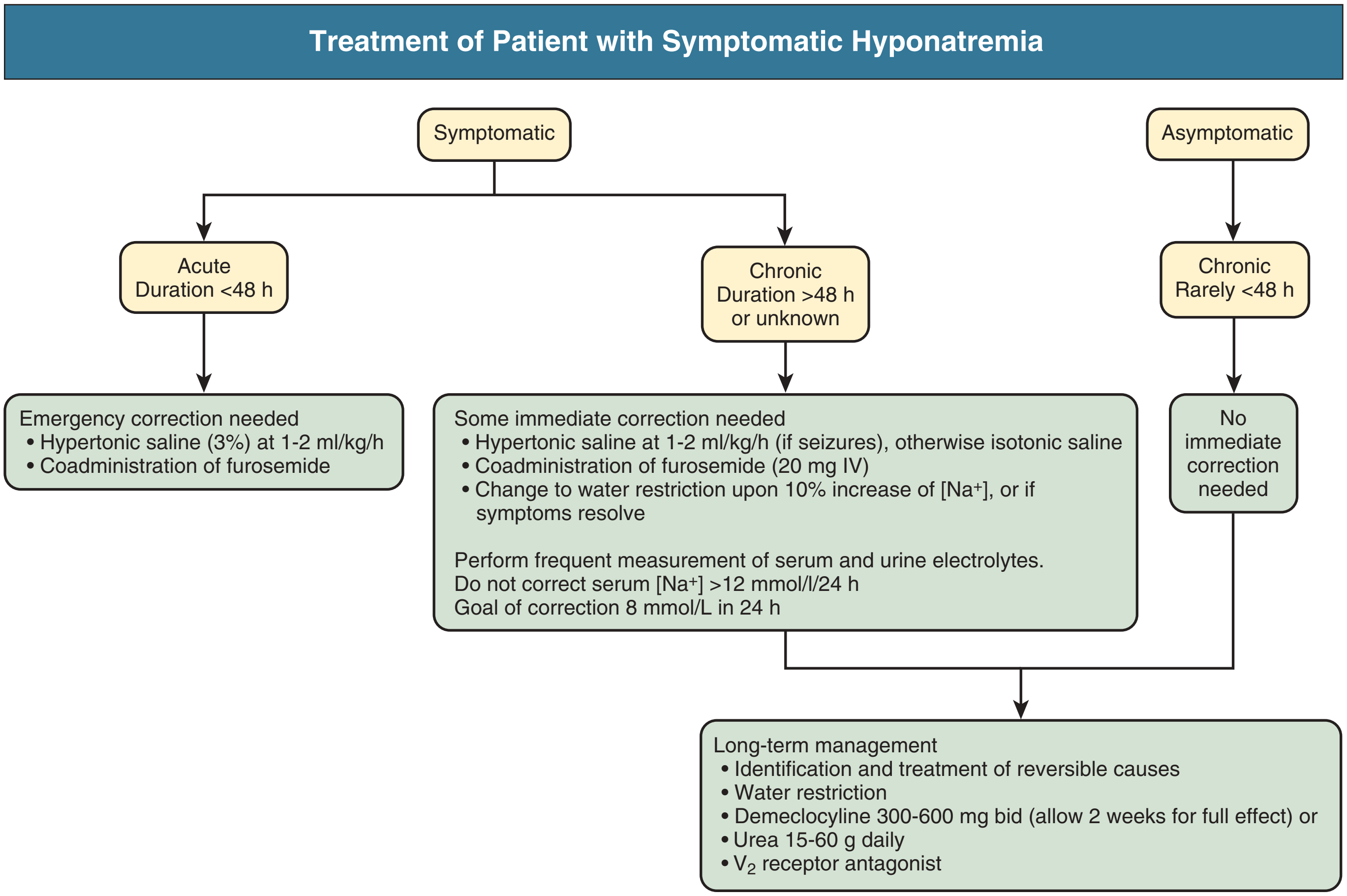
Treatment of Patient with Symptomatic Hyponatremia
Symptomatic
Asymptomatic
Acute
Duration <48 h
Chronic
Duration >48 h
or unknown
Chronic
Rarely <48 h
Emergency correction needed
• Hypertonic saline (3%) at 1-2 ml/kg/h
• Coadministration of furosemide
Some immediate correction needed
• Hypertonic saline at 1-2 ml/kg/h (if seizures), otherwise isotonic saline
• Coadministration of furosemide (20 mg IV)
• Change to water restriction upon 10% increase of [Na+], or if symptoms resolve
Perform frequent measurement of serum and urine electrolytes.
Do not correct serum [Na+] >12 mmol/l/24 h
Goal of correction 8 mmol/L in 24 h
No immediate correction needed
Long-term management
• Identification and treatment of reversible causes
• Water restriction
• Demeclocyline 300-600 mg bid (allow 2 weeks for full effect) or
• Urea 15-60 g daily
• V2 receptor antagonist

Fig. 8.8 Algorithm for management of the patient with symptomatic (and "asymptomatic") hyponatremia. (Modified from reference 21.)

2. A correction rate of 1.0 to 1.5 mmol/l in any given hour should not be exceeded.
3. The goal of treatment is an increase of 6 to 10 mmol/l/24 h, but do not increase by more than 12 mmol/l/24 h and 18 mmol/l/48 h.

Numerous formulas have been used to assess the expected changes in serum sodium with various infusions[18] but the one proposed by Adrogue and Madias[28] is the most widely employed. Although helpful in the initial treatment phase, it does not take into account ongoing renal and extrarenal losses, thus commonly resulting in correction larger than those predicted by the formula.[29] The risk for overcorrection can be mitigated by the coadministration of DDAVP, thus preventing the excretion of hypotonic urine.[30] If the previously noted limits are exceeded, relowering of serum sodium can be achieved by the infusion of dextrose and water and the administration of DDAVP.[30]

Chronic "Asymptomatic" Hyponatremia

Patients with chronic hyponatremia are often asymptomatic. However epidemiologic data consistently show higher mortality rates than matched controls with normal serum sodium levels.[31] Formal neurologic testing frequently reveals subtle impairments, including gait disturbances that reverse with correction of the hyponatremia. This results in an increased risk for falls and fractures.[32] Therefore, even "asymptomatic" patients should be treated in an attempt to restore serum sodium to near-normal levels, particularly if they display gait instability or have sustained a fall. These patients should also be evaluated for hypothyroidism, adrenal insufficiency, and SIADH and should have their medications reviewed.

Fluid restriction. Stopping any medication associated with hyponatremia and fluid restriction is the cornerstone of therapy in patients with chronic asymptomatic hyponatremia (Table 8.5). Intake of all fluids should be restricted, and fructose-containing fluids should be avoided because fructose stimulates AVP release independently of osmolarity. This approach is usually successful if patients are compliant. It involves a calculation of the fluid restriction that will maintain a specific serum [Na^+]. The daily osmolar load and the minimal urinary osmolality $(U_{osm})_{min}$ determine a patient's maximal urine volume (V_{max}), as follows:

$$V_{max} = \frac{OL}{(U_{osm})_{min}}$$

The value of $(U_{osm})_{min}$ is a function of the severity of the diluting disorder. In the absence of circulating AVP, it can be as low as 50 mOsm/kg H_2O. In a normal North American diet, the daily osmolar load is approximately 10 mOsm/kg (700 mOsm for 70-kg person). Assuming that a patient with SIADH has U_{osm} that cannot be lowered to less than 500 mOsm/kg H_2O, the same osmolar load of 700 mOsm allows only 1.4 liters of urine to be excreted daily. Therefore, if the intake exceeds 1.4 l/day, the serum Na^+ concentration will decrease. Measurement of urine [Na^+] and [K^+] can guide the required degree of water restriction.[33] Unless the ratio of urine [Na^+] plus [K^+] over serum [Na] is 0.5 or less, compliance with the needed water restriction is not likely to occur. Likewise a urinary osmolality greater than 500 mOSm/kg also predicts poor response to water restriction.[1] In a report from a hyponatremia registry, the increment in serum sodium observed in patients

TABLE 8.5 Treatment of Patients With Chronic Asymptomatic Hyponatremia

Treatment	Mechanism of Action	Dose	Advantages	Limitations
Fluid restriction	Decreases availability of free water	Variable	Effective and inexpensive; not complicated	Noncompliance
Pharmacologic Inhibition of Vasopressin Action				
Lithium	Inhibits kidney's response to vasopressin	900-1200 mg/day	Unrestricted water intake	Polyuria, narrow therapeutic range, neurotoxicity
Demeclocycline	Inhibits kidney's response to vasopressin	300-600 mg twice daily	Effective; unrestricted water intake	Neurotoxicity, polyuria, photosensitivity, nephrotoxicity
V_2 receptor antagonist	Antagonizes vasopressin action	—	Addresses underlying mechanisms	Limited clinical experience
Increased Solute (Salt) Intake				
With furosemide	Increases free water clearance	Titrate to optimal dose; coadminister 2-3 g NaCl	Effective	Ototoxicity, K^+ depletion
With urea	Osmotic diuresis	30-60 g/day	Effective; unrestricted water intake	Polyuria, unpalatable, gastrointestinal symptoms

placed on water restriction did not achieve statistical significance when compared to their baseline admission serum sodium.[34] If the diluting defect is so severe that fluid restriction to less than 1 liter is necessary or if the serum Na^+ concentration remains low (<130 mmol/l), an alternative approach to treatment should be considered, such as increasing solute excretion or pharmacologic inhibition of AVP.

Increase solute excretion. If the patient remains unresponsive to fluid restriction, solute intake can be increased to facilitate an obligatory increase in excretion of solute and free water.[35] This can be achieved by increasing oral salt and protein intake in the diet to increase the C_{osm} of the urine. Loop diuretics combined with high sodium intake (2 to 3 g of additional salt) are effective in the management of hyponatremia. A single dose of diuretic (40 mg furosemide) is usually sufficient but should be doubled if the diuresis induced in the first 8 hours is less than 60% of the total daily urine output.

The administration of urea increases urine flow by causing an osmotic diuresis. This permits a more liberal water intake without worsening the hyponatremia and altering urine concentration. The dose of urea is usually 30 to 60 g/day. The limitations are gastrointestinal distress and unpalatability.

Pharmacologic inhibition of vasopressin. *Vaptans* are novel oral V_2 receptor antagonists that block AVP binding to the collecting duct tubular epithelial cells and increase free water excretion without significantly altering electrolyte excretion.[36-38] Vaptans are effective in the treatment of hyponatremia in euvolemic and hypervolemic patients, as reported in two meta-analyses.[39,40] Conivaptan, a V_2 and V_{1a} antagonist, is the only vaptan available for intravenous use,[38] but treatment should be limited to 4 days because it is a potent cytochrome P-450 3A4 (CYP3A4) inhibitor. Tolvaptan, an oral V_2 antagonist, is now available at doses of 15 to 60 mg/day. In the Tolvaptan trials in patients with polycystic kidney disease (TEMPO), higher doses were used and some cases of hepatic toxicity, as well as rhabdomyolysis, were encountered. This has led to a U.S. Food and Drug Administration warning requiring careful monitoring of liver function tests and creatine kinase (CK, CPK) levels.

An alternative pharmacologic treatment is demeclocycline 600 to 1200 mg/day given 1 to 2 hours after meals; calcium-, aluminum-, and magnesium-containing antacids should be avoided. Onset of action is usually 3 to 6 days after initiation of treatment. Dose should be titrated to the minimum that keeps serum $[Na^+]$ within the desired range with unrestricted water intake. Photosensitivity may develop, and tooth or bone abnormalities may occur in children. Polyuria leads to noncompliance, and nephrotoxicity may occur, especially in patients with underlying liver disease. Lithium was previously used to antagonize AVP action but has been superseded by the vaptans and demeclocycline.

Hypovolemic Hyponatremia

When thiazides are prescribed, especially in elderly women, serum $[Na^+]$ should be monitored and water intake restricted. If hyponatremia develops, the thiazide should be discontinued.

Neurologic syndromes directly related to hyponatremia are unusual in hypovolemic hyponatremia because both Na^+ and water loss limits any osmotic shifts in the brain. Restoration of ECF volume with crystalloids or colloids interrupts the nonosmotic release of AVP. AVP antagonists should not be used in these patients.[41]

Hypervolemic Hyponatremia

Congestive heart failure. In patients with CHF, sodium and water restriction is critical. Treatment with a combination of angiotensin-converting enzyme (ACE) inhibitors and loop diuretics increase cardiac output thereby decreasing the neurohumoral mediators that impair water excretion. Loop diuretics also diminish the action of AVP on the collecting tubules. Thiazides should be avoided because they impair urinary dilution and may worsen hyponatremia. V_2 antagonists increase serum $[Na^+]$ in patients with heart failure[36] and correction of serum $[Na^+]$ is associated with better long-term outcomes.[42] However, in the much larger randomized controlled EVEREST trial in patients with decompensated heart failure, tolvaptan did not affect long-term clinical outcomes. In principle, a vaptan with V_1 antagonist activity could have additional benefit in the CHF patient, but this remains unproven.

Cirrhosis. In patients with cirrhosis, water and sodium restriction is the mainstay of therapy. Loop diuretics increase C_{water}. V_2 antagonists increase water excretion and increase serum $[Na^+]$.[41] The response to vaptans in cirrhosis is more attenuated than in patients with SIADH or CHF, which suggests that AVP-independent mechanisms also may contribute to the hyponatremia. The administration of V_2 antagonists to patients with liver failure is not associated with decrements in blood pressure. Combined V_1 and V_2 antagonists (e.g., conivaptan) should not be used in these patients, and in view of the potential liver toxicity the use of tolvaptan should probably be limited to management of serum hyponatremia before liver transplant.[41]

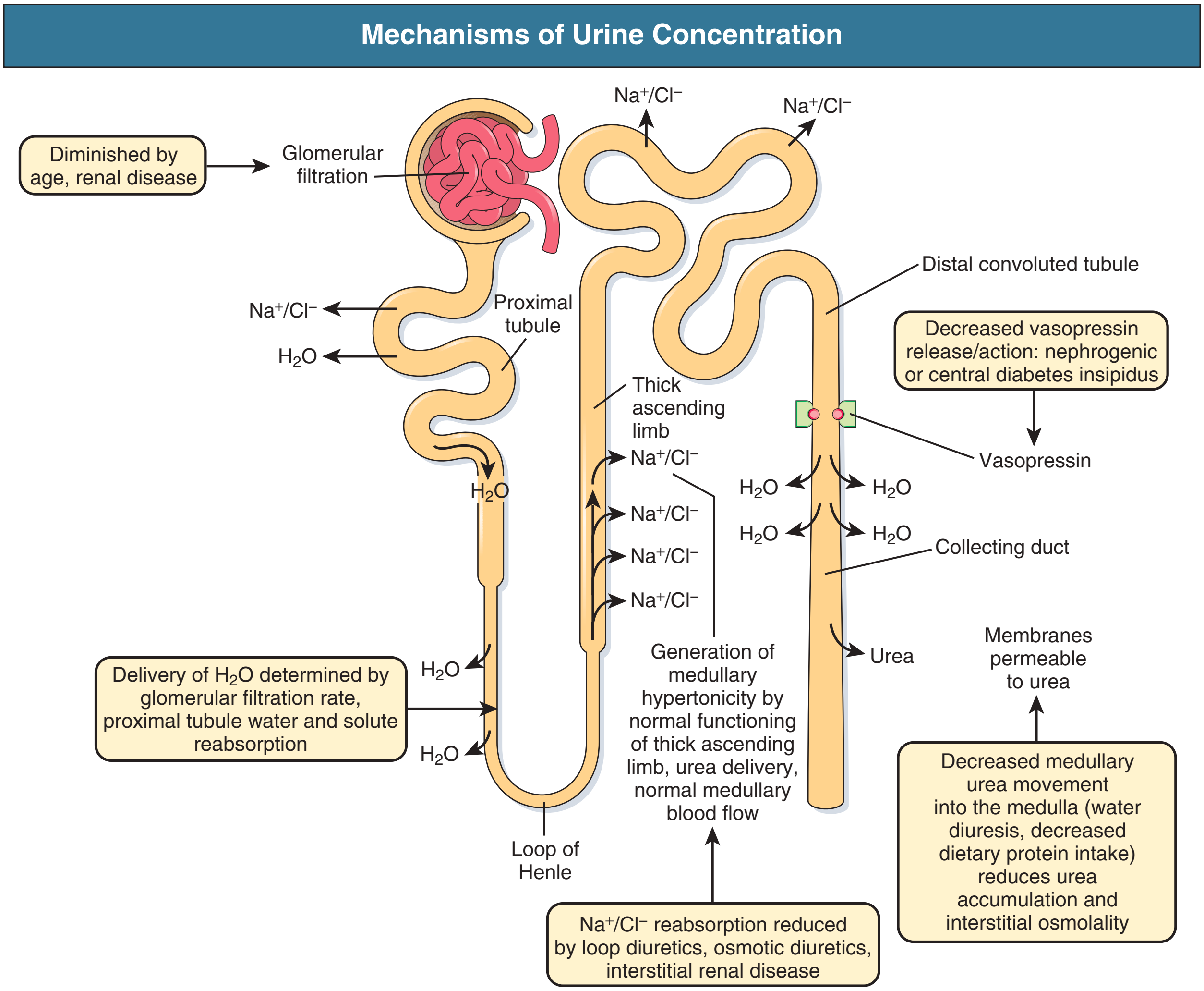
Mechanisms of Urine Concentration
Diminished by age, renal disease
Glomerular filtration
Na^+/Cl^-
Na^+/Cl^-
Na^+/Cl^-
H_2O
Proximal tubule
Distal convoluted tubule
Decreased vasopressin release/action: nephrogenic or central diabetes insipidus
Thick ascending limb
Na^+/Cl^-
H_2O
Na^+/Cl^-
Na^+/Cl^-
Na^+/Cl^-
H_2O
H_2O
Vasopressin
H_2O
H_2O
Collecting duct
Delivery of H_2O determined by glomerular filtration rate, proximal tubule water and solute reabsorption
H_2O
H_2O
Generation of medullary hypertonicity by normal functioning of thick ascending limb, urea delivery, normal medullary blood flow
Urea
Membranes permeable to urea
Loop of Henle
Decreased medullary urea movement into the medulla (water diuresis, decreased dietary protein intake) reduces urea accumulation and interstitial osmolality
Na^+/Cl^- reabsorption reduced by loop diuretics, osmotic diuretics, interstitial renal disease

Fig. 8.9 Urine-concentrating mechanisms. Determinants of normal urine concentration and disorders causing hypernatremia. (Modified from reference (10).)

HYPERNATREMIC DISORDERS

Hypernatremia is defined as serum [Na^+] above 145 mmol/l and reflects serum hyperosmolarity. The renal concentrating mechanism provides the first defense mechanism against water depletion and hyperosmolarity. The components of the normal concentrating mechanism are shown in Fig. 8.9. Disorders of urine concentration may result from decreased delivery of solute (with decreasing GFR) or the inability to generate interstitial hypertonicity because of decreased Na^+ and Cl^- reabsorption in the ascending limb of Henle's loop (loop diuretics), decreased medullary urea accumulation (poor dietary intake), or alterations in medullary blood flow. Hypernatremia also may result from failure to release or respond to AVP. Thirst is the first and most important defense mechanism in preventing hypernatremia.

Etiology and Classification of Hypernatremia

Patients with hypernatremia fall into three broad categories based on volume status.[43] A diagnostic algorithm is helpful in the evaluation of these patients (Fig. 8.10).

Hypovolemia: Hypernatremia Associated With Low Total Body Sodium

Patients with hypovolemic hypernatremia sustain losses of both Na^+ and water, but with a relatively greater loss of water. On physical examination, there are signs of hypovolemia, including orthostatic hypotension, tachycardia, flat neck veins, poor skin turgor, and altered mental status. Patients generally have hypotonic water loss from the kidneys or the gastrointestinal (GI) tract; in the GI tract, the urine [Na^+] will be low.

Hypervolemia: Hypernatremia Associated With Increased Total Body Sodium

Hypernatremia with increased total body Na^+ is the least common form of hypernatremia. It results from the administration of hypertonic solutions such as 3% NaCl and $NaHCO_3$ for the treatment of metabolic acidosis, hyperkalemia, and cardiorespiratory arrest. It also may result from inadvertent dialysis against a dialysate with a high Na^+ concentration or from consumption of salt tablets. Therapeutic hypernatremia is also becoming common as hypertonic saline solutions have emerged as an alternative to mannitol for treatment of increased intracranial pressure.[27] Hypernatremia is also increasingly recognized in hypoalbuminemic hospitalized patients with renal failure who are edematous and unable to concentrate their urine.

Euvolemia: Hypernatremia Associated With Normal Body Sodium

Most patients with hypernatremia secondary to water loss appear euvolemic with normal total body Na^+ because loss of water without Na^+ does not lead to overt volume contraction unless severe. Water

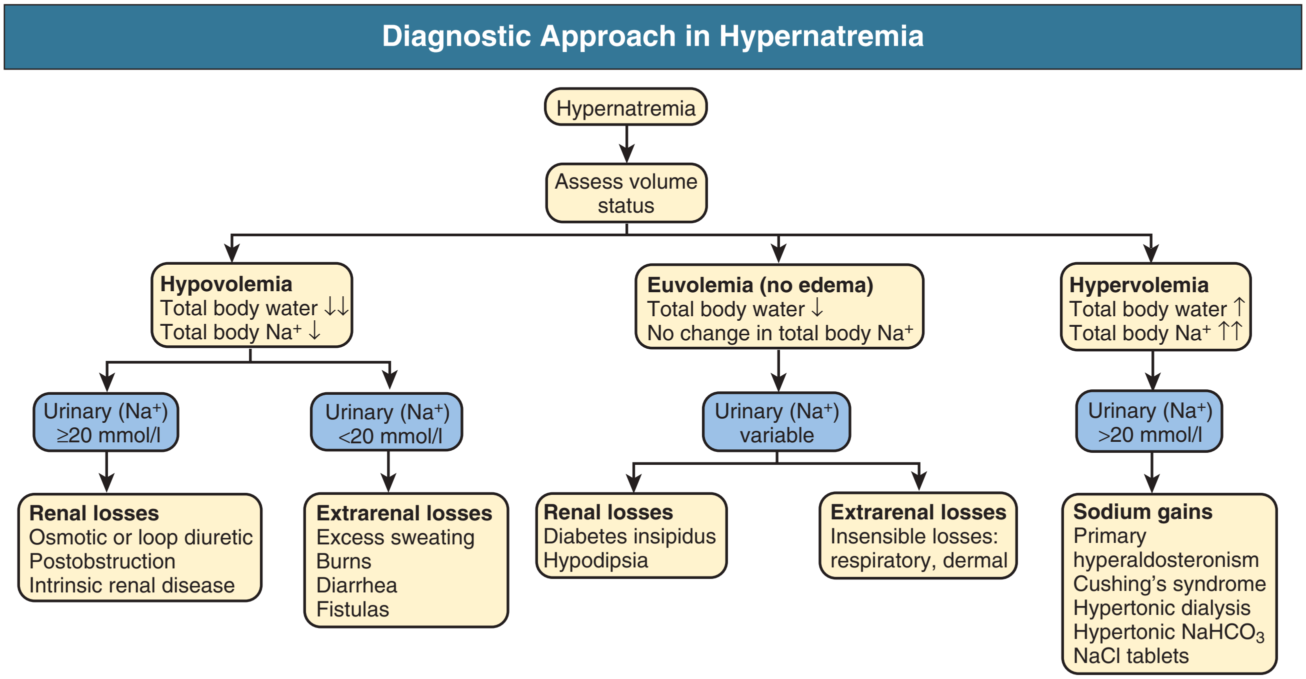
Diagnostic Approach in Hypernatremia
Hypernatremia
Assess volume status
Hypovolemia
Total body water ↓↓
Total body Na$^+$ ↓
Euvolemia (no edema)
Total body water ↓
No change in total body Na$^+$
Hypervolemia
Total body water ↑
Total body Na$^+$ ↑↑
Urinary (Na$^+$) ≥20 mmol/l
Urinary (Na$^+$) <20 mmol/l
Urinary (Na$^+$) variable
Urinary (Na$^+$) >20 mmol/l
Renal losses
Osmotic or loop diuretic
Postobstruction
Intrinsic renal disease
Extrarenal losses
Excess sweating
Burns
Diarrhea
Fistulas
Renal losses
Diabetes insipidus
Hypodipsia
Extrarenal losses
Insensible losses: respiratory, dermal
Sodium gains
Primary hyperaldosteronism
Cushing's syndrome
Hypertonic dialysis
Hypertonic $NaHCO_3$
NaCl tablets

Fig. 8.10 Algorithm for diagnostic assessment of the patient with hypernatremia. (Modified from reference 8.)

loss need not result in hypernatremia unless unaccompanied by water intake. Because hypodipsia is uncommon, hypernatremia usually develops only in those who have no access to water and in very young children and old persons, who may have an altered perception of thirst. Extrarenal water loss occurs from the skin and respiratory tract in febrile or other hypermetabolic states and is associated with high urine osmolality because the osmoreceptor-AVP-renal response is intact. The urine Na^+ concentration varies with intake. Renal water loss leading to euvolemic hypernatremia results either from a defect in AVP production or release (central diabetes insipidus [DI]) or from a failure of the collecting duct to respond to the hormone (nephrogenic DI). Defense against the development of hyperosmolality requires the appropriate stimulation of thirst and the patient's ability to respond by drinking water.

Polyuric disorders can result from either an increase in C_{osm} or an increase in C_{water}. An increase in C_{osm} occurs with loop diuretic use, renal salt wasting, excess salt ingestion, vomiting (bicarbonaturia), alkali administration, and administration of mannitol (as a diuretic, for bladder lavage, or for the treatment of cerebral edema). An increase in C_{water} occurs with excess ingestion of water (psychogenic polydipsia) or in abnormalities of the renal concentrating mechanism (DI).

Diabetes Insipidus

DI is characterized by polyuria and polydipsia and is caused by defects in AVP action. Patients with central and nephrogenic DI and primary polydipsia present with polyuria and polydipsia. These entities can be differentiated by clinical evaluation, with measurements of AVP levels and response to a water deprivation test, followed by AVP administration (Table 8.6).[44]

Central diabetes insipidus

Clinical features. Central DI usually has an abrupt onset. Patients have a constant need to drink, have a predilection for cold water, and typically have nocturia. By contrast, the compulsive water drinker may give a vague history of the onset and has large variations in water intake and urine output. Nocturia is unusual in compulsive water drinkers. A

WATER DEPRIVATION TEST

Test procedure: water intake is restricted until the patient loses 3% to 5% of body weight or until three consecutive hourly determinations of urinary osmolality are within 10% of each other. (Caution must be exercised to ensure patient does not become excessively dehydrated.) Aqueous vasopressin is given, 5 units subcutaneously, and urinary osmolality is measured after 60 minutes. Expected responses are outlined in the Table.

TABLE 8.6 Interpretation of Water Deprivation Test

Condition	Urinary Osmolality with Water Deprivation (mOsm/kg H_2O)	Serum Vasopressin After Dehydration (pg/ml)	Increase in Urinary Osmolality with Exogenous Vasopressin or Desmopressin
Normal	>800	>2	Little or no increase
Complete central diabetes insipidus	<300	Undetectable	Substantially increased
Partial central diabetes insipidus	300-800	<1.5	Increase of >10% of urinary osmolality after water deprivation
Nephrogenic diabetes insipidus	<300-500	>5	Little or no increase
Primary polydipsia	>500	<5	Little or no increase

From reference 44.

BOX 8.2 Causes of Central Diabetes Insipidus

Congenital Causes

- Autosomal dominant
- Autosomal recessive

Acquired Causes

- Post-traumatic
- Iatrogenic (postsurgical)
- Tumors (metastatic from breast, craniopharyngioma, pinealoma)
- Histiocytosis
- Granuloma (tuberculosis, sarcoid)
- Aneurysm
- Meningitis
- Encephalitis
- Guillain-Barré syndrome
- Drugs
- Idiopathic

Entries in italics are the most common causes.

TABLE 8.7 Treatment of Central Diabetes Insipidus

Disease	Drug	Dose	Interval (hours)
Complete central diabetes insipidus	Desmopressin (DDAVP)	10-20 mcg intranasally	12-24
	Desmopressin (DDAVP)	0.1-0.8 mg orally	Every 12
Partial central diabetes insipidus	Desmopressin (DDAVP)	10-20 mcg intranasally	12-24
	Aqueous vasopressin	5-10 units subcutaneously	4-6
	Chlorpropamide	250-500 mg	24
	Clofibrate	500 mg	6 or 8
	Carbamazepine	400-600 mg	24

serum osmolality of more than 295 mOsm/kg H_2O suggests central DI, and less than 270 mOsm/kg H_2O suggests compulsive water drinking.

Causes. Central DI is caused by infection, tumors, granuloma, and trauma affecting the CNS in 50% of patients; in the other 50% it is idiopathic (Box 8.2). In a survey of 79 children and young adults, central DI was idiopathic in half the patients. The other half had tumors or Langerhans cell histiocytosis; these patients had an 80% risk for development of anterior pituitary hormone deficiency compared with the patients with idiopathic disease.[5]

Autosomal dominant DI is caused by point mutations in a precursor gene for AVP that cause "misfolding" of the provasopressin peptide, preventing its release from the hypothalamic and posterior pituitary neurons.[5] Patients present with a mild polyuria and polydipsia in the first year of life. These children have normal physical and mental development. There is a rare autosomal recessive central DI associated with diabetes mellitus, optic atrophy, and deafness (Wolfram syndrome).[45] DI is usually partial and gradual in onset in Wolfram syndrome. It is linked to chromosome 4 and involves abnormalities in mitochondrial DNA.

A rare clinical entity involving the combination of central DI and deficient thirst has been reported in approximately 100 patients. When AVP secretion and thirst are both impaired, affected patients are vulnerable to recurrent episodes of hypernatremia. Formerly called *essential hypernatremia,* the disorder is now called central DI with deficient thirst, or *adipsic* DI.[46]

Differential diagnosis. Measurement of circulating AVP by radioimmunoassay, or more recently, measurement of copeptin levels, is preferred to the tedious water deprivation test. Under basal conditions, AVP levels are unhelpful because there is a significant overlap among the polyuric disorders. Measurement after a water deprivation test is more useful (see Table 8.6).

Treatment. Central DI is treated with hormone replacement or pharmacologic agents (Table 8.7). In acute settings, when renal water losses are extensive, desmopressin has replaced aqueous AVP (Pitressin) as the treatment of choice. For chronic central DI, desmopressin acetate is the agent of choice. It has a long half-life and none of the significant vasoconstrictive effects of aqueous AVP. Desmopressin is administered at the dose of 10 to 20 mcg intranasally every 12 to 24 hours. It is tolerated well, safe to use in pregnancy, and resistant to degradation by circulating AVPase. Oral desmopressin (0.1 to 0.8 mg every 12 hours) is available as second-line therapy. In patients with partial DI, in addition to desmopressin itself, agents that potentiate the release of AVP may be used, including chlorpropamide, clofibrate, and carbamazepine.

Congenital nephrogenic diabetes insipidus. Inherited forms of DI are caused by mutations in genes for AVP V2-receptors or AQP2.[5] These entities are discussed further in Chapter 47. Urine volumes are typically very high, and there is a risk for severe hypernatremia if patients do not have free access to water. Thus patients must drink enough water to match urine output and prevent dehydration. Therapy for congenital nephrogenic DI is only partially effective and includes a thiazide diuretic, a very-low-salt diet, and indomethacin. Sildenafil improved urine concentration in a patient with congenital nephrogenic DI.[47] Simvastatin induces an increase in urine AQP2 and osmolality in hypercholesterolemic patients, suggesting that it may be useful in congenital nephrogenic DI.[47] Metformin results in a sustained increase in urine osmolality in rodent models of nephrogenic DI, but it has not been tested in patients.[47]

Acquired nephrogenic diabetes insipidus. Acquired nephrogenic DI is more common than congenital nephrogenic DI but rarely as severe. In patients with acquired nephrogenic DI, the ability to elaborate a maximal concentration of urine is impaired, but urine-concentrating mechanisms are partially preserved. For this reason, urine volumes are less than 3 to 4 l/day, which contrasts with the much higher volumes seen in patients with congenital or central DI or compulsive water drinking. Table 8.8 outlines the causes and mechanisms of acquired nephrogenic DI.

Chronic kidney disease. A defect in urine-concentrating ability may develop in patients with CKD of any cause, but this defect is most prominent in tubulointerstitial diseases, particularly medullary cystic disease. (A complete discussion on the mechanisms of abnormalities in urine concentration and dilution in CKD can be found in reference 12). Disruption of inner medullary structures and diminished medullary concentration are thought to play a role; alterations in V_2 receptor and AQP2 expression also contribute (see Fig. 8.6). To achieve daily osmolar clearance, patients should be advised to maintain a fluid intake that matches their urine volume.

Electrolyte disorders. Hypokalemia causes a reversible abnormality in urine-concentrating ability. Hypokalemia stimulates water intake and reduces interstitial tonicity, which relates to the decreased Na^+-Cl^- reabsorption in the TAL. Hypokalemia resulting from diarrhea, chronic diuretic use, and primary aldosteronism also decreases

TABLE 8.8 Acquired Nephrogenic Diabetes Insipidus: Causes and Mechanisms

Disease State	Defect in Medullary Interstitial Tonicity	Defect in cAMP Generation	Downregulation of Aquaporin 2	Other
Chronic kidney disease	Yes	Yes	Yes	Downregulation of V_2 receptor message
Hypokalemia	Yes	Yes	Yes	—
Hypercalcemia	Yes	Yes	—	—
Sickle cell disease	Yes	—	—	—
Protein malnutrition	Yes	—	Yes	—
Demeclocycline therapy	—	Yes	—	—
Lithium therapy	—	Yes	Yes	—
Pregnancy	—	—	—	Placental secretion of vasopressinase

cAMP, Cyclic adenosine monophosphate.

intracellular cyclic adenosine monophosphate accumulation and causes a reduction in AVP-sensitive AQP2 expression (see Fig. 8.6).

Hypercalcemia also impairs urine-concentrating ability, resulting in mild polydipsia. The pathophysiologic mechanism is multifactorial and includes a reduction in medullary interstitial tonicity caused by decreased AVP-stimulated adenylyl cyclase in the TAL and a defect in adenylyl cyclase activity with decreased AQP2 expression in the collecting duct, mediated by the calcium-sensing receptor.[6]

Pharmacologic agents. Lithium is the most common cause of nephrogenic DI, occurring in up to 50% of patients receiving long-term lithium therapy. Lithium causes downregulation of AQP2 in the collecting duct; experimentally, it also increases cyclooxygenase-2 (COX-2) expression and urinary prostaglandins, which may contribute to the polyuria.[6] The concentrating defect of lithium may persist even when the drug is discontinued. The epithelial sodium channel (ENaC) is the entrance pathway for lithium into collecting duct principal cells. Amiloride inhibits lithium uptake through ENaC and has been used clinically to treat nephrogenic DI caused by lithium. Aldosterone administration dramatically increased urine production in experimental nephrogenic DI caused by lithium (an effect associated with decreased expression of AQP2 on luminal membranes of collecting duct), whereas administration of the mineralocorticoid receptor blocker spironolactone decreased urine output and increased AQP2 expression.[6] Clopidogrel, P2Y12-R purinergic receptor antagonist, ameliorates lithium-induced nephrogenic DI in mice by increasing water and sodium reabsorption in the collecting duct.[47] It is not yet known if spironolactone or clopidogrel will be a useful treatment for lithium-induced nephrogenic DI in patients.

Other drugs impairing urine-concentrating ability include amphotericin, foscarnet, and demeclocycline, which reduce renal medullary adenylyl cyclase activity, thereby decreasing the effect of AVP on the collecting ducts.

Sickle cell anemia. Patients with sickle cell disease and trait often have a urine-concentrating defect. In the hypertonic medullary interstitium, the "sickled" red cells cause occlusion of the vasa recta and papillary damage. Although initially reversible, medullary infarcts occur with sickle cell disease in the second to third decades of life, and even with sickle cell trait by the fourth to fifth decade, and the concentrating defects become irreversible.

Dietary abnormalities. Extensive water intake or a marked decrease in salt and protein intake leads to impairment of maximal urine-concentrating ability through a reduction in medullary interstitial tonicity. On a low-protein diet with excessive water intake, there is a decrease in AVP-stimulated osmotic water permeability that is reversed with feeding.

BOX 8.3 Patient Groups at Risk for Development of Severe Hypernatremia

- Elderly patients
- Infants
- Hospitalized patients
  - Hypertonic infusions
  - Tube feedings
  - Osmotic diuretics
  - Lactulose
  - Mechanical ventilation
- High-risk patient groups
  - Altered mental status
  - Uncontrolled diabetes mellitus
  - Underlying polyuric disorders

From reference 21.

Gestational diabetes insipidus. In gestational DI, there is an increase in circulating AVPase, which is produced by the placenta. Patients are typically unresponsive to AVP but respond to desmopressin, which is resistant to vasopressinase.

Clinical Manifestations of Hypernatremia

Certain patients are at increased risk for development of severe hypernatremia (Box 8.3). Signs and symptoms mostly relate to the CNS and include altered mental status, lethargy, irritability, restlessness, seizures (usually in children), muscle twitching, hyperreflexia, and spasticity. Fever, nausea or vomiting, labored breathing, and intense thirst also can occur. In children, mortality of acute hypernatremia ranges from 10% to 70%; as many as two thirds of survivors have neurologic sequelae. In contrast, mortality in patients with chronic hypernatremia is 10%.

In adults, serum [Na^+] above 160 mmol/l is associated with 75% mortality, although this may reflect associated comorbidities rather than hypernatremia. Chronic hypernatremia is independently associated with higher mortality in patients with CKD.[48] Patients presenting to the intensive care unit with a serum [Na^+] above 155 mmol/l have a significantly increased risk for mortality, with an odds ratio of 3.64.[49] Thus both acute and chronic hypernatremia are associated with an increased risk for mortality.

Treatment of Hypernatremia

Hypernatremia occurs in predictable clinical settings, allowing opportunities for prevention. Elderly and hospitalized patients are at high

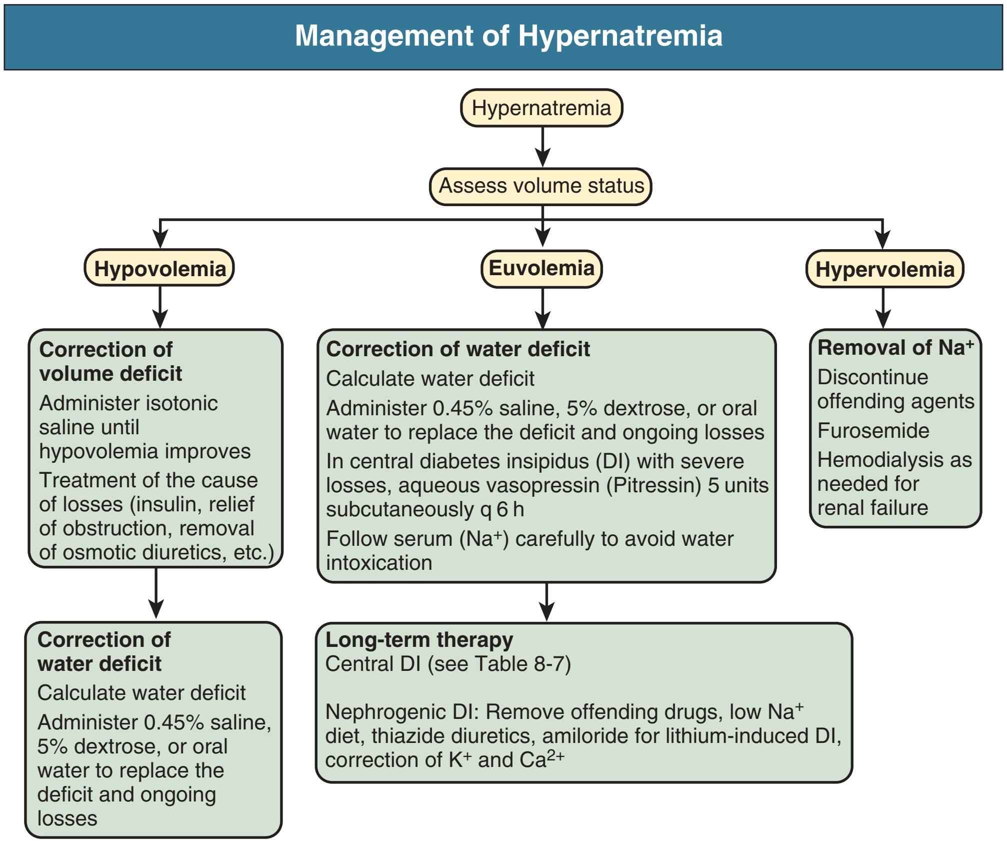
Management of Hypernatremia
Hypernatremia
Assess volume status
Hypovolemia
Euvolemia
Hypervolemia
Correction of volume deficit
Administer isotonic saline until hypovolemia improves
Treatment of the cause of losses (insulin, relief of obstruction, removal of osmotic diuretics, etc.)
Correction of water deficit
Calculate water deficit
Administer 0.45% saline, 5% dextrose, or oral water to replace the deficit and ongoing losses
In central diabetes insipidus (DI) with severe losses, aqueous vasopressin (Pitressin) 5 units subcutaneously q 6 h
Follow serum (Na+) carefully to avoid water intoxication
Removal of Na+
Discontinue offending agents
Furosemide
Hemodialysis as needed for renal failure
Correction of water deficit
Calculate water deficit
Administer 0.45% saline, 5% dextrose, or oral water to replace the deficit and ongoing losses
Long-term therapy
Central DI (see Table 8-7)
Nephrogenic DI: Remove offending drugs, low Na+ diet, thiazide diuretics, amiloride for lithium-induced DI, correction of K+ and Ca2+

Fig. 8.11 Algorithm for management of the patient with hypernatremia. (From reference 21.)

risk because of impaired thirst and inability to access free water independently.[50] Certain clinical situations, such as recovery from acute kidney injury, catabolic states, therapy with hypertonic solutions, uncontrolled diabetes, and burns, should prompt close attention to serum sodium concentration and increased administration of free water.

Hypernatremia always reflects a hyperosmolar state. The primary goal in the treatment of these patients is the restoration of serum tonicity. Fig. 8.11 outlines specific management options.[21] Restoration of volume takes precedence over restoration of tonicity; thus, in hypovolemic hypernatremic patients, sodium-containing solutions should be used until euvolemia is achieved. Thereafter, dextrose in water or oral water intake should be given to decrease serum sodium concentration.

The rapidity with which hypernatremia should be corrected is controversial. Some animal studies and case series in pediatric patients suggest that a correction rate of more than 0.5 mmol/l/h in [Na$^+$] can cause seizures. Cerebral edema also can be caused by rapid correction of hypernatremia by the net movement of water into the brain. Most clinicians believe that even in adults, correction should be achieved during 48 hours at a rate no greater than 2 mmol/l/h.

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SELF-ASSESSMENT QUESTIONS

1. A 78-year-old woman sustained a stroke and is receiving enteral nutrition by nasoduodenal tube at a nursing home. She is transferred to the hospital with altered mental status. Nursing home staff reported that she had plentiful urine output 2 days before transfer. Laboratory data on hospital arrival reveal serum sodium of 165 mmol/l, blood urea nitrogen (BUN) 60 mg/dl, and creatinine 1.6 mg/dl; all were normal 6 weeks earlier. Additional laboratory data include serum osmolality of 341 mOsm/kg and urine osmolality 690 mOsm/kg, urine sodium 7 mmol/l, and urine potassium 32 mmol/l.

   The most likely explanation for this patient's polyuria and hypernatremia and the most appropriate confirmatory test are:

   A. Nephrogenic diabetes insipidus and measurement of ADH
   B. Central diabetes insipidus and measurement of ADH
   C. Lithium toxicity and measurement of serum lithium level
   D. Increased solute load and measurement of electrolyte-free water clearance

2. A 71-year-old woman with a history of coronary artery disease and mild hypertension is seen in the clinic. She is free of complaints. Her medications include lisinopril (20 mg/day), occasional zolpidem tartrate (Ambien), and multivitamins. Her blood pressure is 140/95 mm Hg, weight 62 kg, and skin turgor normal. Examination reveals no evidence of edema or ascites. Laboratory results are as follows:

   - Serum creatinine: 0.9 mg/dl
   - Sodium: 120 mmol/l
   - Potassium: 3.9 mmol/l
   - Chloride: 95 mmol/l
   - HCO_3^-: 22 mmol/l
   - U_{osm}: 686 mOsm/kg
   - U_{Na}: 127 mmol/l
   - Normal thyroid and adrenal function
   - Chest x-ray film unremarkable

   Which of the following statements explains this patient's status?

   A. Patient is unlikely to have improved water excretion because she is not taking a thiazide diuretic
   B. Patient probably has idiopathic SIADH
   C. The hyponatremia is probably a consequence of poor solute intake
   D. Patient's hyponatremia is caused by age-related decrements in vasopressin metabolism

3. A 74-year-old man with a history of heart failure is admitted with increasing shortness of breath. He is treated with lisinopril 20 mg/day, HCTZ 50 mg/day, and digoxin 0.25 mg/day. Examination reveals blood pressure of 145/90 mm Hg, pulse rate 88/min, respiratory rate 24/min, O_2 saturation 90% on 2 liters. His electrolytes are normal. The patient is prescribed a low-sodium restricted diet, furosemide 40 mg bid, and fluid restriction. In the next 24 hours, he excretes 2.5 liters of urine. Laboratory results are as follows:

   - Serum creatinine: 1.8 mg/dl
   - BUN: 25 mg/dl
   - Sodium: 147 mmol/l
   - Potassium: 3.7 mmol/l
   - HCO_3^-: 26 mmol/l
   - Chloride: 120 mmol/l
   - U_{osm}: 392 mOsm/kg
   - U_{Na}: 59 mmol/l
   - U_K: 32 mmol/l

   Which of the following treatment regimens is most likely to prevent worsening of this patient's hypernatremia?

   A. 1 ml of half-normal per milliliter of urine
   B. 0.5 ml of 5% dextrose in water per milliliter of urine
   C. 0.5 ml of normal saline per milliliter of urine
   D. 0.5 ml of normal saline per milliliter of urine

9

Disorders of Potassium Metabolism

I. David Weiner, Stuart L. Linas, Charles S. Wingo

Potassium disorders are some of the most frequently encountered fluid and electrolyte abnormalities in clinical medicine. Patients with disorders of potassium metabolism may be asymptomatic or they may have symptoms ranging from mild weakness to sudden death. An abnormal serum potassium level once verified should be promptly addressed, but inappropriate treatment can worsen symptoms and even lead to death.

NORMAL PHYSIOLOGY OF POTASSIUM METABOLISM

Potassium Intake

Potassium is essential for many cellular functions, is present in most foods, and is excreted primarily by the kidney. The typical Western diet provides about 70 mmol of potassium daily, even though the recommended intake for people with normal renal function is closer to 120 mmol per day.[1] The gastrointestinal (GI) tract efficiently absorbs potassium, and total dietary potassium intake depends on the composition of the diet. Table 9.1 shows the potassium content of several foods high in potassium.

Potassium Distribution

After absorption from the GI tract, potassium distributes rapidly into the extracellular fluid (ECF) and intracellular fluid (ICF) compartments. Cellular potassium uptake is rapid and limits the magnitude of changes in serum potassium concentration. Conversely, during states of potassium loss, shift of potassium from intracellular to extracellular compartments limits the change in extracellular potassium concentration.

Unlike many other ions in the ECF, the majority of total body potassium is intracellular. Potassium is the major intracellular cation, with cytosolic K^+ concentrations about 100 to 120 mmol/l. Total intracellular K^+ content is 3000 to 3500 mmol in healthy adults and is found primarily in muscle (70%), with a lesser amount in bone, red blood cells, liver, and skin (Table 9.2). Only 1% to 2% of total body potassium is present in the ECF. The electrogenic sodium pump, Na^+,K^+-ATPase, is the primary effector of this asymmetric potassium distribution; it transports two potassium ions into cells in exchange for extrusion of three sodium ions, which results in high intracellular potassium concentration (high $[K^+_i]$) and low intracellular sodium concentration (low $[Na^+_i]$). Potassium-selective ion channels are the predominant determinant of the resting membrane potential. Therefore the intracellular-to-extracellular $[K^+]$ ratio largely determines the resting cell membrane potential and the intracellular electronegativity. Normal maintenance of this ratio and membrane potential is critical for normal nerve conduction and muscular contraction.

Under some conditions, the normal distribution of potassium between the extracellular and intracellular pools is altered (Fig. 9.1). Causes of these potassium shifts include acid-base disorders, several hormones, plasma osmolality, and exercise. Because the amount of extracellular K^+, relative to intracellular K^+, is low, modest movements of K^+ into or out of the extracellular pool can result in substantial changes in extracellular K^+ concentration.

Metabolic acidosis is frequently associated with abnormal serum potassium. Acidosis caused by inorganic anions (e.g., NH_4Cl, HCl) can cause hyperkalemia, but the mechanism is not fully understood, and changes in renal potassium excretion are often not observed. In contrast, organic acids (e.g., lactic acid) generally do not cause transcellular potassium shifts. Although hyperkalemia may be seen with lactic acidosis, it is more likely related to tissue ischemia leading to cellular death and subsequent release of cytoplasmic K^+ into extracellular fluid compartments. In type 4 (hyperkalemic) renal tubular acidosis (RTA), hyperkalemia may contribute to the metabolic acidosis by inhibiting net acid excretion in the form of ammonia.[2]

Several hormones, most prominently catecholamines, insulin, and aldosterone, have important roles in regulating serum K^+. The effect of catecholamines differs depending on which adrenergic receptor subtype they activate. Activation of β_2-adrenergic receptors stimulates Na^+,K^+-ATPase, inducing cellular potassium uptake and decreasing serum K^+, whereas α_1-adrenergic receptor activation has the opposite effect. Thus drugs that block the β_2-adrenoreceptor tend to increase serum K^+ and those that block the α_1-adrenoreceptor tend to lower serum K^+.

Insulin has important effects on serum K^+. It activates Na^+,K^+-ATPase, directly increasing cellular K^+ uptake and decreasing serum K^+. This effect is rapid and enables insulin administration to be a component of the acute therapy of hyperkalemia. Importantly, insulin stimulates Na^+,K^+-ATPase through a mechanism that is distinct from its stimulation of glucose entry and does not involve effects on either α- or β-adrenoreceptors. Thus the effects of insulin and β_2-adrenoceptor activation are synergistic. In diabetic ketoacidosis, the lack of insulin-induced cellular K^+ uptake contributes to the hyperkalemia that is often observed in this condition.

Aldosterone regulates serum potassium at least in part by altering the distribution of potassium between ECF and ICF. It does so predominantly by enhancing cellular potassium uptake through stimulation of Na^+,K^+-ATPase.[3] Indeed, aldosterone administration can cause hypokalemia in the absence of altered renal potassium excretion through mechanisms involving altered cellular K^+ distribution.[3,4]

Serum osmolality is another important factor that alters cellular potassium distribution. Hyperosmolality can cause hyperkalemia when the result of “effective osmoles,” such as mannitol, or hyperglycemia. The likely mechanism is that increased serum osmolality induces water movement out of the cells, decreasing cell volume and increasing intracellular $[K^+]$. This in turn causes stimulation of K^+-permeable cation

TABLE 9.1 Amount of Potassium (K^+) in Select Foods With High K^+ Content

Food	Portion Size	K^+ (mmol)
Artichoke, boiled	1, medium	27
Avocado	1, medium	38
Sirloin steak	8 oz	23
Hamburger, lean	8 oz	18
Cantaloupe, cut up	1 cup	13
Grapefruit juice	8 oz	10
Milk	8 oz	10
Orange juice	8 oz	12
Potato, baked	7 oz	22
Prunes	10	16
Raisins	2/3 cup	19
Squash	1 cup	15-20
Tomato paste	½ cup	31
Tomato juice	6 oz	10
Banana	Medium size	12

Data from reference 43. 1 oz = 28.4 gram.

TABLE 9.2 Distribution of Total Body Potassium in Organs and Body Compartments

Organ/Fluid	Total K^+ Amount	Body Compartment	K^+ Concentration
Muscle	2650 mmol	Intracellular fluid (ICF)	100-120 mmol/l
Liver	250 mmol	Extracellular fluid (ECF)	~4 mmol/l
Interstitial fluid	35 mmol	—	—
Red blood cells	350 mmol	—	—
Plasma	15 mmol	—	—

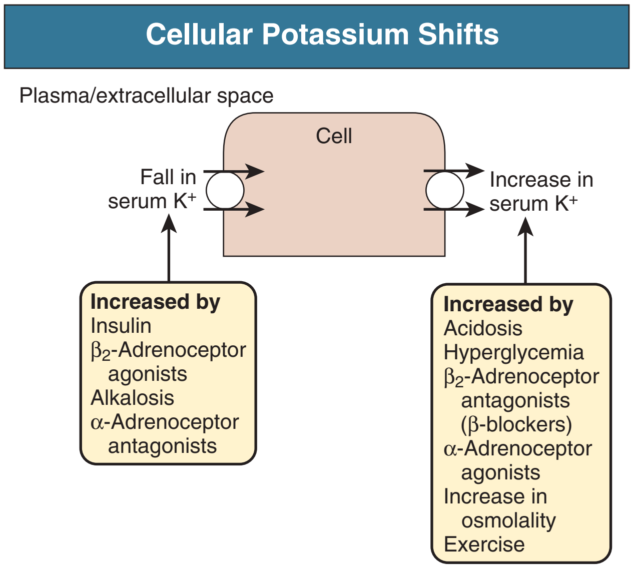

Cellular Potassium Shifts
Plasma/extracellular space
Cell
Fall in serum K+
Increase in serum K+
Increased by
Insulin
β2-Adrenoceptor agonists
Alkalosis
α-Adrenoceptor antagonists
Increased by
Acidosis
Hyperglycemia
β2-Adrenoceptor antagonists (β-blockers)
α-Adrenoceptor agonists
Increase in osmolality
Exercise

Fig. 9.1 Regulation of extracellular/intracellular potassium shifts.

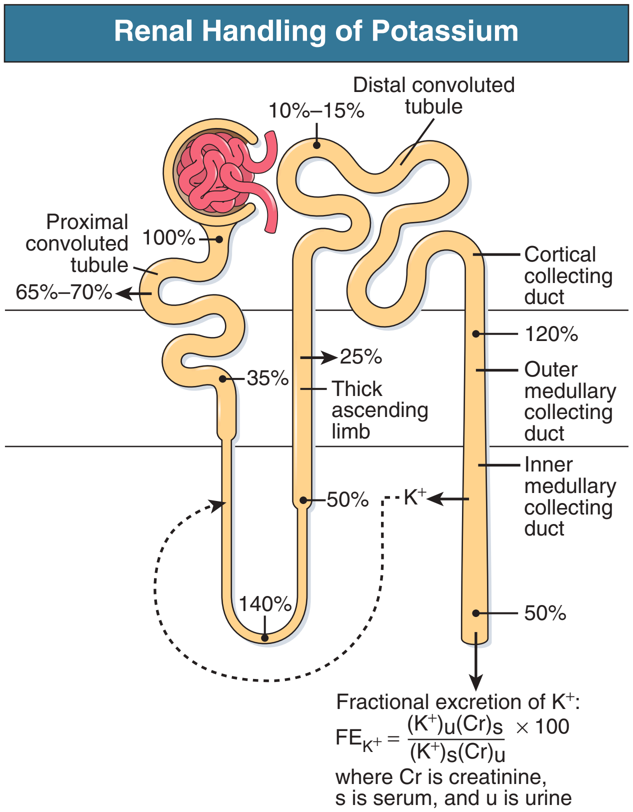

Renal Handling of Potassium
Distal convoluted tubule
10%–15%
Proximal convoluted tubule
100%
65%–70%
Cortical collecting duct
120%
35%
25%
Thick ascending limb
Outer medullary collecting duct
Inner medullary collecting duct
50%
K+
140%
50%
Fractional excretion of K+:
FEK+ = (K+)u(Cr)s / (K+)s(Cr)u × 100
where Cr is creatinine, s is serum, and u is urine

Fig. 9.2 Renal handling of potassium.

channels, increasing transport of K^+ out of cells and normalizing intracellular [K^+]. Both glucose in patients with intact insulin secretion and urea in patients with high blood urea nitrogen levels are "ineffective osmoles" because they rapidly cross plasma membranes, do not alter cell volume, and do not alter transcellular K^+ shifts. Administering a glucose load to a nondiabetic patient, because it stimulates insulin secretion, can stimulate insulin-induced cellular potassium uptake and decrease serum K^+.

Exercise has multiple effects on K^+. Cellular K^+ release is a critical component of repolarization of contracting skeletal muscle cells and can cause mild hyperkalemia during strenuous physical exercise. Catecholamines released during exercise can contribute to this hyperkalemia because α_1-adrenergic receptor activation shifts potassium out of cells. The local increase in extracellular potassium induces arterial dilation in normal blood vessels, which increases skeletal muscle blood flow and acts as an adaptive mechanism during exercise. Catecholamines released during exercise also activate β_2-adrenoceptors, which stimulates skeletal muscle cellular potassium uptake and minimizes the severity of exercise-induced hyperkalemia, but can also lead to hypokalemia after cessation of exercise. With preexisting potassium depletion, postexercise hypokalemia may be severe and can cause rhabdomyolysis.[5]

Renal Potassium Handling With Normal Renal Function

Long-term potassium homeostasis occurs primarily through changes in renal potassium excretion. Serum potassium is almost completely ionized, is not bound to plasma proteins, and is filtered efficiently by the glomerulus (Fig. 9.2). The proximal tubule reabsorbs the majority (~65% to 70%) of filtered potassium, but there is relatively little variation in proximal tubule potassium reabsorption in response to hypokalemia or hyperkalemia. In the loop of Henle, potassium is secreted in the descending loop, at least in deep nephrons, particularly with

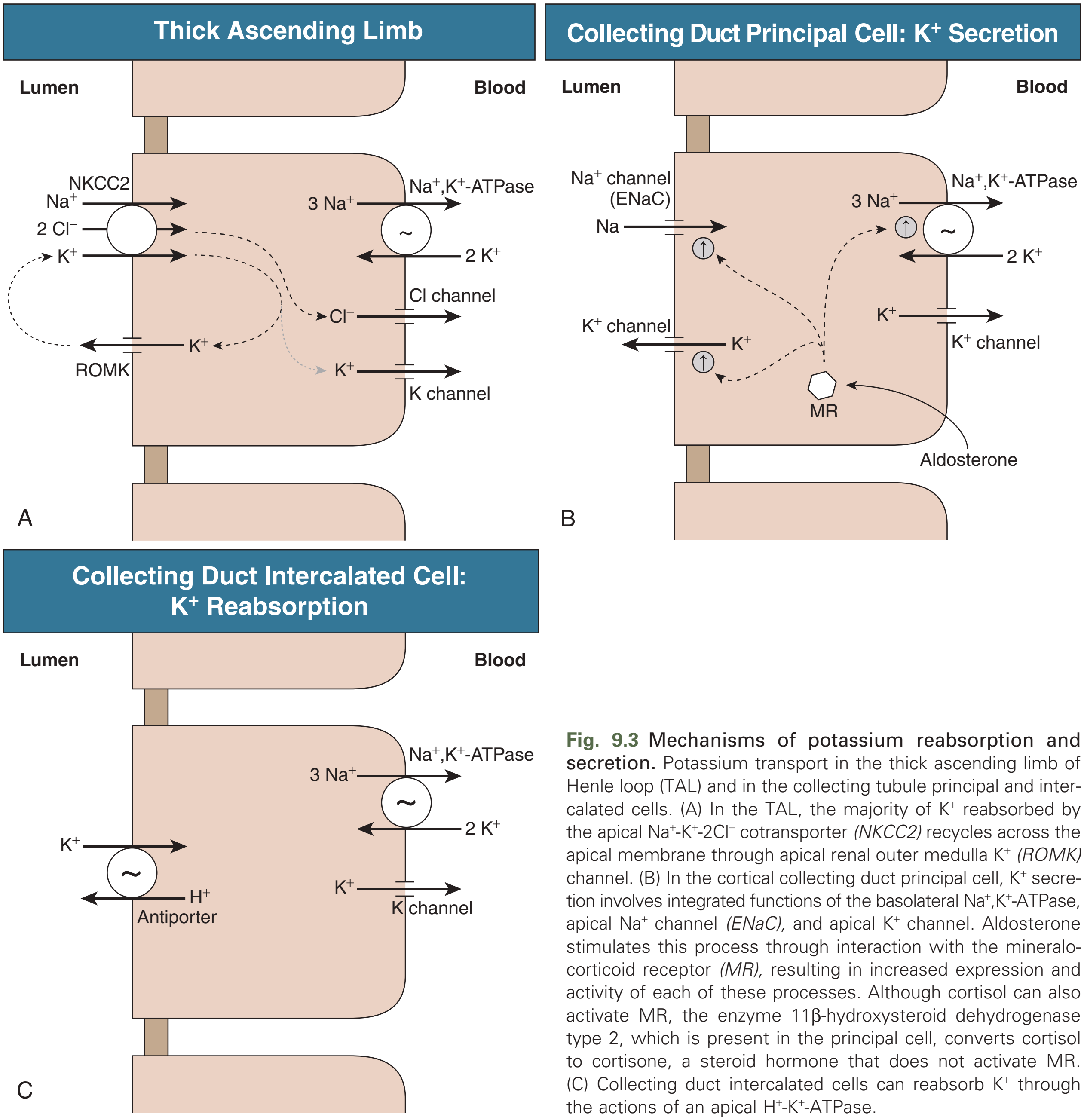


Fig. 9.3 Mechanisms of potassium reabsorption and secretion. Potassium transport in the thick ascending limb of Henle loop (TAL) and in the collecting tubule principal and intercalated cells. (A) In the TAL, the majority of K^+ reabsorbed by the apical Na^+-K^+-$2Cl^-$ cotransporter *(NKCC2)* recycles across the apical membrane through apical renal outer medulla K^+ *(ROMK)* channel. (B) In the cortical collecting duct principal cell, K^+ secretion involves integrated functions of the basolateral Na^+,K^+-ATPase, apical Na^+ channel *(ENaC),* and apical K^+ channel. Aldosterone stimulates this process through interaction with the mineralocorticoid receptor *(MR),* resulting in increased expression and activity of each of these processes. Although cortisol can also activate MR, the enzyme 11β-hydroxysteroid dehydrogenase type 2, which is present in the principal cell, converts cortisol to cortisone, a steroid hormone that does not activate MR. (C) Collecting duct intercalated cells can reabsorb K^+ through the actions of an apical H^+-K^+-ATPase.

adaptation to a large K^+ intake, and is reabsorbed in the ascending loop through the action of the Na^+-K^+-$2Cl^-$ cotransporter (Fig. 9.3A). However, the majority of K^+ transported by this protein is recycled back into the tubular lumen through an apical K^+ channel. As a result, there is only modest net potassium reabsorption in the loop of Henle. This absorption can be reversed to secretion, however, by administration of a loop diuretic or substantial potassium loading. Nonetheless, the magnitude of the change in Henle loop potassium transport in various physiologic conditions is relatively small.

The collecting duct is the primary site at which the kidney regulates urinary K^+ excretion. The collecting duct has the ability both to secrete K^+, enabling adaptation to K^+ excess states, and to actively reabsorb K^+, enabling adaptation to K^+ depletion states. The principal cell, particularly in the cortical collecting duct, secretes potassium, whereas intercalated cells throughout the entire collecting duct reabsorb potassium. In the principal cell, sodium is reabsorbed through the apical epithelial sodium channel (ENaC), which stimulates basolateral Na^+,K^+-ATPase (Fig. 9.3B); active potassium uptake by this protein maintains a high intracellular K^+. Subsequent to basolateral potassium uptake, K^+ is secreted across the apical plasma membrane of principal cells into the luminal fluid by apical potassium channels and KCl cotransporters. Intercalated cells, in contrast, actively reabsorb potassium through an apical H^+-K^+-ATPase[6] (Fig. 9.3C); this protein actively secretes H^+ into the luminal fluid in exchange for reabsorption of luminal potassium. The presence of two separate potassium transport processes, secretion by principal cells and reabsorption by intercalated cells, contributes to rapid and effective regulation of renal potassium excretion.

Several factors influence principal cell potassium secretion. In relative order of importance these include luminal flow rate, distal sodium delivery, aldosterone, extracellular potassium intake, and extracellular pH. Under conditions in which Na^+ delivery or luminal $[Na^+]$ is drastically reduced, K^+ excretion falls precipitously due to decreased K^+ secretion. However, whether Na^+ delivery is normally rate limiting to K excretion in euvolemic subjects is an important area of investigation. An increase in luminal flow rate reduces changes in luminal $[K^+]$ that would otherwise result from K^+ secretion, thereby minimizing changes in the concentration gradient across the apical membrane and facilitating continued K^+ transport. In addition, flow rate directly influences cellular potassium secretion by modulating the activity of potassium channels. Consequently, reduced luminal flow, such as occurs in pre-renal azotemia and obstruction, may contribute to the hyperkalemia that is often seen in these conditions. Decreased sodium reabsorption, whether from reduced luminal sodium delivery or treatment with sodium channel inhibitors, i.e., potassium-sparing diuretics, decreases K^+ secretion by altering electrochemical forces for K^+ secretion. Conversely, increased sodium delivery to the collecting duct, as may occur with either a high-salt diet or administration of either loop or thiazide diuretics, increases principal cell sodium reabsorption and causes a secondary increase in potassium secretion. Aldosterone has many effects that increase principal cell potassium secretion, including increased Na^+,K^+-ATPase, increased apical expression of ENaC, and increased apical K^+ channels. The net effect is increased principal cell-mediated K^+ secretion. Changes in extracellular potassium directly alter Na^+,K^+-ATPase activity, thereby altering increased K^+ secretion. Metabolic acidosis decreases K^+ secretion, both through direct effects on potassium channels and through changes in interstitial ammonia concentration, both of which decrease K^+ secretion.[7] Respiratory acidosis has minimal effect on K^+ secretion, whereas acute respiratory alkalosis can cause marked increases in K^+ excretion associated with increases in urinary bicarbonate excretion.

Intercalated cell-mediated potassium reabsorption occurs in parallel with principal cell-mediated potassium secretion. Active potassium reabsorption occurs through the action of the potassium-reabsorbing protein, H^+-K^+-ATPase. The major factors regulating H^+-K^+-ATPase expression and activity include potassium balance, aldosterone, and acid-base status. Potassium depletion increases H^+-K^+-ATPase expression, resulting in increased active potassium reabsorption and decreased net potassium excretion. Aldosterone increases H^+-K^+-ATPase expression and activity and, by decreasing net potassium excretion, may minimize changes in urinary potassium excretion during aldosterone excess that otherwise would lead to more severe hypokalemia. Metabolic acidosis has both direct and indirect effects, mediated through alterations in ammonia metabolism, that increase H^+-K^+-ATPase potassium reabsorption.[2]

Fundamental regulators of renal K^+ transport in the distal nephron include the "with no lysine" or "WNK" kinases.[8,9] WNK kinases activate Na^+ reabsorption in the distal convoluted tubule as well as inhibiting the renal outer medulla potassium (ROMK) channel. This combination of effects, increased DCT Na^+ reabsorption, which decreases collecting duct Na^+ delivery, in conjunction with decreased ROMK expression, promotes decreased K^+ secretion. Extracellular K alters intracellular Cl^- through direct effects on membrane voltage; the former appears to directly regulates WNK activity.[8,9] This results in hypokalemia activating and hyperkalemia inhibiting WNK activity. Medications targeting WNK inhibition are in development and may in the future enable entirely new treatments of hypertension and K^+ disorders.[10]

Finally, in the intestinal tract, gut or portal potassium sensors can elicit a rapid increase in renal potassium excretion through mechanisms independent of serum potassium and aldosterone.[3,11] This reflex system, which is still not understood fully, provides a mechanism to "sense" dietary potassium intake and alter renal potassium excretion before changes in serum potassium and without involving aldosterone concentration.

Renal Potassium Handling in Chronic Kidney Disease

Because the kidneys are the major route for elimination of potassium, as renal function declines the balance among dietary potassium intake, renal potassium excretion, and baseline serum potassium changes. In general, most patients with chronic kidney disease (CKD) are able to maintain their serum potassium in the normal range, although there is a graded increase in mean serum K^+ as the glomerular filtration rate (GFR) declines. The risk for developing hyperkalemia is increased in patients with stage IV CKD; patients with stage III CKD who have diabetes mellitus, tubulointerstitial disease, or receive certain drugs also are at increased risk.

Many of the medications used in the treatment of patients with CKD have important effects on potassium homeostasis. Common medications that predispose to hyperkalemia (Table 9.3) include agents that inhibit

TABLE 9.3 Classes of Drugs Associated With Hyperkalemia

Class	Mechanism	Representative Example(s)
Potassium-containing drugs	Increased potassium intake	KCl, PCN G, K citrate
β-Adrenergic receptor blockers (β-blockers)	Inhibit renin release	Propranolol, metoprolol, atenolol
Angiotensin-converting enzyme (ACE) inhibitors	Inhibit conversion of angiotensin I (Ang I) to Ang II	Captopril, lisinopril
Angiotensin receptor blockers (ARBs)	Inhibit activation of AT_1 receptor by Ang II	Losartan, valsartan, irbesartan
Direct renin inhibitors	Inhibit renin activity, leading to decreased Ang II production	Aliskiren
Heparin	Inhibit aldosterone synthase, rate-limiting enzyme for aldosterone synthesis	Heparin sodium
Aldosterone receptor antagonists	Block aldosterone receptor activation	Spironolactone, eplerenone
Potassium-sparing diuretics	Block collecting duct apical ENaC Na channel, decreasing gradient for K^+ secretion	Amiloride, triamterene; certain antibiotics, specifically trimethoprim and pentamidine
NSAIDs and COX-2 inhibitors	Inhibit prostaglandin stimulation of collecting duct K^+ secretion; inhibit renin release	Ibuprofen
Digitalis glycosides	Inhibit Na^+,K^+-ATPase necessary for collecting duct K^+ secretion and regulation of K^+ distribution into cells	Digoxin
Calcineurin inhibitors	Inhibit Na^+,K^+-ATPase necessary for collecting duct K^+ secretion	Cyclosporine, tacrolimus

COX-2, Cyclooxygenase; *ENaC,* amiloride-sensitive epithelial sodium channel; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PCN G,* penicillin G.

the ENaC or renin-angiotensin-aldosterone system (RAAS), nonsteroidal antiinflammatory drugs (NSAIDs), and calcineurin inhibitors. Medications that can directly inhibit ENaC, such as amiloride, triamterene, trimethoprim, and pentamidine, may acutely reduce the rate of renal K^+ excretion and cause hyperkalemia. Drugs that inhibit the RAAS, such as mineralocorticoid receptor (MR) blockers, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, direct renin inhibitors, and heparin, have the potential to inhibit the action of aldosterone, which reduces renal clearance of K^+. Mineralocorticoid blockers are increasingly used in patients with congestive heart failure and refractory hypertension and have potential benefit to slow the progression of CKD. NSAIDs that inhibit prostaglandin synthesis and β-blockers that inhibit renin release and catecholamine action also can increase the risk for hyperkalemia. In contrast, both loop and thiazide diuretics increase renal K^+ excretion and predispose to hypokalemia.

Patients with CKD generally tolerate hyperkalemia with fewer cardiac and electrocardiographic (ECG) abnormalities than do patients with normal renal function. The mechanism of this adaptation is incompletely understood. In particular, patients with CKD appear to tolerate serum [K^+] of 5.0 to 5.5 mmol/l with no significant adverse effect, and levels of 5.5 to 6.0 mmol/l are associated with lower mortality than [K^+] of 3.5 to 3.9 mmol/l.[12] Nevertheless, severe hyperkalemia (>6.0 mmol/l or presence of ECG changes) can have lethal effects and should be treated aggressively.

HYPOKALEMIA

Epidemiology

The incidence of potassium disorders depends greatly on the patient population. Less than 1% of adults with normal renal function who are not receiving medications develop hypokalemia or hyperkalemia; however, diets with high sodium and low potassium content may lead to potassium depletion. Thus identification of hypokalemia or hyperkalemia suggests either that an underlying disease is present or that the individual is taking drugs that alter potassium handling. For example, hypokalemia may be present in as many as half of patients taking diuretics[13] and is present in many patients with primary or secondary hyperaldosteronism.

Clinical Manifestations

Potassium deficiency, because it alters the ratio of extracellular to intracellular potassium, alters the resting membrane potential, which can impair normal functioning of almost every cell in the body. Several studies have shown that hypokalemia, even when mild, is associated with increased long-term mortality. Overall, children and young adults tolerate hypokalemia better than elderly persons. Prompt correction is warranted in patients with coronary heart disease or in patients receiving digitalis glycosides, because hypokalemia increases the risk for lethal cardiac arrhythmias.

Cardiovascular

Potassium deficiency affects blood pressure and increases sensitivity to cardiac arrhythmias. Epidemiologic studies link hypokalemia and a low-potassium diet with an increased prevalence of hypertension, and experimental studies show that hypokalemia increases blood pressure by 5 to 10 mm Hg and that potassium supplementation can lower blood pressure by a similar amount.[14] Potassium deficiency also increases the magnitude of salt-dependent changes in blood pressure. Potassium deficiency increases blood pressure through multiple mechanisms, including stimulating sodium retention and increasing intravascular volume, and by sensitizing the vasculature to endogenous vasoconstrictors.[14] In part, sodium retention is related to decreased expression of the kidney-specific isoform of WNK1, which leads to increased NaCl cotransporter (NCC)–mediated and ENaC-mediated sodium reabsorption in the distal convoluted tubule and cortical collecting duct, respectively.[15]

Hypokalemia also predisposes to arrhythmia, including ventricular tachycardia and ventricular fibrillation[16] and the risk for sudden cardiac death. Diuretic-induced hypokalemia is of particular concern, because sudden cardiac death may occur more frequently in those treated with thiazide diuretics.[16] Ventricular arrhythmias are also more common in patients receiving digoxin who develop hypokalemia.

Hormonal

Hypokalemia impairs insulin release and induces insulin resistance, resulting in worsened glucose control in patients with diabetes.[17] The insulin resistance that usually occurs with thiazide diuretic therapy is caused by endothelial dysfunction mediated by thiazide-induced hypokalemia and hyperuricemia.[18]

Muscular

Hypokalemia can lead to skeletal muscle weakness and increased sensitivity to developing exertion-related rhabdomyolysis. Hypokalemia hyperpolarizes skeletal muscle cells, thereby impairing the ability to generate the action potential needed for muscle contraction. Hypokalemia also reduces skeletal muscle blood flow, possibly by impairing local nitric oxide release; this effect can predispose patients to rhabdomyolysis during vigorous exercise.[19]

Renal

Hypokalemia leads to several important disturbances of renal function. Reduced medullary blood flow and increased renal vascular resistance may predispose to hypertension, tubulointerstitial and cystic changes, alterations in acid-base balance, and impairment of renal concentrating mechanisms.

Potassium depletion causes tubulointerstitial fibrosis that is generally greatest in the outer medulla. The degree of reversibility is related to the duration of hypokalemia, and, if prolonged, hypokalemia may result in renal failure. Experimental studies suggest an increased risk for irreversible renal injury when hypokalemia is present during the neonatal period.[20]

Long-standing potassium depletion also causes renal hypertrophy and predisposes to renal cyst formation, particularly when there is increased mineralocorticoid activity.

Metabolic alkalosis is a common acid-base consequence of potassium depletion and results primarily from increased renal net acid excretion caused by increased renal ammonia excretion.[21] Conversely, metabolic alkalosis may increase renal potassium excretion and cause potassium depletion. Severe hypokalemia can lead to respiratory muscle weakness and development of respiratory acidosis, and, if severe, respiratory failure.

Severe hypokalemia can cause mild polyuria, typically 2 to 3 l/day. Both increased thirst and mild nephrogenic diabetes insipidus contribute to the polyuria.[22] The nephrogenic diabetes insipidus is caused by decreased expression of several proteins, such as the water transporter aquaporin 2 (AQP2) and the urea transporters UT-A1, UT-A3, and UT-B, which are involved in urine concentration and water reabsorption.

Hypokalemia substantially increases renal ammonia production. Some ammonia is excreted in the urine, increasing net acid excretion and leading to development of metabolic alkalosis. In addition, approximately half of this increase returns to the systemic circulation via the renal veins. In patients with acute or chronic liver disease, this increased ammonia delivery may exceed hepatic ammonia clearance capacity, increase plasma ammonia levels, and either precipitate or worsen hepatic encephalopathy.[2]

Etiology

Hypokalemia results typically from one of four causes: pseudohypokalemia, redistribution, extrarenal potassium loss, or renal potassium loss. However, multiple causes may coexist in a specific patient.

Pseudohypokalemia

Pseudohypokalemia refers to the condition in which serum potassium decreases, artifactually, after phlebotomy. The most common cause is acute leukemia; the large numbers of abnormal leukocytes take up potassium when the blood is stored in a collection vial for prolonged periods at room temperature. Rapid separation of plasma and storage at 4° C is used to confirm this diagnosis and should be used for subsequent testing once pseudohypokalemia is diagnosed, to avoid this artifact leading to inappropriate treatment.

Redistribution

Because less than 2% of total body potassium is in the ECF compartment, quantitatively small potassium shifts from the ECF to the ICF compartment can cause substantial hypokalemia. A chronic increase in aldosterone secretion increases the pump-leak kinetics and reduces plasma K^+ in the absence of perceptible increases in urinary K^+ excretion if intake is constant.

A rare, but important, cause of redistribution-induced hypokalemia is hypokalemic periodic paralysis. In this condition, attacks characterized by flaccid paralysis or severe muscular weakness occur typically during the night or the early morning or after a carbohydrate-rich meal, and persist for 6 to 24 hours. A genetic defect in a dihydropyridine-sensitive calcium channel has been identified in some patients, whereas other cases are associated with hyperthyroidism.

Nonrenal Potassium Loss

The skin and the GI tract excrete small amounts of potassium under normal circumstances. Occasionally, excessive sweating or chronic diarrhea results in substantial potassium loss and leads to hypokalemia.[23] Vomiting or nasogastric suction also may result in loss of potassium, although gastric fluids typically contain only 5 to 8 mmol/l of potassium. The concomitant metabolic alkalosis, however, can increase urinary potassium loss and contribute to development of hypokalemia.[24]

Renal Potassium Loss

The most common cause of hypokalemia is renal potassium loss, which typically results from drugs, endogenous hormone production, or, more rarely, intrinsic renal defects.

Drugs. Both thiazide and loop diuretics increase urinary potassium excretion, and the incidence of diuretic-induced hypokalemia is related to both dose and treatment duration. When loop and thiazide diuretics are dosed to produce similar effects on sodium excretion, thiazide diuretics have greater effects on urinary potassium and are more likely to lead to hypokalemia. Some penicillin analogues, such as piperacillin/tazobactam, increase distal tubular delivery of a nonreabsorbable anion, which obligates the presence of a cation such as potassium, and increases urinary potassium excretion.[25] The antifungal agent amphotericin B directly increases collecting duct potassium secretion. Aminoglycosides may cause hypokalemia either with or without simultaneous nephrotoxicity. The mechanism is incompletely understood but may relate to magnesium depletion (see later discussion). Cisplatin is an antineoplastic agent that can induce hypokalemia from renal potassium wasting; the increased potassium excretion may persist after discontinuation of the medication. Toluene exposure, from sniffing certain glues, also can cause RTA with renal potassium wasting, leading to hypokalemia.[26] In addition, certain herbal products, including herbal cough mixtures, licorice tea, licorice root, and *gan cao,* contain glycyrrhizic and glycyrrhetinic acids, which have mineralocorticoid-like effects.[27]

Endogenous hormones. Aldosterone is an important hormone regulating total body potassium homeostasis. Aldosterone predominantly causes hypokalemia by stimulating cellular potassium uptake.[3] Aldosterone also has direct effects to increase both collecting duct potassium secretion and reabsorption. During states of chronic aldosterone excess, urinary potassium excretion may not appropriately decrease despite the presence of low serum potassium, thus contributing to the maintenance of hypokalemia (see Chapter 38).

Genetic causes. Genetic defects leading to excessive aldosterone production are occasionally seen that result in hypokalemia (see Chapter 47). These include glucocorticoid-remediable aldosteronism, congenital adrenal hyperplasia, *and* apparent mineralocorticoid excess. These conditions are discussed in detail in Chapter 47.

Magnesium depletion. Magnesium deficiency can cause inappropriately high renal potassium excretion despite hypokalemia.[28] This appears to occur because intracellular magnesium inhibits the apical ROMK channels critical for distal nephron K^+ secretion. In magnesium deficiency, decreased intracellular magnesium reduces the magnesium-mediated inhibition of ROMK channels, leading to increased ROMK-mediated K^+ secretion and thereby to increased net K^+ secretion.[29] Magnesium deficiency occurs most frequently as a complication of prolonged diuretic use and also can result from proton pump inhibitor drugs or aminoglycoside- or cisplatin-induced renal toxicity. Magnesium deficiency should be suspected when potassium replacement does not correct hypokalemia; treatment with magnesium replacement generally reverses the potassium wasting. Proton pump inhibitors should be discontinued.

Primary renal defect. Intrinsic renal potassium transport defects leading to hypokalemia are rare. They include Bartter and Gitelman syndromes, which have clinical phenotypes similar to those that follow use of loop and thiazide diuretics, respectively, and Liddle syndrome. These are discussed in Chapter 47.

Bicarbonaturia. Bicarbonaturia can result from metabolic alkalosis, distal RTA, or treatment of proximal RTA. In each case, the increased distal tubular bicarbonate delivery increases potassium secretion.

Diagnostic Evaluation

The evaluation of hypokalemia is summarized in Fig. 9.4. The clinician should first exclude pseudohypokalemia or potassium redistribution from the extracellular to the intracellular space. Insulin, aldosterone, fludrocortisone, and sympathomimetic agents such as theophylline and β_2-adrenoceptor agonists, are common causes of potassium redistribution. In the hypertensive patient, frank hypokalemia in the absence of diuretic use suggests primary aldosteronism.

If neither pseudohypokalemia nor potassium redistribution is present, hypokalemia represents total body potassium depletion caused by renal, GI, or skin losses. Renal potassium loss is caused most frequently by diuretics. Hypomagnesemia can also cause renal potassium wasting and is frequently a complication of diuretic use. Less common causes of renal potassium loss include proximal and distal RTA, diabetic ketoacidosis, and ureterosigmoidostomy. Primary aldosteronism, surreptitious diuretic use or vomiting, laxative abuse, concomitant magnesium depletion, and Bartter or Gitelman syndrome should be considered when the cause of the hypokalemia is not obvious. Excessive potassium loss also may result from skin losses from excessive sweating or from the GI tract from diarrhea, vomiting, nasogastric suction, or GI fistula. Occasionally, patients are reluctant to admit to self-induced diarrhea, and the diagnosis may need to be confirmed by direct testing of the stool for cathartic agents.

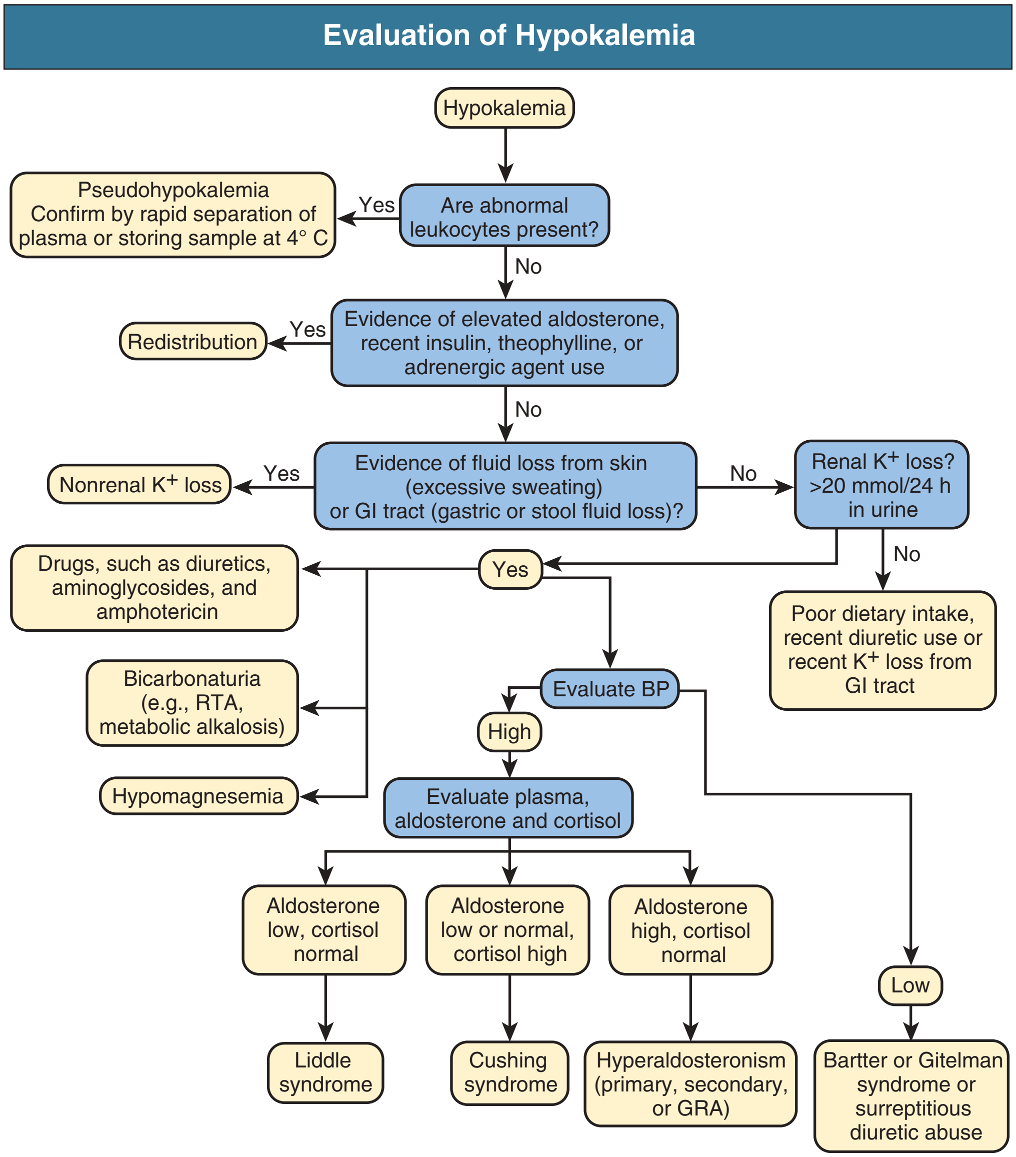

Evaluation of Hypokalemia
Hypokalemia
Are abnormal leukocytes present?
Yes
Pseudohypokalemia Confirm by rapid separation of plasma or storing sample at 4° C
No
Evidence of elevated aldosterone, recent insulin, theophylline, or adrenergic agent use
Yes
Redistribution
No
Evidence of fluid loss from skin (excessive sweating) or GI tract (gastric or stool fluid loss)?
Yes
Nonrenal K+ loss
No
Renal K+ loss? >20 mmol/24 h in urine
No
Poor dietary intake, recent diuretic use or recent K+ loss from GI tract
Yes
Drugs, such as diuretics, aminoglycosides, and amphotericin
Bicarbonaturia (e.g., RTA, metabolic alkalosis)
Hypomagnesemia
Evaluate BP
High
Low
Evaluate plasma, aldosterone and cortisol
Aldosterone low, cortisol normal
Aldosterone low or normal, cortisol high
Aldosterone high, cortisol normal
Liddle syndrome
Cushing syndrome
Hyperaldosteronism (primary, secondary, or GRA)
Bartter or Gitelman syndrome or surreptitious diuretic abuse

Fig. 9.4 Diagnostic evaluation of hypokalemia. *BP,* Blood pressure; *GI,* gastrointestinal; *GRA,* glucocorticoid-remediable aldosteronism; *RTA,* renal tubular acidosis.

Treatment

Primary short-term risks of hypokalemia are cardiovascular arrhythmias and neuromuscular weakness. Overly rapid therapy can cause acute hyperkalemia, which can cause ventricular fibrillation and sudden death.

Conditions requiring urgent therapy are rare. The clearest indications include hypokalemic periodic paralysis, severe hypokalemia in a patient requiring urgent surgery, and the patient with an acute myocardial infarction and life-threatening ventricular ectopy. In these patients, potassium chloride (KCl) can be administered intravenously at a dose of 5 to 10 mmol over 15 to 20 minutes. This dose can be repeated as needed. Close and continuous monitoring of the serum [K^+] and the electrocardiogram are necessary to reduce the risk for potentially lethal acute hyperkalemia.

In the great majority of hypokalemic patients, emergency therapy is not necessary. The body responds to potassium losses by shifting potassium from ICF to ECF, thereby minimizing the change in extracellular [K^+]. During potassium replacement, there is shift of potassium back into ICF. Consequently, the amount of potassium replacement needed is much greater than predicted by the change in extracellular [K^+] and the ECF volume (Fig. 9.5).

Oral or enteral potassium administration is preferred if the patient can take oral medication and has normal GI tract function. Acute hyperkalemia is highly unusual when potassium is given orally. This reflects several factors, most prominently gut sensors that minimize changes in serum potassium levels. When potassium is given intravenously, acute hyperkalemia can occur if the administration rate is too rapid and can cause sudden cardiac death. Intravenous replacement can generally be given safely at a rate of 10 mmol KCl/h. If more rapid replacement is necessary, 20 or 40 mmol/h can be administered through a central venous catheter, but continuous ECG monitoring should be used under these circumstances.

The choice of the parenteral fluid, used to administer the potassium can affect the response. In patients without diabetes mellitus, dextrose leads to a reflex increase in serum insulin levels, which causes redistribution of potassium from ECF to ICF. As a result, administering KCl in dextrose-containing solutions, such as dextrose 5% in water (D5W), can stimulate cellular potassium uptake to an extent that it exceeds the

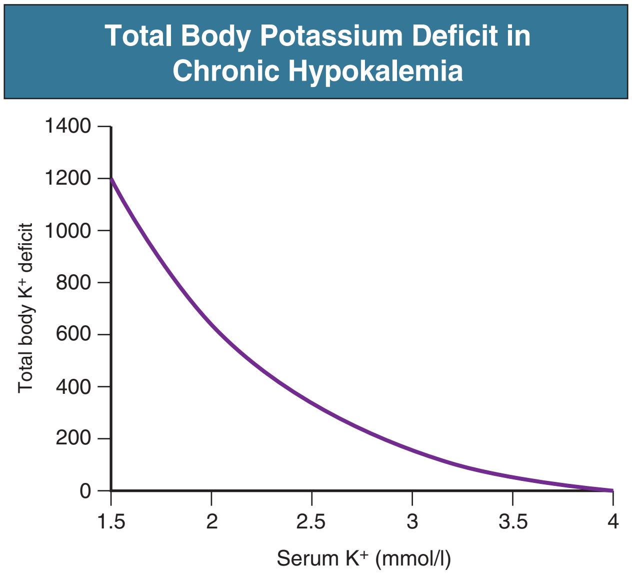


Fig. 9.5 **Total body potassium deficit in hypokalemia.** Because of shift of potassium from the intracellular fluid (ICF) to the extracellular fluid (ECF) compartment during chronic potassium depletion, the magnitude of deficiency can be masked and is generally much larger than would be calculated solely from the ECF volume and the change in serum potassium.

ECG Changes in Hyperkalemia

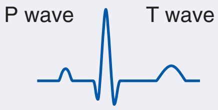
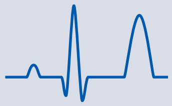
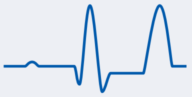
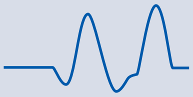
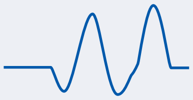
QRS Complex	Approximate Serum Potassium (mmol/l)	ECG Change
	4-5	Normal
	6-7	Peaked T waves
	7-8	Flattened P wave, prolonged PR interval, depressed ST segment, peaked T wave
	8-9	Atrial standstill, prolonged QRS duration, further peaking T waves
	>9	Sinusoid wave pattern

Fig. 9.6 **Electrocardiographic (ECG) changes in hyperkalemia.** Progressive hyperkalemia results in identifiable changes in the electrocardiogram. These include peaking of the T wave, flattening of the P wave, prolongation of the PR interval, depression of the ST segment, prolongation of the QRS complex, and eventually, progression to a sine wave pattern. Ventricular fibrillation may occur at any time during this ECG progression.

KCl replacement rate, resulting in paradoxical worsening of the hypokalemia.[30] Consequently, in the presence of hypokalemia, parenteral KCl should be administered in dextrose-free solutions.

The underlying condition should be treated whenever possible. If patients with diuretic-induced hypokalemia require ongoing diuretic administration, addition of potassium-sparing diuretics may be considered. When oral replacement therapy is required, KCl is the preferred drug in all patients, except those with metabolic acidosis, in whom potassium citrate may be considered a concomitant alkali source. If clinically indicated for other reasons, the use of β-blockers, ACE inhibitors, or ARBs can assist in maintaining serum potassium levels.

Hypomagnesemia can lead to refractoriness to potassium replacement because of inability of the kidneys to decrease potassium excretion.[28] Correction of the hypokalemia may not occur until the hypomagnesemia is corrected. Patients with unexplained hypokalemia or with diuretic-induced hypokalemia should have serum magnesium checked and, if indicated, magnesium replacement therapy instituted.

HYPERKALEMIA

Epidemiology

Hyperkalemia is distinctly unusual in healthy individuals with normal renal function not being treated with drugs that alter renal K^+ handling, with less than 1% of normal healthy adults developing hyperkalemia. This low frequency is a testament to the potent renal mechanisms for potassium excretion. Accordingly, the presence of chronic hyperkalemia, if not due to pseudohyperkalemia or redistribution, should strongly suggest impaired renal potassium excretion, whether from decreased nephron/collecting duct number, medications that decrease renal potassium excretion, or adrenal insufficiency.

Clinical Manifestations

Hyperkalemia can be asymptomatic, cause mild symptoms, or be life threatening. Importantly, the mortality risk of hyperkalemia is independent of the patient's clinical symptoms and reflects acute effects of hyperkalemia on cardiac conduction and repolarization. This is demonstrable on the electrocardiogram (Fig. 9.6). The initial effect of hyperkalemia is a generalized increase in the height of the T waves, most evident in the precordial leads, but typically present in all leads, which is known as "tenting." More severe hyperkalemia is associated with delayed electrical conduction, resulting in an increased PR interval and a widened QRS complex. This is followed by progressive flattening and eventual absence of the P waves. Under extreme conditions, the QRS complex widens sufficiently that it merges with the T wave, resulting in a sine-wave pattern. Finally, ventricular fibrillation develops. Although the ECG findings correlate generally with the degree of hyperkalemia, the rate of progression from mild to severe cardiac effects may be unpredictable and may not correlate well with changes in the serum potassium concentration. Chronic hyperkalemia is also associated with increased long-term mortality. This could reflect an increased predisposition to severe hyperkalemia with subsequent cardiac rhythm disturbances, other direct effects of chronic hyperkalemia, or a marker of more severe underlying disease that leads to the chronic hyperkalemia.

Hyperkalemia also has effects on noncardiac tissues. Skeletal muscle cells are particularly sensitive to hyperkalemia, causing generalized weakness. In patients with severe hyperkalemia, diaphragmatic muscle weakness may lead to respiratory failure.

Etiology

Hyperkalemia can result from pseudohyperkalemia, potassium redistribution from intracellular to extracellular space, or imbalances between

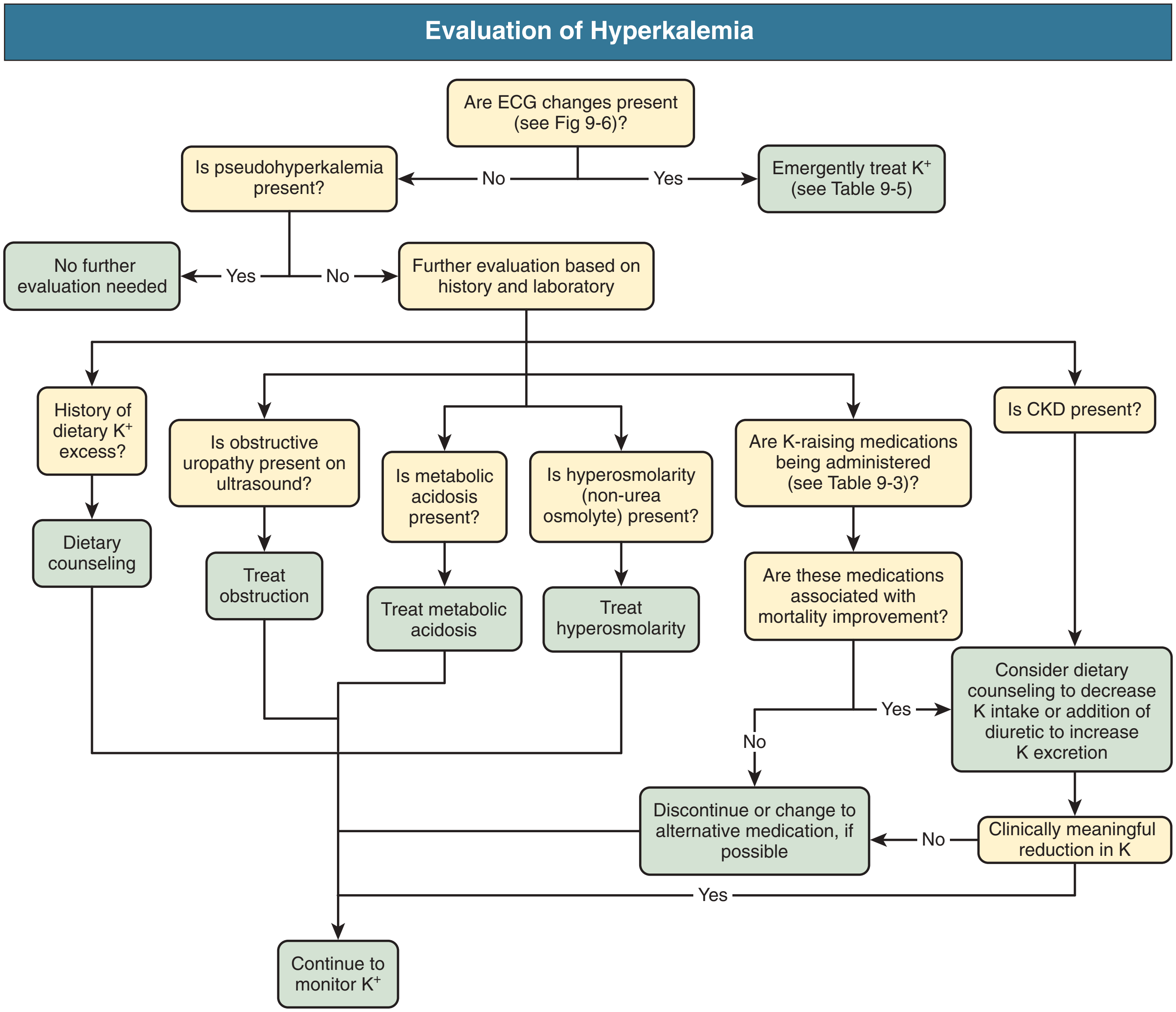

Evaluation of Hyperkalemia
Are ECG changes present (see Fig 9-6)?
No
Yes
Is pseudohyperkalemia present?
Emergently treat K+ (see Table 9-5)
No further evaluation needed
Yes
No
Further evaluation based on history and laboratory
History of dietary K+ excess?
Is obstructive uropathy present on ultrasound?
Is metabolic acidosis present?
Is hyperosmolarity (non-urea osmolyte) present?
Are K-raising medications being administered (see Table 9-3)?
Is CKD present?
Dietary counseling
Treat obstruction
Treat metabolic acidosis
Treat hyperosmolarity
Are these medications associated with mortality improvement?
Yes
No
Consider dietary counseling to decrease K intake or addition of diuretic to increase K excretion
Discontinue or change to alternative medication, if possible
No
Clinically meaningful reduction in K
Yes
Continue to monitor K+

Fig. 9.7 Workup of hyperkalemia. *CKD*, Chronic kidney disease.

potassium intake and renal potassium excretion. A diagnostic approach is shown in Fig. 9.7.

Pseudohyperkalemia

Pseudohyperkalemia refers to the condition in which potassium release from blood cells occurs after the phlebotomy procedure. This most commonly results from damaged erythrocytes and is identified clinically by the presence of free hemoglobin in the plasma, reported as "hemolysis" by most clinical laboratories. If hemolysis is present, the reported serum [K^+] measurement does not accurately reflect the actual serum [K^+]. Treatment should not be prescribed based on this value, and repeat measurement is necessary. Ischemia from prolonged tourniquet time or from exercise of the limb in the presence of a tourniquet also can lead to abnormally increased potassium values. Potassium can be released from the other cellular elements present in blood during clotting. This can occur in patients with severe leukocytosis (>70,000/cm^3) or thrombocytosis. About one third of patients with platelet counts of 500 to 1000 × 10^9/l exhibit pseudohyperkalemia.

Pseudohyperkalemia is diagnosed by showing that the serum [K^+] is more than 0.3 mmol/l higher than in a simultaneous plasma sample. If not caused by hemolysis, future potassium levels may need to be measured in plasma samples to allow accurate measurement of extracellular [K^+].

Redistribution

Redistribution of potassium from ICF to ECF may occur with severe hyperglycemia (from development of hyperosmolarity), during insulin deficiency, and with administration of drugs that alter cellular K^+ uptake, such as β_2-adrenoceptor blockers, ACE inhibitors, ARBs, and MR blockers. During diabetic ketoacidosis, both the hyperosmolarity that results from the hyperglycemia and the insulin deficiency contribute to transcellular K^+ shifts that are the primary cause of the often observed hyperkalemia. During treatment with insulin, resolution of both the hyperglycemia and resultant hyperosmolarity, and of the insulin deficiency, can lead to rapid stimulation of cellular potassium uptake, and a subsequent decrease in the serum potassium. In the patient with diabetic ketoacidosis who presents with a normal serum potassium, potassium redistribution from the insulin deficiency and hyperglycemia-induced hyperosmolarity may be masking substantial total body potassium deficiency resulting from hyperglycemia-induced polyuria. In this case, severe hypokalemia may develop during insulin treatment. Close and careful management of serum potassium may be needed. Patients who have received mannitol also may develop hyperosmolarity-induced hyperkalemia. Digoxin overdose can block cellular potassium uptake and lead to hyperkalemia that requires rapid treatment.

Excess Intake

Excessive potassium ingestion generally does not lead to chronic hyperkalemia unless other contributing factors are present. Under normal conditions, the kidney has the capacity to excrete several multiples of the mean daily potassium intake. However, if renal potassium excretion is impaired, as from drugs, acute kidney injury (AKI), or CKD, excessive potassium intake can contribute to the development of hyperkalemia.

Common sources of excess potassium intake are potassium supplements, salt substitutes, enteral nutrition products, and several common foods. As many as 4% of patients receiving potassium supplements develop hyperkalemia. Salt substitutes contain an average of 10 to 13 mmol K/g. Many enteral nutrition products contain at least 40 mmol/l KCl; administration of 100 ml/h of such products can result in a potassium intake of about 100 mmol/day. Also, many food products are particularly high in potassium (see Table 9.1). In some countries, pharmacies routinely label medication bottles containing diuretics with recommendations to increase intake of high-potassium dietary sources such as bananas.

Impaired Renal Potassium Excretion

Chronic hyperkalemia typically involves a component of impaired renal potassium excretion. As discussed previously, renal potassium excretion is determined primarily by potassium secretion in the collecting duct. Typically, the number of collecting duct segments parallels GFR, and therefore most patients have impaired capacity to excrete potassium when GFR is decreased. In CKD, adaptive increases in the ability of each collecting duct segment to secrete potassium may allow renal potassium excretion to remain moderately well preserved until the GFR is reduced to 10 to 20 ml/min. Multiple drugs affect renal potassium secretion (see Table 9.3); these drugs are sometimes used in combination, which further exacerbates the risk for hyperkalemia in this patient population.

Obstructive uropathy leads frequently to hyperkalemia, at least in part from decreased Na^+,K^+-ATPase expression and activity. In many patients, hyperkalemia may persist for months or even years after relief of the obstruction.[31] This impairment appears to be related to a persistent defect in collecting duct K^+ secretion and not to aldosterone deficiency.[31]

Mineralocorticoid hormones are necessary for the normal response to hyperkalemia. Lack of these hormones both causes potassium redistribution from ICF to ECF and reduces the maximal ability of the kidneys to secrete potassium. Primary adrenal insufficiency should be strongly considered in the patient with chronic hyperkalemia and other clinical factors suggestive of adrenal insufficiency, particularly spontaneous hypotension and hyponatremia.

The colon can excrete potassium, but adaptive changes in enteric potassium excretion are quantitatively small and generally are not sufficient to maintain normal potassium homeostasis.

A rare genetic disorder, pseudohypoaldosteronism type 2 (PHA2; also known as Gordon syndrome) is characterized by hypertension, hyperkalemia, non–anion gap metabolic acidosis, and normal GFR[32]; it is discussed in Chapter 47.

Determining the Role of Excessive Potassium Intake in Chronic Hyperkalemia

In most patients, a careful history and measurement of K^+ in a 24-hour urine collection will identify the role of excessive dietary potassium intake in the development of chronic hyperkalemia. In selected patients, specifically those not using diuretics and either unable to be compliant with or preferring not to perform a 24-hour urine collection, assessment of the urine potassium-to-creatinine ratio in a random urine specimen may be used, with potassium excretion greater than 60 mmol K^+/g creatinine suggesting that excessive dietary K^+ intake contributes to the persistent hyperkalemia. However, urinary K^+ measurements may be difficult to interpret, because K^+ excretion depends on multiple factors, including GFR, tubule lumen flow, time of day, and water reabsorption in the distal tubule and collecting duct. If there is a clinical concern about possible hypoaldosteronism as a primary cause of the hyperkalemia, such as in a patient with concomitant normal or low blood pressure and hyponatremia, the transtubular K^+ gradient (TTKG), when considered in context with assessment of K^+ intake, can be helpful (Table 9.4).

Treatment

Acute Therapy

Acute therapies for hyperkalemia are divided into those that minimize the cardiac effects of hyperkalemia, those that induce potassium uptake by cells resulting in a decrease in serum potassium, and those that remove potassium from the body (Table 9.5). Treatment of hyperkalemia should not include sodium bicarbonate ($NaHCO_3$) therapy unless the

TABLE 9.4 Transtubular Potassium Gradient

Transtubular potassium gradient (TTKG) is a measurement of net K^+ secretion by the collecting duct after correcting for changes in urinary osmolality and is often used to determine whether hyperkalemia is caused by aldosterone deficiency/resistance or whether the hyperkalemia is secondary to nonrenal causes. As with all diagnostic aids, clinical correlation is indicated, and potassium intake should be assessed.

$$TTKG = \frac{[K^+]_U / [K^+]_S}{Osmo_U / Osmo_S}$$

Where $[K^+]_U$ and $[K^+]_S$ are the concentration of K^+ in urine and serum, respectively, and $Osmo_U$ $Osmo_S$ are the osmolality of urine and serum, respectively.

TTKG Value	Indication
6-12	Normal.
>10	Suggests normal aldosterone action and extrarenal cause of hyperkalemia.
<5-7	Suggests aldosterone deficiency or resistance.

PHA, Pseudohypoaldosteronism.
If TTKG remains >10 after 0.05 mg of 9α-fludroxortisone, hypoaldosteronism is likely. Suggests a renal tubule defect from either K^+-sparing diuretics (amiloride, triamterene, spironolactone), aldosterone resistance (interstitial renal disease, sickle cell disease, urinary tract. obstruction, PHA1), or increased distal K^+ reabsorption (PHA2, urinary tract obstruction).

TABLE 9.5 Acute Treatment of Hyperkalemia

Mechanism	Therapy	Dose	Onset	Duration
Antagonize membrane effects	Calcium	Calcium gluconate, 10% solution, 10 ml IV over 10 min	1-3 min	30-60 min
Cellular potassium uptake	Insulin	Regular insulin, 10 U IV, with dextrose 50%, 50 ml, if plasma glucose <250 mg/dl	30 min	4-6 hr
	β_2-Adrenergic agonist	Nebulized albuterol, 10 mg	30 min	2-4 hr
Potassium removal	Sodium polystyrene sulfonate or calcium polystyrene sulfonate (calcium resonium)*	30-60 g PO in 20% sorbitol *or* 30-60 g in water, per retention enema	1-2 hr	4-6 hr
	Hemodialysis	—	Immediate	Until dialysis completed

*A newer K-binding resin, patiromer, should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

patient is frankly acidotic (pH <7.2) or unless there is substantial endogenous renal function. Administering hypertonic $NaHCO_3$ (e.g., 50 mmol in 50 ml of sterile water) can worsen intravascular volume overload, as frequently seen in the patient with oliguric AKI, can cause acute hypernatremia, and can acutely increase serum potassium in the anephric patient.[33]

Blocking cardiac effects. Intravenous calcium administration does not produce changes in extracellular potassium but rapidly antagonizes the effects of hyperkalemia on the myocardial conduction system and on myocardial repolarization. Calcium should be given intravenously as the initial therapy if unambiguous ECG changes of hyperkalemia are present. If the electrocardiogram is ambiguous, comparison to a previous electrocardiogram may be helpful. Patients with a prolonged PR interval, a widened QRS complex, or the absence of P waves should receive intravenous calcium in the form of either calcium chloride or calcium gluconate without delay. Responses can occur within 1 to 3 minutes, but typically last for only 20 to 60 minutes. Doses may be repeated as needed if ECG changes persist or they recur. If a delay in more definitive therapy, such as institution of dialysis, is anticipated, a continuous calcium infusion can be used.

Intravenous calcium is relatively safe if certain precautions are taken. Intravenous calcium should not be administered in $NaHCO_3$-containing solutions because calcium carbonate ($CaCO_3$) precipitation can occur. Hypercalcemia, which occurs during rapid calcium infusion, can potentiate the myocardial toxicity of digoxin. Patients taking digoxin, particularly if they have evidence of digoxin toxicity as a contributing cause of hyperkalemia, should be given calcium as a slow infusion over 20 to 30 minutes.

Cellular potassium uptake. The second most rapid way to treat hyperkalemia is to stimulate cellular potassium uptake using either insulin or β_2-adrenergic agonist administration. Insulin rapidly stimulates cellular potassium uptake and should be administered intravenously to ensure rapid and predictable bioavailability. The effect of insulin on serum [K^+] is seen generally within 10 to 20 minutes and can last for 4 to 6 hours. Glucose is generally coadministered to avoid hypoglycemia but may not be needed if hyperglycemia coexists. This is particularly important because extracellular glucose in patients with diabetes mellitus can function as an "ineffective osmole" and can increase serum potassium. Conversely, in patients with impaired renal function, there is delayed insulin clearance, and hypoglycemia can result from intravenous insulin administration, even if glucose is coadministered, because glucose uptake may occur more rapidly than insulin clearance. Accordingly, patients given intravenous insulin for treatment of hyperkalemia should be closely monitored for the development of hypoglycemia. If dialysis is indicated and a delay in its initiation is anticipated, administering a continuous infusion of insulin, 4 to 10 U/h (with 10% dextrose in water, D10W), may be beneficial; periodic monitoring of serum glucose and potassium is required.

β_2-Adrenoceptor agonists directly stimulate cellular potassium uptake and can be administered intravenously, subcutaneously, or by inhalation. However, β_2-agonist therapy frequently induces substantial tachycardia, and as many as 25% of patients do not respond to β_2-agonist therapy given by nebulizer.[34] A frequent mistake when administering nebulized β_2-adrenoceptor agonists is underdosage; the dose required is two to eight times that usually given for bronchodilation and is 50 to 100 times greater than the dose administered by metered dose inhalers.

Potassium removal. Most patients with persistent, severe hyperkalemia will benefit from K^+ removal from the ECF. Definitive treatment of these patients requires potassium elimination, through the kidneys, GI tract, or dialysis. Patients with chronic hyperkalemia may benefit from drugs that stimulate renal or stool K^+ excretion.

With chronic or mild hyperkalemia, loop or thiazide diuretics increase renal potassium excretion; this is particularly important for patients with hyperkalemic RTA (type 4 RTA), in whom the hyperkalemia is an important causative factor in the development of the metabolic acidosis.[35] With life-threatening hyperkalemia, diuretics are usually not effective because the rate of renal potassium excretion is usually inadequate and most patients will have renal impairment, which decreases the response to diuretic therapy. If a rapidly reversible cause of renal failure is identified (e.g., obstructive uropathy, or pre-renal azotemia and renal failure from volume depletion), treating the underlying condition may be sufficient therapy, along with close observation of serum potassium and continuous ECG monitoring.

A second mode of potassium elimination is with cation exchange resins such as sodium polystyrene sulfonate (Kayexalate) or calcium polystyrene sulfonate (calcium resonium). These resins exchange sodium or calcium, respectively, for potassium in the GI tract, enabling potassium elimination. They can be administered orally or as a retention enema. The rate of potassium removal is relatively slow, requiring about 4 hours for full effect, although administering the resin as a retention enema results in more rapid onset of action. When given orally, cation exchange resins are generally administered with 20% sorbitol to avoid constipation. If given as an enema, sorbitol should be avoided, because rectal administration of cation exchange resins with sorbitol may increase the risk for colonic perforation.[36] Questions have been raised recently as to the efficacy of these compounds and whether the risk for colonic perforation exceeds their benefits.[37] Two new enteric potassium-binding medications, patiromer and sodium zirconium silicate (ZS-9),[38,39] have been developed. All testing of these was against placebo and not against the previously mentioned established agents. Moreover, their effectiveness in acute hyperkalemia associated with cardiac effects is currently unknown, and we are hesitant to recommend their use for this indication at present.

Acute hemodialysis is the primary method of potassium removal in AKI or advanced CKD, when hyperkalemia is life-threatening. Serum potassium can decrease as much as 1.2 to 1.5 mmol/h with a low-potassium (2 mmol/l) dialysate. In general, the more severe the hyperkalemia, the more rapid should be the reduction in serum potassium until K^+ is less than 6.0 mEq/L. However, care should be taken to avoid reducing the serum potassium too rapidly in patients with coronary heart disease or severe cardiac arrhythmias. In these patients, longer dialysis with dialysate potassium of 3 mmol/l allows serum potassium to equilibrate to that level. Continuous dialysis modalities, such as peritoneal dialysis and continuous venovenous hemodialysis, generally do not remove potassium sufficiently quickly for use in patients with life-threatening hyperkalemia, but may be justified under unusual circumstances in which hemodialysis is not available.

If dialysis is delayed, as when access to equipment or nursing support is not immediate, or while vascular access is established, other therapies should be instituted and continued until hemodialysis is begun.

Specific therapies are available for certain causes of hyperkalemia. For example, digoxin-specific Fab fragments are beneficial in patients with severe digitalis glycoside toxicity.[40] Hyperkalemia in patients with acute urinary tract obstruction may be treated by relieving the obstruction, but the rate of potassium excretion afterward is variable and frequent measurement of serum potassium is necessary.

Chronic Treatment

Management of chronic hyperkalemia is a common and often challenging problem, particularly in the patient with CKD. Patients with CKD have impaired capacity to excrete a potassium load rapidly and are often treated with many drugs, including ACE inhibitors, ARBs, β-blockers, and MR antagonists—all of which can cause hyperkalemia.

The optimal serum potassium level for patients with CKD and the serum potassium level that requires management may differ from the laboratory's report of the normal range of serum potassium. As noted previously, patients with CKD tolerate hyperkalemia with fewer cardiac side effects than do most patients with normal renal function. Recent studies have suggested that serum potassium levels of up to 5.5 mmol/l may be associated with optimal reduction of cardiovascular risk and that levels between 5.5 and 6.0 mmol/l are associated with only a minimal increase in risk.[12]

Although the majority of patients with chronic hyperkalemia are receiving medicines associated with the development of hyperkalemia, discontinuing all drugs that can cause hyperkalemia may not be the correct approach. Many medicines, such as ACE inhibitors, ARBs, β-blockers, and MR blockers, have significant benefits. Discontinuing these drugs simply because of mild hyperkalemia is therefore not recommended in first-line management. However, if the patient is receiving combined therapy with an ACE inhibitor and ARB, discontinuing one of these drugs may decrease the risk for further hyperkalemia, and this does not appear to be associated with adverse renal effects. Similarly, if a patient is receiving combination therapy of either an ACE inhibitor or an ARB with a direct renin inhibitor, such as aliskiren, the direct renin inhibitor may be discontinued.

Instead of immediately discontinuing such beneficial drugs without review, a careful assessment should be made for medicines that cause hyperkalemia but are not necessary for renoprotective or cardioprotective benefits and therefore can be discontinued, such as NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, potassium-sparing diuretics (e.g., amiloride, triamterene), and oral KCl or potassium citrate supplementation. If hyperkalemia persists, addition of diuretics to increase renal potassium excretion can be considered. Thiazide diuretics may be preferred, because when adjusted for their effect on sodium excretion, thiazide diuretics are associated with a greater increase in renal potassium excretion than loop diuretics. In the patient with CKD, the thiazide diuretic metolazone may be effective.[41] Combination of thiazide and loop diuretics is more effective than either alone. Finally, screening for and treating metabolic acidosis may facilitate correction of the hyperkalemia. Alkali therapy also may increase K^+ clearance.

A dietary history should be obtained, and if the patient is ingesting a diet with potassium-rich foods, instruction on avoidance of these foods should be provided. However, routine instruction in a low-potassium diet for patients with CKD is not recommended. Recent studies have suggested that a diet higher in potassium-rich foods may be associated with slower progression of CKD.[42]

Finally, chronic therapy with drugs that increase enteric K^+ excretion can be considered. Intermittent administration of exchange resins, sodium polystyrene sulfonate (Kayexalate), or calcium polystyrene sulfonate (calcium resonium) may be helpful for selected patients with persistent hyperkalemia. This should be limited to intermittent use because of the risk for bowel infarction.

Two new drugs that increase enteric K^+ excretion have been developed: patiromer and sodium zirconium cyclosilicate (ZS-9).[38,39] Both appear to decrease serum K^+ within the first 24 hours of use, with few side-effects, with the exception of an increased risk for peripheral edema with high-dose ZS-9 and, if used long-term, can reduce the recurrence of hyperkalemia. Whether these drugs, if used on a chronic basis, will alter the long-term mortality associated with hyperkalemia is as yet undetermined. These drugs also may allow greater use of drugs that improve mortality in selected patient populations but whose use is otherwise limited because of development of hyperkalemia, for example, ACE inhibitors and ARB. Additional studies are required to examine long-term effects of these new drugs on mortality and other firm clinical end-points beyond changes in serum $[K^+]$.

Synthetic mineralocorticoid therapy, such as fludrocortisone, has been used for the treatment of chronic hyperkalemia. This approach may be helpful in patients with chronic hypotension secondary to adrenal insufficiency who have normal renal function. In patients with CKD, the accompanying renal sodium retention, intravascular volume expansion, and increased blood pressure are relative contraindications to synthetic mineralocorticoids. Furthermore, selective blockade of the MRs appears to decrease renal injury in several experimental models of renal injury, suggesting administration of synthetic mineralocorticoids may be injurious. As a result, their adverse effects may exceed their benefits in patients with CKD.

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SELF-ASSESSMENT QUESTIONS

1. Deficiency of which of the following ions can result in renal potassium wasting?
   - **A.** Phosphate
   - **B.** Calcium
   - **C.** Sulfate
   - **D.** Magnesium
2. Which of the following drugs is *not* associated with development of hyperkalemia?
   - **A.** Terazosin
   - **B.** Propranolol
   - **C.** Spironolactone
   - **D.** Cyclosporine
3. Hypokalemia is associated with which of the following conditions?
   - **A.** Decreased insulin sensitivity
   - **B.** Increased renal interstitial fibrosis
   - **C.** Increased risk for hepatic encephalopathy
   - **D.** Polyuria
   - **E.** All of the above

10

Disorders of Calcium, Phosphate, and Magnesium Metabolism

Bryan Kestenbaum, Pascal Houillier

CALCIUM HOMEOSTASIS AND DISORDERS OF CALCIUM METABOLISM

Distribution of Calcium in the Organism

Most (>99%) calcium is bound and associated with bony structures. Free calcium, either in diffusible (ultrafilterable) nonionized form or in ionized form (Ca^{2+}), is found in the intracellular fluid (ICF) and extracellular fluid (ECF) compartments. Similar to potassium, there is a steep concentration gradient between Ca^{2+} in the intracellular and extracellular compartments (Fig. 10.1).

The serum concentration of Ca^{2+} is tightly regulated within a narrow range by the actions of parathyroid hormone (PTH, parathormone) and calcitriol (1,25-dihydroxycholecalciferol). The physiologic role of other regulatory hormones, such as calcitonin, estrogens, and prolactin, in calcium homeostasis is less clear. Fig. 10.2 demonstrates the physiologic defense mechanisms used to counter changes in serum Ca^{2+} levels.[1] Circulating Ca^{2+} levels are also influenced by acid-base status, with acute alkalosis causing a decrease in serum Ca^{2+} and acute acidosis an increase in Ca^{2+}. Long-term maintenance of calcium homeostasis depends on (1) the adaptation of intestinal Ca^{2+} absorption to the needs of the organism, (2) the balance between bone accretion and resorption, and (3) urinary excretion of calcium (Fig. 10.3).

Intestinal, Skeletal, and Renal Handling of Calcium

Gastrointestinal (GI) calcium absorption is a selective process; only about 25% of total dietary calcium is absorbed under normal conditions. The proportion of calcium absorbed in the GI tract can fall precipitously in the setting of chronic kidney disease (CKD) due to decline in 1,25-dihydroxycholecalciferol synthesis. Ca^{2+} transport across the intestinal wall occurs in two directions: absorption and secretion. Absorption can be subdivided into transcellular and paracellular flow (Fig. 10.4). Transcellular calcium flux takes place through the apical transient receptor potential TRPV6 calcium channel.[2] Calcitriol is the most important hormonal regulatory factor for calcium absorption. After binding to and activating the vitamin D receptor (VDR), calcitriol increases active transport by inducing the expression of transient receptor potential channel vanilloid subtype 6 (TRPV6), calbindin-D_{9k}, and Ca^{2+}-ATPase (PMCA1b).[3] Other hormones, including estrogens, prolactin, growth hormone, and PTH, also stimulate Ca^{2+} absorption, either directly or indirectly. The amount of dietary calcium intake regulates the proportion of GI calcium absorption (Fig. 10.5).[5]

Cutaneous synthesis on exposure to ultraviolet (UV) light converts 7-dehydrocholesterol into cholecalciferol, which is also obtained through supplementation and diet; however, the cholecalciferol content of most foods is low. Cholecalciferol and ergocalciferol (which contains an additional methyl group) have minimal inherent biologic activity and require two hydroxylation steps for full hormonal activity. 25-Hydroxylation occurs in the liver and is thought to be non–rate limiting. Circulating 25-hydroxyvitamin D concentrations are widely accepted as a measure of vitamin D stores. Further hydroxylation to 1,25-dihydroxyvitamin D (calcitriol) occurs predominantly in the kidney, but can also occur in macrophages, parathyroid glands, and other tissues.

Increased calcium absorption is required in puberty and pregnancy, whereas in lactation, calcium is mostly obtained from maternal bone,[4] In puberty and pregnancy, calcitriol synthesis is increased to enhance GI calcium absorption. Intestinal Ca^{2+} absorption is also increased in states of vitamin D excess and acromegaly. Rarely, ingestion of calcium and alkali in large quantities can overwhelm GI checks on calcium absorption, resulting in hypercalcemia (milk-alkali syndrome). A decrease in intestinal Ca^{2+} transport occurs in advanced age, CKD, gastrectomy, intestinal malabsorption syndromes, diabetes mellitus, corticosteroid treatment, and estrogen deficiency and with dietary factors such as high vegetable fiber and fat content, low Ca^{2+}-to-phosphate ratio in food, and fructose ingestion. The decrease in Ca^{2+} absorption in older adults probably results from multiple factors in addition to lower serum calcitriol and intestinal VDR levels.[6]

The net balance between Ca^{2+} entry and exit is positive during skeletal growth in children, zero in young adults, and negative in the elderly. Exchangeable skeletal Ca^{2+} contributes to maintaining extracellular Ca^{2+} homeostasis. Several growth factors, hormones, and genetic factors participate in the differentiation from the mesenchymal precursor cell to the osteoblast and the maturation of the osteoclast from its granulocyte-macrophage precursor cell (Fig. 10.6). The regulation of bone formation and resorption involves many hormones, growth factors, and mechanical factors[7,8] (Fig. 10.7).

The kidneys play a major role in the minute-by-minute regulation of calcium, and the intestine, kidney, and skeleton ensure homeostasis in the mid and long term (Fig. 10.8).[9] Moreover, the kidney controls conversion of substrate 25-hydroxyvitamin D to calcitriol, which then regulates GI calcium absorption through the TRPV6 channel. Renal calcitriol production is stimulated by PTH and inhibited by fibroblast growth factor 23 (FGF-23) and perhaps hyperphosphatemia. The adjustment of blood Ca^{2+} is mainly achieved by modulation of tubular Ca^{2+} reabsorption, perfectly compensating minor increases or decreases in the filtered load of calcium, which is normally approximately 220 mmol (8800 mg) in 24 hours (see Fig. 10.3). In the proximal tubule, Ca^{2+} reabsorption follows the convective flow of salt and water, whereas the transport mechanisms are more complex in the distal segments.

States of excess volume delivery to the kidney, such as a high-sodium diet, diminish the concentration gradient between proximal tubule and

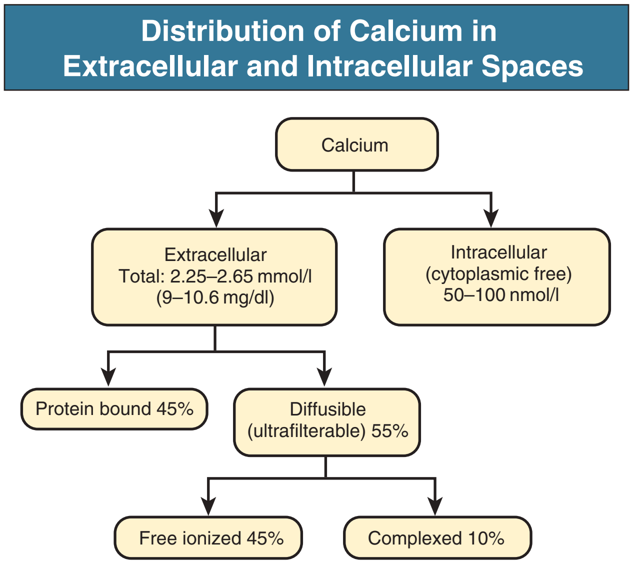
Distribution of Calcium in Extracellular and Intracellular Spaces
Calcium
Extracellular Total: 2.25–2.65 mmol/l (9–10.6 mg/dl)
Intracellular (cytoplasmic free) 50–100 nmol/l
Protein bound 45%
Diffusible (ultrafilterable) 55%
Free ionized 45%
Complexed 10%

Fig.10.1 Calcium distribution in extracellular and intracellular spaces.

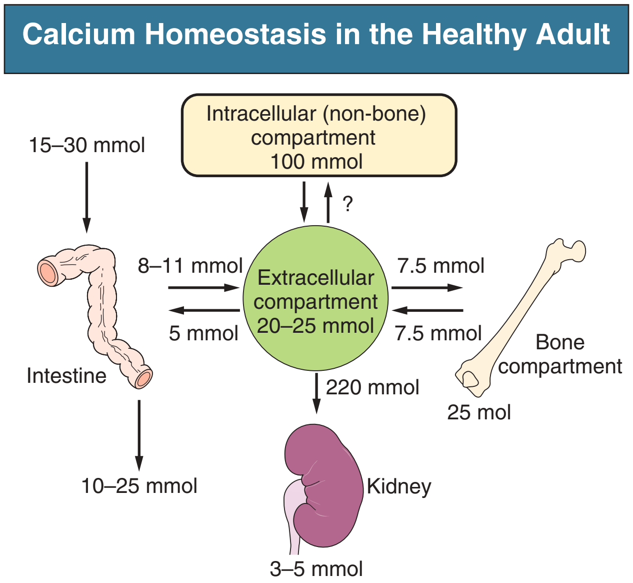
Calcium Homeostasis in the Healthy Adult
Intracellular (non-bone) compartment 100 mmol
?
15–30 mmol
8–11 mmol
5 mmol
Intestine
10–25 mmol
Extracellular compartment 20–25 mmol
7.5 mmol
7.5 mmol
Bone compartment
25 mol
220 mmol
Kidney
3–5 mmol

Fig.10.3 Calcium homeostasis in healthy adults. Net zero Ca^{2+} balance is the result of net intestinal absorption (absorption minus secretion) and urinary excretion, which by definition are the same. After its passage into the extracellular fluid, Ca^{2+} enters the extracellular space, is deposited in bone, or is eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also of identical magnitude under steady-state conditions.

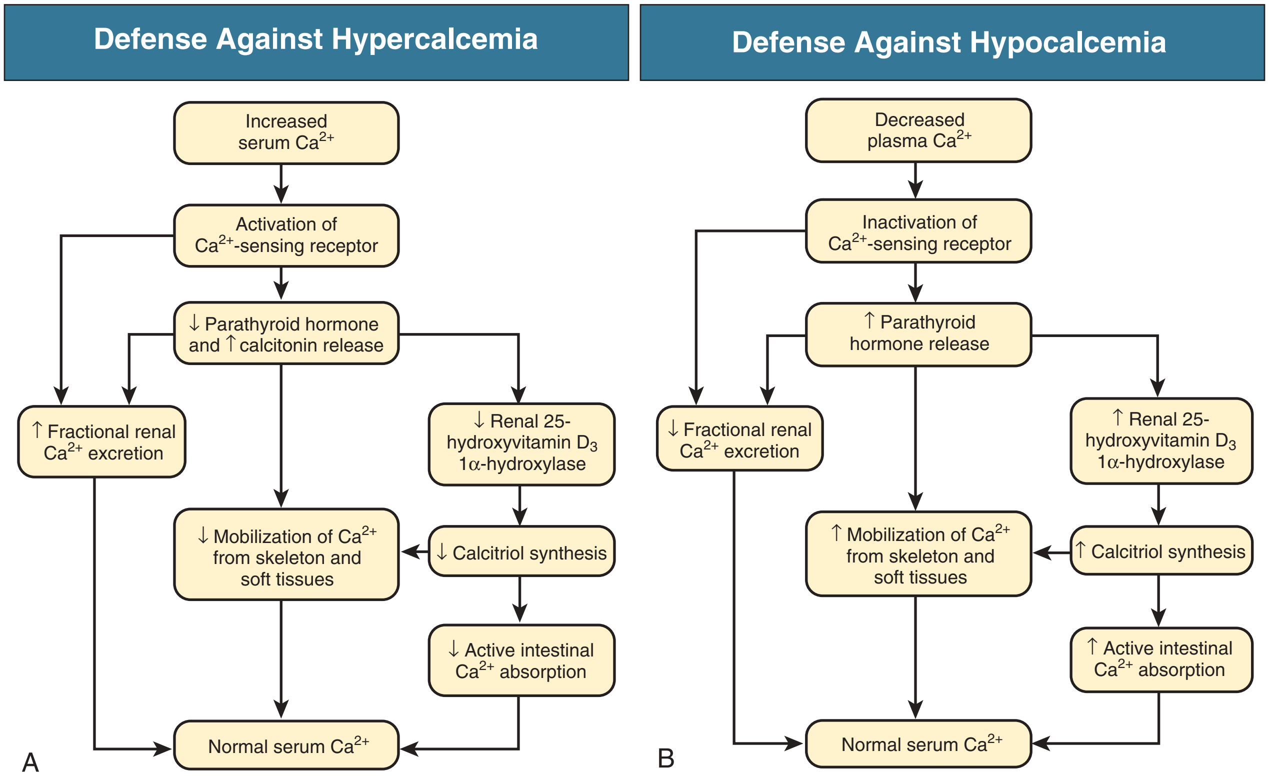
Defense Against Hypercalcemia
Increased serum Ca^{2+}
Activation of Ca^{2+}-sensing receptor
↓ Parathyroid hormone and ↑ calcitonin release
↑ Fractional renal Ca^{2+} excretion
↓ Renal 25-hydroxyvitamin D$_3$ 1α-hydroxylase
↓ Mobilization of Ca^{2+} from skeleton and soft tissues
↓ Calcitriol synthesis
↓ Active intestinal Ca^{2+} absorption
Normal serum Ca^{2+}
A
Defense Against Hypocalcemia
Decreased plasma Ca^{2+}
Inactivation of Ca^{2+}-sensing receptor
↑ Parathyroid hormone release
↓ Fractional renal Ca^{2+} excretion
↑ Renal 25-hydroxyvitamin D$_3$ 1α-hydroxylase
↑ Mobilization of Ca^{2+} from skeleton and soft tissues
↑ Calcitriol synthesis
↑ Active intestinal Ca^{2+} absorption
Normal serum Ca^{2+}
B

Fig.10.2 Calcium regulation. Physiologic defense mechanisms against increases or decreases in serum calcium levels. (A) Hypercalcemia; (B) hypocalcemia. (Modified from reference 1.)

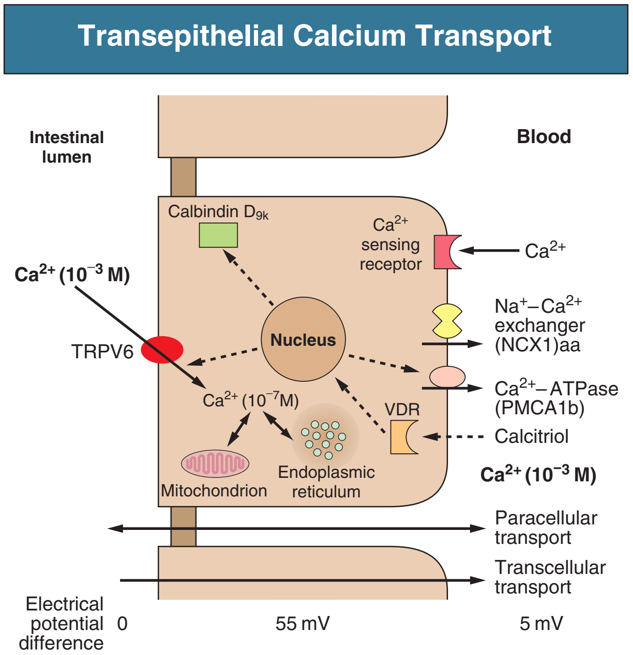
Transepithelial Calcium Transport
Intestinal lumen
Blood
Calbindin D_{9k}
Ca^{2+} sensing receptor
Ca^{2+}
Ca^{2+} (10^{-3} M)
Na^+–Ca^{2+} exchanger (NCX1)aa
Nucleus
TRPV6
Ca^{2+}–ATPase (PMCA1b)
Ca^{2+} (10^{-7}M)
VDR
Calcitriol
Mitochondrion
Endoplasmic reticulum
Ca^{2+} (10^{-3} M)
Paracellular transport
Transcellular transport
Electrical potential difference
0
55 mV
5 mV

Fig.10.4 Transepithelial calcium transport in small intestine. Calcium penetrates into the enterocyte channels via a transient receptor potential calcium channel *(TRPV6)* through the brush border membrane along a favorable electrochemical gradient. Under physiologic conditions, the cation is pumped out of the cell at the basolateral side against a steep electrochemical gradient by the adenosine triphosphate–consuming pump Ca^{2+}-ATPase. When there is a major elevation of intracytoplasmic Ca^{2+}, the cation leaves the cell using the Na^+-Ca^{2+} exchanger. Passive Ca^{2+} influx as well as efflux is sensitive to calcitriol, which binds the vitamin D receptor *(VDR)*.

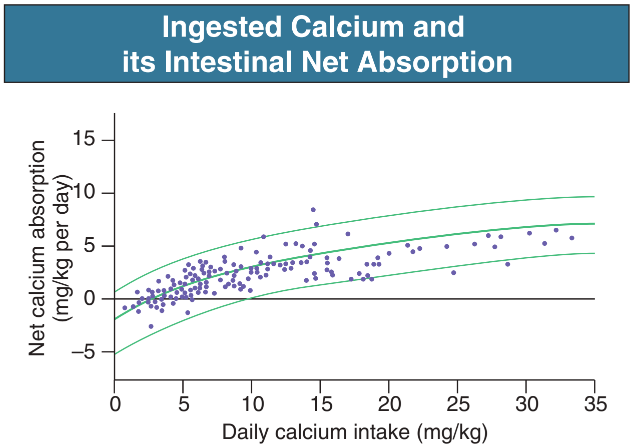

Fig.10.5 Calcium ingestion and absorption. Relationship between ingested calcium and its absorption in the intestinal tract (net) in healthy young adults. (From reference 5.)

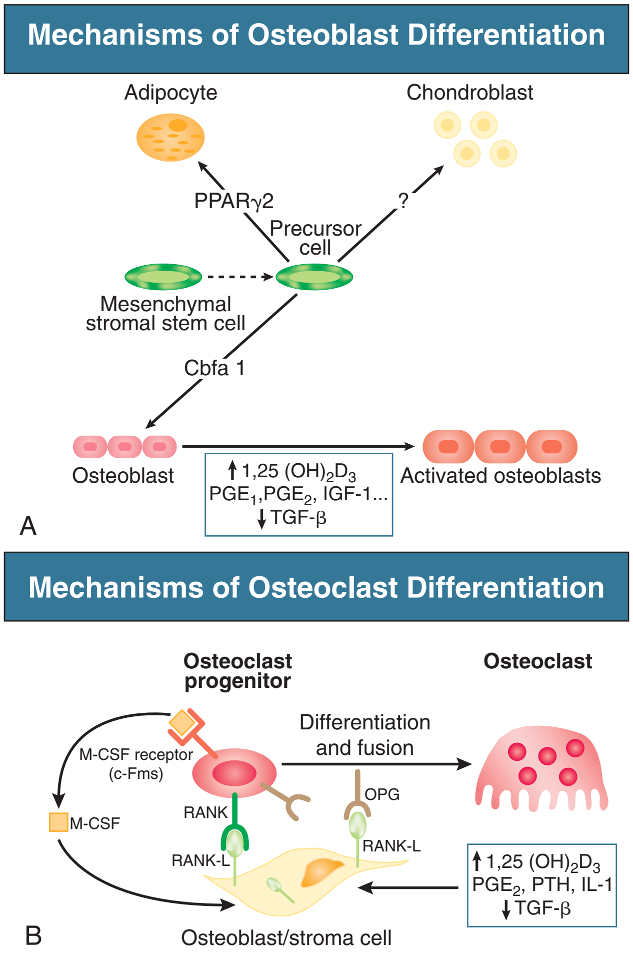
Mechanisms of Osteoblast Differentiation
Adipocyte
Chondroblast
PPARγ2
?
Precursor cell
Mesenchymal stromal stem cell
Cbfa 1
Osteoblast
↑1,25 $(OH)_2D_3$
PGE_1,PGE_2, IGF-1...
↓TGF-β
Activated osteoblasts
A
Mechanisms of Osteoclast Differentiation
Osteoclast progenitor
Osteoclast
Differentiation and fusion
M-CSF receptor (c-Fms)
M-CSF
RANK
OPG
RANK-L
RANK-L
↑1,25 $(OH)_2D_3$
PGE_2, PTH, IL-1
↓TGF-β
B
Osteoblast/stroma cell

Fig.10.6 Mechanisms of osteoblast differentiation. (A) Major growth factors and hormones controlling the differentiation from the mesenchymal precursor cell to the osteoblast. (B) The major growth factors, cytokines, and hormones controlling osteoblast and osteoclast activity. *IGF,* Insulin-like growth factor; *IL,* interleukin; *M-CSF,* macrophage colony-stimulating factor; *OPG,* osteoprotegerin; *PGE_2,* prostaglandin E_2; *PPAR,* peroxisome proliferator–activated receptor; *PTH,* parathyroid hormone; *RANKL,* receptor activator of nuclear factor-κβ ligand; *TGF,* transforming growth factor.

peritubular capillary, reducing calcium absorption and increasing calcium in the urine. This mechanism likely plays a role in the pathogenesis of calcium-based kidney stones. On the other hand, volume depletion increases salt, water, and (by convection) calcium reabsorption in the proximal tubule, exacerbating states of hypercalcemia. For this reason, intravascular volume repletion is an essential component of the treatment for hypercalcemia. In the thick ascending limb (TAL) of the Henle loop, Ca^{2+} transport is linked with activity of the Na^+-K^+-$2Cl^-$ transporter. Stimulation of the Ca^{2+}-sensing receptor (CaSR) on the basolateral membrane decreases the permeability of the paracellular pathway to Ca^{2+}.[9] The result is decreased calcium reabsorption through Claudin-16 and -19 in the tight junction. In contrast, understimulation of CaSR because of lower serum calcium levels results in greater calcium reabsorption. In the distal tubule, active Ca^{2+} transport occurs via the transcellular route through the calcium transient receptor potential channel V5 (TRPV5) located in the apical membrane and coupled with a specific basolateral calcium-ATPase (PMCa1b) and a Na^+-Ca^{2+} exchanger (NCX1). Both PTH and calcitriol regulate distal tubular Ca^{2+} transport. The expression and role of CaSR in tubular segments other than TAL has recently been questioned.[10]

Numerous factors influence glomerular filtration and tubular Ca^{2+} reabsorption.[2,9,11,12] Elevated renal blood flow and glomerular filtration pressure (during ECF volume expansion) lead to an increase in the filtered calcium load, as do changes in the ultrafiltration coefficient K_f and an increase in glomerular surface. True (nonfactitious) hypercalcemia (see later discussion) also increases ultrafilterable calcium, whereas true hypocalcemia decreases it. PTH decreases glomerular K_f and thus reduces the ultrafiltered calcium load; PTH increases Ca^{2+} reabsorption

Determinants of Skeletal Homeostasis and Bone Mass

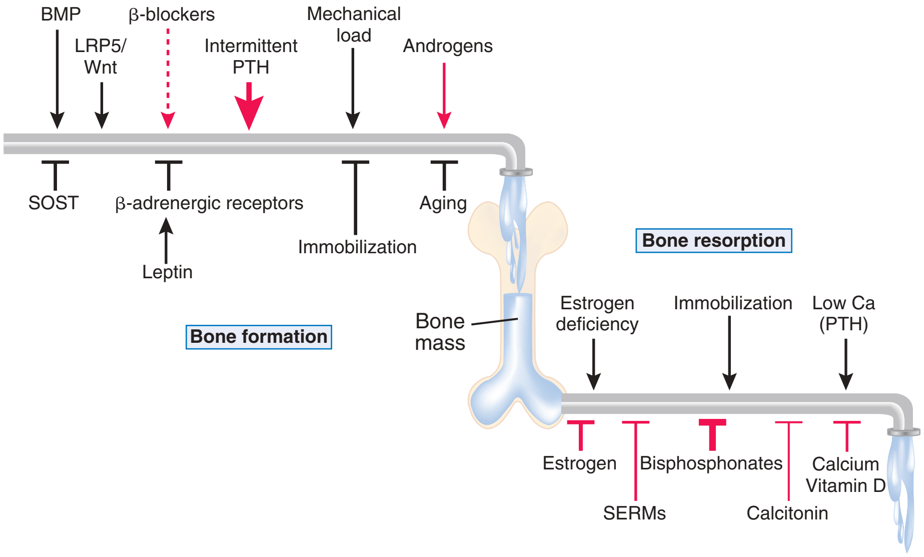
BMP
β-blockers
Mechanical load
LRP5/ Wnt
Intermittent PTH
Androgens
SOST
β-adrenergic receptors
Aging
Leptin
Immobilization
Bone formation
Bone mass
Bone resorption
Estrogen deficiency
Immobilization
Low Ca (PTH)
Estrogen
Bisphosphonates
Calcium Vitamin D
SERMs
Calcitonin

Fig.10.7 Determinants of skeletal homeostasis and bone mass. Physiologic *(black)* and pharmacologic *(red)* stimulators and inhibitors of bone formation and resorption are listed with the relative impact (represented by thickness of *arrows*). *BMP,* Bone morphogenetic protein; *LRP5,* low-density lipoprotein receptor–related protein 5; *PTH,* parathyroid protein; *SERMs,* selective estrogen receptor modulators; *SOST,* sclerostin. (From reference 7.)

Calcium Reabsorption in the Kidney

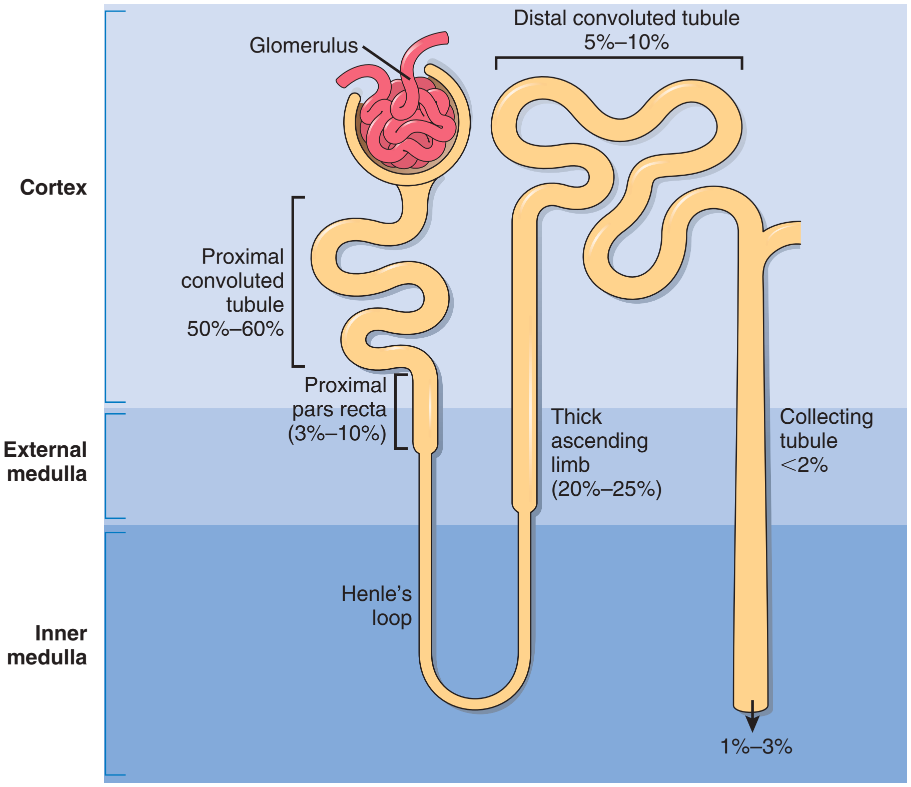
Glomerulus
Distal convoluted tubule 5%–10%
Cortex
Proximal convoluted tubule 50%–60%
Proximal pars recta (3%–10%)
External medulla
Thick ascending limb (20%–25%)
Collecting tubule <2%
Inner medulla
Henle's loop
1%–3%

Fig.10.8 Sites of calcium reabsorption. Percentage of Ca^{2+} absorbed in various segments of the renal tubule after glomerular ultrafiltration. (Redrawn from reference 9.)

in the distal nephron. However, PTH and PTH-related peptide (PTHrp) also induce hypercalcemia via bone demineralization, and, because of the increase in serum calcium, the excretion of filtered calcium is elevated overall. An excess of both extracellular Ca^{2+} and intracellular Ca^{2+} reduce tubular calcium reabsorption by activating CaSR, and the effect of extracellular Ca^{2+} is enhanced by treatment with calcimimetics (see later discussion). Both respiratory and metabolic acidosis lead to hypercalciuria through an inhibitory effect on tubular Ca^{2+} reabsorption. Conversely, alkali ingestion reduces renal excretion of calcium. The enhancing effect of phosphate depletion on urinary calcium elimination can partly occur through changes in PTH and calcitriol secretion. Dietary factors modify urinary excretion of calcium mostly by their effects on intestinal Ca^{2+} absorption. Several classes of diuretics act directly on the tubules. Loop diuretics increase urinary calcium excretion via inhibition of the Na^+-K^+-$2Cl^-$ channel in the TAL, whereas thiazide diuretics and amiloride increase tubular calcium absorption.

HYPERCALCEMIA

Increased total serum calcium concentration (S_{Ca}) can result from increase in serum proteins (false hypercalcemia) or serum ionized Ca^{2+} (true hypercalcemia). Only increased Ca^{2+} leads to clinically relevant hypercalcemia. Usually only the value for the total S_{Ca} is available rather than the free ion level. Serum $[Ca^{2+}]$ can then be estimated by taking into account serum albumin; an increase in albumin of 1.0 g/dl reflects a concomitant increase of 0.20 to 0.25 mmol/l (0.8 to 1.0 1.0 mg/dl) S_{Ca}. However, simple correction of S_{Ca} for serum albumin may not be valid in patients with CKD stages 3 to 5.[13] Moreover, the two most common assays used to measure serum albumin yield discordant results in patients with CKD stages 3 to 5, the bromocresol purple method providing lower albumin values than the bromocresol green method.

CaSR has been identified in numerous tissues.[14] Mutations of the gene for CaSR result in various clinical syndromes characterized by hypercalcemia or hypocalcemia (see later discussion). Other Ca^{2+} receptors subsequently cloned include GPRC6A, which is expressed in osteoblasts and is clearly distinct from CaSR.[15] The role of GPRC6A in regulation of osteoblast function and in human disease is still unknown.

Causes of Hypercalcemia

True hypercalcemia results from an increase in intestinal Ca^{2+} absorption, a stimulation of bone resorption, an increase in renal reabsorption of Ca^{2+}, or a combination of these processes. Enhanced bone resorption is the predominant mechanism in most cases of hypercalcemia, and secondary volume depletion commonly prolongs the condition by interfering with urinary calcium excretion (Fig. 10.9).

Malignant Neoplasias

The main cause of hypercalcemia is excessive bone resorption induced by neoplastic processes, usually solid tumors. Tumors of the neck, breast, lung, and kidney are the most common, followed by hematopoietic neoplasias, particularly myeloma. Most hypercalcemic tumors act on the skeleton by direct invasion (metastases) or by producing factors that stimulate osteoclastic activity, including most frequently PTHrp, as well as other factors activating osteoclasts, transforming growth factors (TGFs), prostaglandin E (PGE), and, rarely, calcitriol, and tumor necrosis factor-α (TNF-α) and even more rarely PTH, as produced by parathyroid cancer. Most PTHrp found in the body is synthesized by solid tumors.

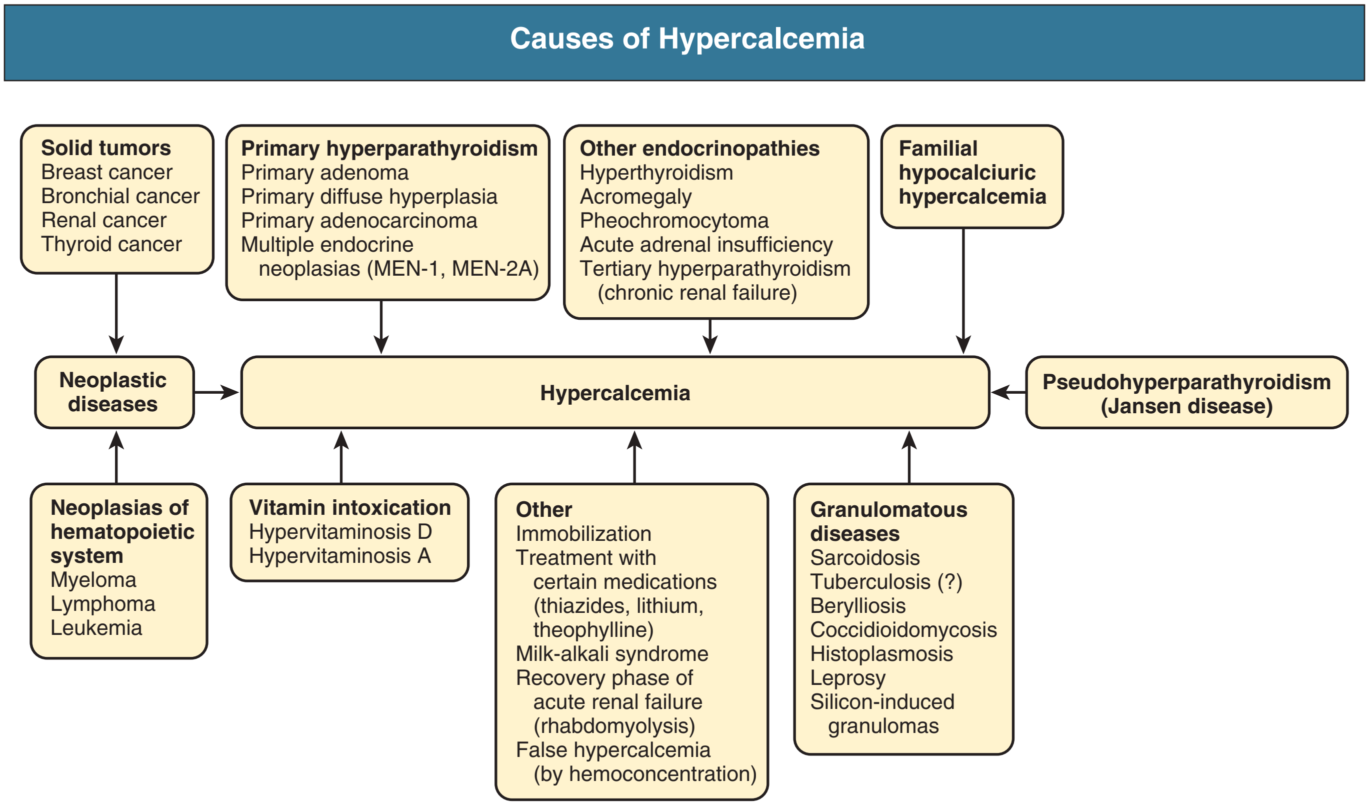
Causes of Hypercalcemia
Solid tumors
Breast cancer
Bronchial cancer
Renal cancer
Thyroid cancer
Primary hyperparathyroidism
Primary adenoma
Primary diffuse hyperplasia
Primary adenocarcinoma
Multiple endocrine neoplasias (MEN-1, MEN-2A)
Other endocrinopathies
Hyperthyroidism
Acromegaly
Pheochromocytoma
Acute adrenal insufficiency
Tertiary hyperparathyroidism (chronic renal failure)
Familial hypocalciuric hypercalcemia
Neoplastic diseases
Hypercalcemia
Pseudohyperparathyroidism (Jansen disease)
Neoplasias of hematopoietic system
Myeloma
Lymphoma
Leukemia
Vitamin intoxication
Hypervitaminosis D
Hypervitaminosis A
Other
Immobilization
Treatment with certain medications (thiazides, lithium, theophylline)
Milk-alkali syndrome
Recovery phase of acute renal failure (rhabdomyolysis)
False hypercalcemia (by hemoconcentration)
Granulomatous diseases
Sarcoidosis
Tuberculosis (?)
Berylliosis
Coccidioidomycosis
Histoplasmosis
Leprosy
Silicon-induced granulomas

Fig.10.9 Causes of hypercalcemia. Neoplastic diseases and primary hyperparathyroidism are the most common causes of hypercalcemia. (From reference 8.)

Only 8 of the 13 first amino acids of PTHrp are identical with those of the N-terminal fragment of PTH, but the effects of both hormones on target cells are mostly the same because they share a common receptor, the PTH/PTHrp receptor, PTH1R.

Osteoclast-activating factors secreted by myeloma plasmocytes and the lymphoblasts of malignant lymphomas include interleukins (IL-1α, IL-1β, IL-6) and TNF-α. Other osteoclast-activating factors include PGE_1 and PGE_2, which can be secreted in large amounts by some tumors, especially renal masses. Some lymphoid tumors synthesize excess quantities of calcitriol, including Hodgkin disease, T-cell lymphoma, and leiomyoblastoma.

Primary Hyperparathyroidism

The second most common cause of hypercalcemia is primary hyperparathyroidism. In more than 80% of patients, the disease is caused by adenoma of a single parathyroid gland; 10% to 15% have diffuse hyperplasia of all glands, and less than 5% have a parathyroid cancer. Primary hyperparathyroidism is most often idiopathic, but can be inherited either as diffuse hyperplasia of the parathyroid glands alone or as a component in multiple glandular hereditary endocrine disorders. Patients with multiple endocrine neoplasia type 1 (MEN-1) have various combinations of parathyroid, anterior pituitary, enteropancreatic, and other endocrine tumors, resulting in hypersecretion of prolactin and gastrin in addition to parathormone. MEN-1 is caused by inactivating germline mutations of a tumor suppressor gene *(MEN-1)* that is inherited as an autosomal dominant trait. In MEN-2A, the thyroid medulla and the adrenal medulla are involved with the parathyroid, resulting in hypersecretion of calcitonin and catecholamines. MEN-2A is caused by activating mutations of the *RET* proto-oncogene. It is also inherited as an autosomal dominant trait. Not all patients with mildly elevated plasma PTH levels develop hypercalcemia, which may require concomitant elevation of plasma calcitriol.

Jansen Disease

Jansen disease is a rare hereditary form of short-limbed dwarfism characterized by severe hypercalcemia, hypophosphatemia, and metaphyseal chondrodysplasia. It is the result of activating mutations of the gene coding for the PTH1R receptor, a particular form of pseudohyperparathyroidism.

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is a rare hereditary disease, most often caused by inactivating mutations in the gene for CaSR with autosomal dominant transmission.[16] The key clinical finding in FHH is an inappropriately low urinary calcium excretion in the setting of high-normal S_{Ca}. Plasma PTH concentration is normal or moderately elevated, and the fractional excretion of calcium (FE_{Ca}) is commonly lower than that observed in primary hyperparathyroidism. FE_{Ca} is best assessed by calculating the calcium-to-creatinine clearance ratio from a 24-hour urine collection, as follows:

$$\text{Calcium-creatinine clearance ratio} = \frac{(\text{24-hour urine calcium}) \times (\text{serum creatinine})}{(\text{24-hour urine calcium}) \times (\text{serum creatinine})}$$

In FHH, FE_{Ca} is usually less than 0.01. The ratio of urine Ca to creatinine concentration is most often less than 0.07 mg/mg (0.2 mmol/mmol), but the values significantly overlap with those in patients with primary hyperparathyroidism.[17] In patients with FHH, hypercalcemia never leads to severe clinical signs, except in the neonatal period, when life-threatening hypercalcemia can be observed in the child with severe hyperparathyroidism.

Other Endocrine Causes

Other endocrine disorders associated with moderate hypercalcemia include hyperthyroidism, acromegaly, and pheochromocytoma. In addition, acute adrenal insufficiency should be considered in the differential diagnosis, although in these patients, hypercalcemia is usually false and results from hemoconcentration. Hypercalcemia also can occur in severe forms of the secondary hyperparathyroidism of CKD, which have been called tertiary hyperparathyroidism. However, this has become relatively uncommon because low circulating calcitriol concentrations in patients with CKD limit GI calcium absorption and overfunctioning parathyroid glands can be controlled more easily. Nonetheless, hypercalcemia in the setting of chronic dialysis does occur and is typically caused by overtreatment of secondary hyperparathyroidism by large dosages of calcium-based phosphate binders plus activated vitamin analogs.

Other Causes

Several other disorders sometimes induce hypercalcemia. Among the granulomatoses, sarcoidosis results in increased serum Ca^{2+}, particularly in patients exposed to sunlight. The cause is uncontrolled production of calcitriol by macrophages, a result of 1α-hydroxylase in the macrophages within the granulomas. Tuberculosis, leprosy, berylliosis, and many other granulomatous diseases are rare causes of hypercalcemia, probably through the same mechanism.

Hypercalcemia also may result from prolonged bed rest, especially in patients with preexisting high bone turnover rates, such as children, adolescents, and patients with Paget disease. Recovery from acute kidney injury (AKI) secondary to rhabdomyolysis has been associated with hypercalcemia in 25% of cases and likely results from mobilization of soft tissue calcium deposits and through increases in PTH and calcitriol. Other causes include intoxication by vitamin D or its derivatives, vitamin A overload, and thiazide diuretics. Large doses of calcium (5 to 10 g/day), especially when ingested with alkali (antacids), also can lead to hypercalcemia and nephrocalcinosis (milk-alkali syndrome).

Clinical Manifestations

The severity of clinical symptoms and signs caused by hypercalcemia depends on not only the degree but also the rapidity of its development. Severe hypercalcemia that progresses slowly can be accompanied by few manifestations in some patients, whereas much less severe hypercalcemia can lead to major disorders if it develops rapidly.

In general, the first symptoms are increasing fatigue, muscle weakness, inability to concentrate, nervousness, increased sleepiness, and depression. Subsequently, GI signs may occur, such as constipation, nausea and vomiting, and, rarely, peptic ulcer disease or pancreatitis. Renal-related signs include polyuria (secondary to nephrogenic diabetes insipidus), renal salt wasting, urinary tract stones and their complications, and, occasionally, tubulointerstitial disease with medullary and to a lesser extent cortical nephrocalcinosis. Patients with chronic hypercalcemia often present with a modest elevation in serum creatinine concentrations, indicating reduced GFR. Neuropsychiatric manifestations include headache, loss of memory, somnolence, stupor, and, rarely, coma. Ocular symptoms include conjunctivitis from crystal deposition and rarely band keratopathy. Osteoarticular pain in primary hyperparathyroidism has become rare in Western countries because of earlier diagnosis of hypercalcemia. High blood pressure can be induced by hypercalcemia, but it is more frequently a chance association. Soft tissue calcifications can occur with long-standing hypercalcemia. The electrocardiogram (ECG) may show shortening of the QT interval and coving of the ST wave. Hypercalcemia may increase cardiac contractility and can amplify digitalis toxicity.

Diagnosis

When the history, clinical examination, and review of medications are unhelpful, primary hyperparathyroidism should be investigated first. Although this is only the second most frequent cause, its laboratory diagnosis is easier than that of tumoral involvement. The initial step should be to measure plasma PTH and total or ionized [Ca^{2+}], as available. When the PTH value is high-normal or high in the presence of high-normal or high [Ca^{2+}], the diagnosis of primary hyperparathyroidism is likely (although FHH is not excluded). Other helpful laboratory tests may include phosphate, creatinine, total alkaline phosphatase, and urinary calcium and creatinine. Neck ultrasound and/or sestamibi isotope scanning and/or computed tomography may be performed to locate a parathyroid adenoma, although some surgeons still consider these examinations unnecessary before an initial neck exploration. However, imaging is indispensable in patients with recurrent hyperparathyroidism and having unilateral neck surgery under local anesthesia. If the plasma PTH level is low-normal or low, the possibility of a neoplastic disorder should be seriously considered. In addition to the usual examinations, such as serum protein electrophoresis, measurement of the plasma PTHrp level can be done in specialized laboratories. Exogenous vitamin D overload is associated with increased serum 25-hydroxyvitamin D levels, and granulomatous diseases such as sarcoidosis are associated with elevated calcitriol levels and increased serum angiotensin-converting enzyme (ACE) activity.

Treatment

Treatment of hypercalcemia is aimed at the underlying cause, although severe (>3.25 mmol/L) and symptomatic hypercalcemia always requires rapid correction. Initially, the patient must be volume expanded with isotonic saline to correct the commonly marked volume depletion, to reduce proximal tubule calcium reabsorption and enhance calcium excretion. Only when euvolemia is established could loop diuretics be used when necessary (e.g., intravenous furosemide 100 to 200 mg every other hour) to facilitate urinary excretion of calcium; however, intravenous saline should be continued to prevent hypovolemia. Oral intake and intravenous administration of fluids and electrolytes should be carefully monitored, and urinary excretions measured if excessive, especially potassium, magnesium, and phosphate. Acid-base balance also should be carefully monitored. Severe cardiac failure and CKD are contraindications to massive ECF volume expansion along with diuretics.

Bisphosphonates are the treatment of first choice, especially in patients with hypercalcemia associated with cancer.[18] These agents inhibit bone resorption as well as calcitriol synthesis. Bisphosphonates can be administered orally in less severe disease or intravenously in severe hypercalcemia. Common bisphosphonates include pamidronate 15 to 90 mg IV over 1 to 3 days, once a month and zoledronate 4 mg IV once; intravenous doses should be infused in 500 ml of isotonic saline or dextrose over at least 2 hours (pamidronate) or 15 minutes (zoledronate). Although package warnings state that bisphosphonates should be used with caution in patients with CKD, this warning pertains to the theoretical possibility of inducing hypocalcemia and does not apply to the treatment of elevated serum calcium levels. Bisphosphonates have been safely used in patients with CKD for the correction of hypercalcemia. A reasonable strategy is first to attempt correcting AKI by volume repletion before administering a bisphosphonate, and to avoid repetitive dosing; a single 60-mg dose of pamidronate can maintain normal [Ca^{2+}] for weeks. Calcitonin acts within hours, especially after intravenous administration. Human, porcine, or salmon calcitonin can be given. However, calcitonin often has no effect, or only a short-term effect, because of the rapid development of tachyphylaxis.

Mithramycin is a cytostatic drug with remarkable power to inhibit bone resorption, which is almost no longer used because of the high toxicity. Denosumab, a monoclonal antibody to the receptor activator of nuclear factor κ-B ligand (RANKL), is a potent inhibitor of bone resorption that can be useful in bisphosphonate-refractory hypercalcemia. Denosumab is not removed by the kidney. The typical dose is 120 mg subcutaneously and can be repeated no earlier than 1 week after the first administration.[19]

Corticosteroids such as prednisone (or prednisolone), 0.5 to 1.0 mg/kg daily, are mainly indicated in hypervitaminosis D of endogenous origin, as in patients with sarcoidosis or tuberculosis, to decrease macrophage synthesis of calcitriol. Corticosteroids also can be used in patients with hypercalcemia associated with some hematopoietic tumors (e.g., myeloma, lymphoma) and even for some solid tumors such as breast cancer. Ketoconazole, an antifungal agent that can inhibit renal and extrarenal calcitriol synthesis, can also be used to treat hypervitaminosis D.

In rare cases of malignant hypercalcemia, treatment with prostaglandin antagonists such as indomethacin or aspirin can be successful. Hyperkalemia and impaired renal function may occur with indomethacin. Hypercalcemia caused by thyrotoxicosis can rapidly resolve with intravenous administration of propranolol or less rapidly with oral administration.

In moderate and nonsymptomatic hypercalcemia secondary to primary hyperparathyroidism, treatment with estrogens has been tried, at least in female patients. In patients with primary hyperparathyroidism, the CaSR agonist cinacalcet (a *calcimimetic*), can reduce serum PTH concentrations and achieve normalization of serum Ca^{2+} in most cases, together with a reduction in serum PTH.[20] However, surgical removal of benign parathyroid adenomas remains the first option in patients with no overt contraindications because this allows definitive cure in most patients at lower cost. Surgical parathyroidectomy remains an important consideration in patients on dialysis who are unresponsive to vitamin D analogues and calcimimetics.[21] Of note, cinacalcet may be effective in patients with parathyroid carcinoma.

HYPOCALCEMIA

As with hypercalcemia, hypocalcemia can be secondary to either reduced plasma albumin (false hypocalcemia) or a change in ionized [Ca^{2+}] (true hypocalcemia). False hypocalcemia can be excluded by directly measuring serum [Ca^{2+}], by determining plasma total protein or albumin levels, by the clinical context, or by other laboratory results (Fig. 10.10). An acute decrease in ionized [Ca^{2+}] is often observed during acute hyperventilation and the respiratory alkalosis that follows, regardless of the cause of hyperventilation. Hyperventilation can result from cardiopulmonary or cerebral diseases. After excluding false hypocalcemia linked to hypoalbuminemia, hypocalcemia can be divided into that associated with elevated plasma phosphate concentration and that associated with low plasma phosphate concentration.

Hypocalcemia Associated With Hyperphosphatemia

CKD leads to diminished calcitriol production and subsequently a low-normal S_{Ca}. In parallel, declining glomerular filtration of phosphate leads to a progressive rise in serum phosphate once the glomerular filtration rate (GFR) falls below approximately 35 ml/min/1.73 m^2. AKI may cause hypocalcemia and hyperphosphatemia through the same mechanisms, as well as specific mechanisms in rhabdomyolysis or pancreatitis.

Hypoparathyroidism may be caused by surgical removal of the parathyroid glands (post-thyroidectomy or parathyroidectomy), radiation, autoimmune destruction of parathyroid tissue, or infiltrative diseases.

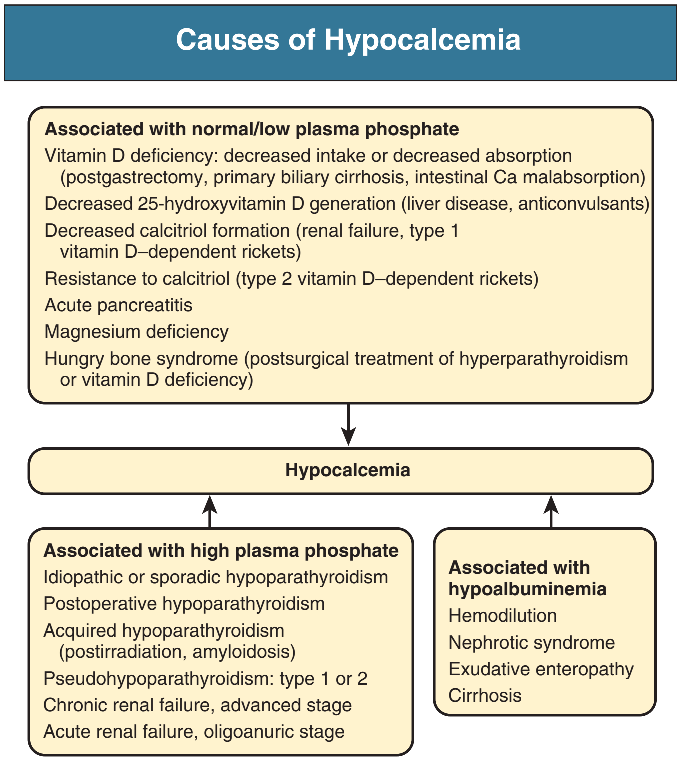
Causes of Hypocalcemia
Associated with normal/low plasma phosphate
Vitamin D deficiency: decreased intake or decreased absorption (postgastrectomy, primary biliary cirrhosis, intestinal Ca malabsorption)
Decreased 25-hydroxyvitamin D generation (liver disease, anticonvulsants)
Decreased calcitriol formation (renal failure, type 1 vitamin D–dependent rickets)
Resistance to calcitriol (type 2 vitamin D–dependent rickets)
Acute pancreatitis
Magnesium deficiency
Hungry bone syndrome (postsurgical treatment of hyperparathyroidism or vitamin D deficiency)
Hypocalcemia
Associated with high plasma phosphate
Idiopathic or sporadic hypoparathyroidism
Postoperative hypoparathyroidism
Acquired hypoparathyroidism (postirradiation, amyloidosis)
Pseudohypoparathyroidism: type 1 or 2
Chronic renal failure, advanced stage
Acute renal failure, oliguanuric stage
Associated with hypoalbuminemia
Hemodilution
Nephrotic syndrome
Exudative enteropathy
Cirrhosis

Fig.10.10 Causes of hypocalcemia.

Sporadic cases of hypoparathyroidism are occasionally seen in patients with pernicious anemia or adrenal insufficiency. Pseudohypoparathyroidism (Albright hereditary osteodystrophy) has a characteristic phenotype including short neck, round face, and short metacarpals, with end-organ resistance to PTH.

In addition, massive oral phosphate administration, such as that used in bowel preparations, also can lead to hypocalcemia with hyperphosphatemia, often with AKI.[22]

Hypocalcemia Associated With Hypophosphatemia

Hypocalcemia with hypophosphatemia may occur in vitamin D–deficient states. This may result from insufficient daylight exposure, dietary deficiency of vitamin D, decreased absorption after GI surgery, intestinal malabsorption syndromes (steatorrhea), or hepatobiliary disease (primary biliary cirrhosis). Hyperuricemia or gout may be associated with low calcitriol levels. Hypocalcemia also may be caused by magnesium deficiency, often in conjunction with hypokalemia, which may be caused by inappropriate kaliuresis or diarrhea. The mechanism for hypocalcemia in this setting appears to be decreased PTH release and end-organ resistance. AKI in the polyuric phase, especially after rhabdomyolysis, also may be associated with hypocalcemia and hypophosphatemia.

Clinical Manifestations

As with hypercalcemia, the symptoms of hypocalcemia depend on the rate of development and severity. The most common manifestations, in addition to fatigue and muscular weakness, are increased irritability, loss of memory, a state of confusion, hallucination, paranoia, and depression. The best known clinical signs are the Chvostek sign (tapping of facial nerve branches leading to twitching of facial muscle) and the Trousseau sign (carpal spasm in response to forearm ischemia caused by inflation of a sphygmomanometer cuff). Patients with acute hypocalcemia may have paresthesias of the lips and the extremities, muscle cramps, and occasionally frank tetany, laryngeal stridor, or seizures. Chronic hypocalcemia may be associated with cataracts, brittle nails with transverse grooves, dry skin, and decreased or even absent axillary and pubic hair, especially in idiopathic hypoparathyroidism.

Laboratory and Radiographic Signs

Plasma phosphate is elevated in hypoparathyroidism, pseudohypoparathyroidism, and advanced CKD, whereas it is decreased in steatorrhea, vitamin D deficiency, acute pancreatitis, persistent hyperparathyroidism after kidney transplantation, and the polyuric phase during recovery from AKI. Plasma PTH is reduced in hypoparathyroidism and during chronic magnesium deficiency, whereas it is normal or increased in pseudohypoparathyroidism and in CKD. Urinary calcium excretion is increased only in patients with hypoparathyroidism receiving calcium or vitamin D derivatives, in whom it may lead to nephrocalcinosis; excretion is low in all other patients with hypocalcemia. *Fractional* urinary calcium excretion is high in hypoparathyroidism, in the polyuric phase during recovery from AKI, and in severe CKD; it is low in all other patients with hypocalcemia. Urinary phosphate excretion increases with intestinal phosphate absorption and thus depends on phosphate intake and calcitriol. Determination of serum 25-hydroxyvitamin D and calcitriol levels may also be useful.

On the ECG the corrected QT interval is frequently prolonged, and arrhythmias may occur. The electroencephalogram shows nonspecific signs such as an increase in slow, high-voltage waves. Intracranial calcifications, notably of the basal ganglia, are observed radiographically in 20% of patients with idiopathic hypoparathyroidism, but much less frequently in patients with postsurgical hypoparathyroidism or pseudohypoparathyroidism.

Treatment

Therapy of hypocalcemia is directed toward the underlying cause. Severe and symptomatic (tetany) hypocalcemia requires rapid treatment. Acute respiratory alkalosis, if present, should be corrected if possible. When the cause is functional, simple carbon dioxide retention, as by breathing into a paper bag, may suffice. In other patients, and to obtain a prolonged effect, intravenous infusion of calcium salts is most often required. In the patient with seizures or tetany, calcium gluconate should be administered as an intravenous bolus (e.g., 10 ml 10% weight/volume [2.2 mmol of calcium], diluted in 50 ml of 5% dextrose in water [D5W] or isotonic saline), followed by 12 to 24 g over 24 hours (in D5W or isotonic saline). Calcium gluconate is preferred to calcium chloride, which can lead to extensive skin necrosis in accidental extravasation.

Treatment of chronic hypocalcemia includes oral administration of calcium salts, thiazide diuretics, or vitamin D. Several oral presentations of calcium are available, each with advantages and disadvantages. It should be remembered that the amount of elemental calcium of the various salts differs greatly. For example, the calcium content is 40% in carbonate, 36% in chloride, 12% in lactate, and only 8% in gluconate salts. The daily amount prescribed can be 1 to 4 g elemental Ca. Concurrent magnesium deficiency (serum $[\mathrm{Mg}^{2+}] < 0.70$ mmol/l) should be treated with oral magnesium oxide or carbonate 100 to 300 mg elemental magnesium/day or with magnesium sulfate 4 to 8 mmol/day intramuscularly or 20 to 40 mmol/day in D5W IV.

Treatment of hypocalcemia secondary to hypoparathyroidism is difficult because urinary calcium excretion increases markedly with calcium and active vitamin D supplementation and can lead to nephrocalcinosis and loss of renal function. To reduce urinary calcium concentration, thiazide diuretics can be used in association with restricted salt intake; high fluid intake is advised.

Therapy with active forms of vitamin D—calcitriol 0.25 to 1.5 μg/day or its analogue 1α-hydroxycholecalciferol (alfacalcidol) 0.25 to 3.0 μg/day—is the treatment of choice for idiopathic or acquired

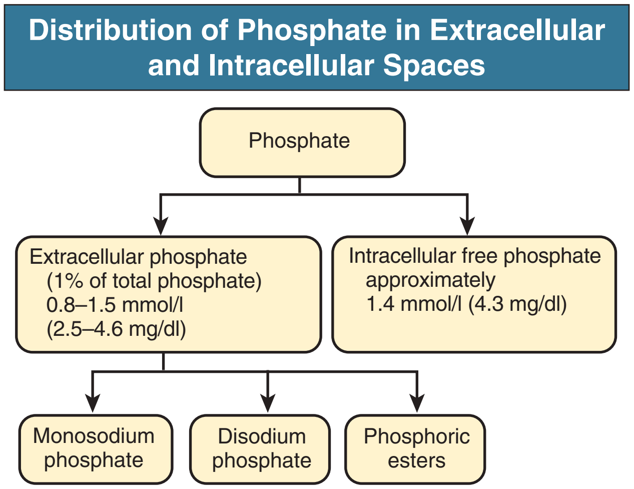
Distribution of Phosphate in Extracellular and Intracellular Spaces
Phosphate
Extracellular phosphate (1% of total phosphate) 0.8–1.5 mmol/l (2.5–4.6 mg/dl)
Intracellular free phosphate approximately 1.4 mmol/l (4.3 mg/dl)
Monosodium phosphate
Disodium phosphate
Phosphoric esters

Fig.10.11 Phosphate distribution in extracellular and intracellular spaces.

hypoparathyroidism because these compounds are better tolerated than massive doses of calcium salts. Administration of vitamin D derivatives generally leads to hypercalciuria and rarely to nephrocalcinosis. The patient requires regular monitoring to avoid hypercalcemia.

In patients with severe bone disease related to hyperparathyroidism, parathyroidectomy can be followed by severe hypocalcemia as a result of massive deposition of calcium salts in bone (hungry bone syndrome); large amounts of calcium and active forms of vitamin D may be needed for days or sometimes weeks.

PHOSPHATE HOMEOSTASIS

Distribution of Phosphate in the Organism

Phosphate plays a crucial role in cell structure, signaling, and metabolism. Phosphate is found in the organism both as mineral phosphate and organic phosphate (phosphoric esters). Most phosphate in the body resides in bone, teeth, and inside cells, with less than 1% circulating in serum. The serum phosphorus concentration is maintained within a narrow range under the direction of hormonal regulators FGF23, PTH, and calcitriol. Phosphate circulates as HPO_4^{2-} and $H_2PO_4^-$, in a 4:1 ratio at normal pH. Normal serum phosphate levels of 2.8 to 4.5 mg/dl in adults (0.9 to 1.5 mmol/l) fluctuate in a circadian rhythm, with levels approximately 0.6 mg/dl higher in the afternoon, compared with an 11 AM nadir. Fig. 10.11 shows the distribution of phosphate in the ECF and ICF compartments.

Fig. 10.12 shows the balance of ingestion, body distribution, and excretion of phosphate in a healthy human. A young adult requires approximately 0.5 mmol/kg of phosphate daily. These needs are much greater in the child during growth. Phosphate is widely found in milk products, meat, eggs, and cereals and is used extensively as a food additive. Bone permanently exchanges phosphate with the surrounding milieu. Entry and exit of phosphate amount to approximately 100 mmol daily (slowly exchangeable phosphate), for a total skeleton content of about 20,000 mmol. The net balance is positive during growth, zero in the young adult, and negative in the elderly adult.

Phosphate enters cells by active transport through a variety of sodium-phosphate (Na-Pi) cotransporters. In the small intestine, phosphate is mainly absorbed through the type 2b Na-Pi cotransporter (NPT2b). The major hormonal regulator of NPT2b is calcitriol, which increases phosphate transport into the body. In contrast, the lipid-lowering agent niacin inhibits NPT2b activity, thereby decreasing phosphate uptake.

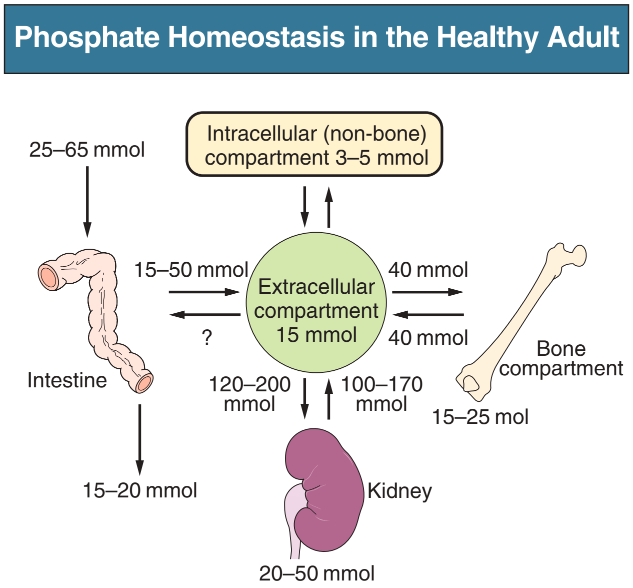
Phosphate Homeostasis in the Healthy Adult
25–65 mmol
Intracellular (non-bone) compartment 3–5 mmol
15–50 mmol
?
Extracellular compartment 15 mmol
40 mmol
40 mmol
Bone compartment
15–25 mol
Intestine
120–200 mmol
100–170 mmol
15–20 mmol
Kidney
20–50 mmol

Fig.10.12 **Phosphate homeostasis in healthy young adults.** At net zero balance, identical net intestinal uptake (absorption minus secretion) and urinary loss occur. After its passage into the extracellular fluid, phosphate enters the intracellular space, is deposited in bone or soft tissue, or is eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also the same under steady-state conditions.

In the proximal tubule of the kidney, most of the filtered phosphate load is reabsorbed through type 2a and type 2c Na-Pi cotransporters (NPT2a, NPT2c). A genome-wide association study of more than 16,000 normal adults found that a common genetic variant in NPT2a was associated with serum phosphate concentrations.[23] The phosphaturic hormones FGF-23 and PTH are the principal factors that downregulate NPT2a in the kidneys, increasing phosphate excretion in the urine. Now recognized as a central hormone in phosphate homeostasis, FGF-23 is produced by osteocytes and possesses weak inherent binding properties, requiring a cofactor, klotho, for optimal binding and function within the kidney.[24] Disruption of klotho or FGF-23 genes in animal models leads to a similar hyperphosphatemic phenotype. In addition to promoting phosphate excretion, FGF-23 potently suppresses calcitriol by inhibiting CYP27B1 and stimulating CYP24A1. Other hormones that may influence phosphate transport within the kidney include growth hormone, insulin-like growth factor 1 (IGF-1), insulin, thyroid hormone, secreted frizzled-related protein 4 (sFRP-4), and FGF-7.

Phosphate transport across the intestinal wall occurs via both the transepithelial and the paracellular routes (Fig. 10.13). GI absorption of phosphate is far more permissive than that of calcium. Absorption is a linear, nonsaturable function of phosphate intake that amounts to 60% to 75% of total phosphate intake (15 to 50 mmol/day) (Fig. 10.14). Cations, such as calcium, magnesium, or aluminum, bind to phosphate in the GI tract, limiting its absorption. In both animals and humans, ingestion of a high-phosphate meal results in the rapid excretion of phosphate in the urine, without detectable changes in serum phosphate levels.

The kidneys play a central role in controlling extracellular phosphate homeostasis.[25,26] Phosphate is minimally protein bound, freely filtered at the glomerulus, and reabsorbed primarily in the proximal tubule. To maintain homeostasis, the daily amount of phosphate excreted in urine must equal that absorbed in the intestine. Normally, the kidneys excrete 5% to 20% of the filtered phosphate load to maintain phosphate

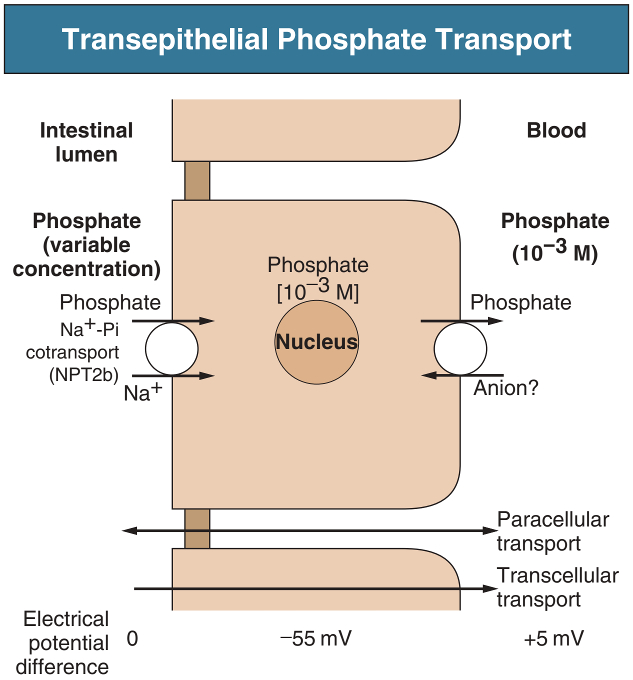

Fig. 10.13 Transepithelial phosphate transport in the small intestine. Phosphate enters the enterocyte (influx) through the brush border membrane using the Na^+/Pi cotransport system, with a stoichiometry of 2 : 1, operating against an electrochemical gradient. Phosphate exit at the basolateral side possibly occurs by passive diffusion or more probably by anion exchange.

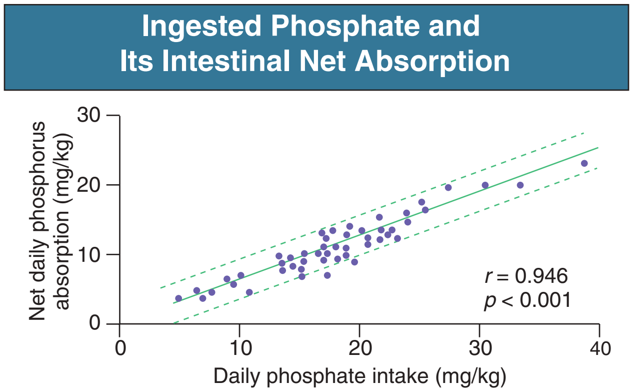

Fig. 10.14 Phosphate ingestion and absorption. Relationship between ingested phosphate and phosphorus absorbed in the digestive tract (net absorption) in healthy young adults. (From reference 5.)

balance. In CKD, fewer functioning nephrons necessitate the excretion of a higher proportion of the filtered phosphate load per nephron to maintain homeostasis and the fractional excretion of phosphate may exceed 50% in late stages of CKD.

The amount of phosphate reabsorbed can be expressed in relation to the amount filtered as the urinary fractional excretion of phosphate (FE_{PO_4}), as follows:

$$FE_{PO_4} = (U_{PO_4} \times S_{Cr})/(S_{PO_4} \times U_{Cr})$$

where U_{PO_4}, S_{PO_4}, U_{Cr}, and S_{Cr} are urinary and serum phosphate and creatinine concentrations, respectively. Ideally FE_{PO_4} should be calculated from 24-hour urine samples to incorporate dietary phosphate consumption and circadian changes in serum phosphate throughout the day. In practice, FE_{PO_4} is typically calculated using spot urine samples, which correlates only modestly with the results obtained from a 24-hour sample[27,28] (Fig. 10.15).

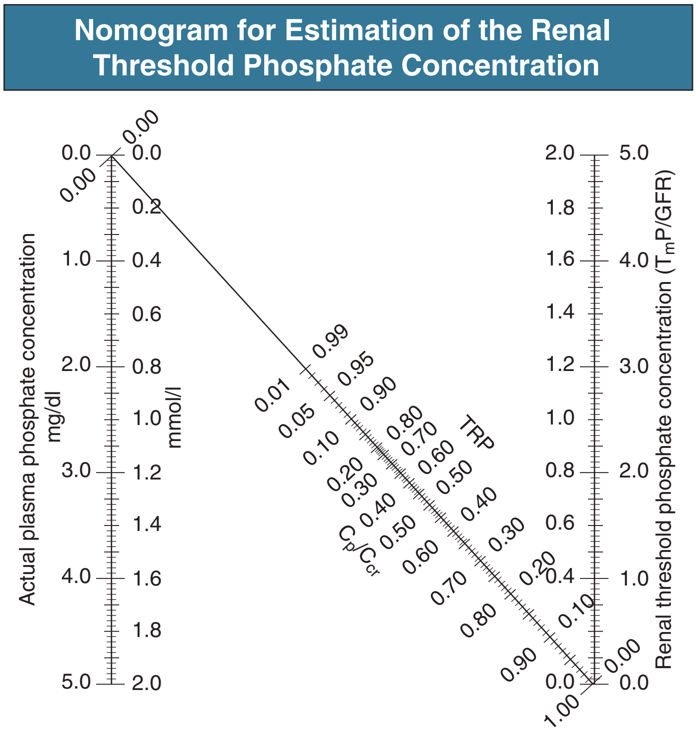

Fig. 10.15 Nomogram for estimation of renal threshold phosphate concentration. A straight line through the appropriate values of phosphate concentration and *TRP* (amount of phosphate reabsorbed, or C_P/C_{cr}, where *C* is clearance for phosphate or creatinine) passes through the corresponding value of T_mP/GFR. (From reference 27.)

HYPERPHOSPHATEMIA

Causes of Hyperphosphatemia

The most common cause of increased serum phosphate levels is reduced urinary excretion caused by acute and chronic kidney diseases.[29] Less frequently, hyperphosphatemia is caused by increased exogenous or endogenous phosphate supply (Fig. 10.16).

Acute Kidney Injury

An acute reduction in GFR leads directly to a rise in the serum phosphate concentration, often in parallel with serum creatinine.

Chronic Kidney Disease

As kidney function slowly declines during CKD, increasing levels of phosphaturic hormones PTH and FGF-23 maintain phosphate balance until about 75% of normal kidney function has been lost. Once GFR falls below about 35 ml/min/1.73 m^2, inadequate nephron mass results in a steady rise in serum phosphate. Similar to acidosis and anemia, the presence of hyperphosphatemia in patients with CKD generally suggests more advanced disease.

The price paid for preservation of serum phosphate in CKD is high circulating levels of FGF-23 and PTH. FGF-23 potently suppresses calcitriol, inhibiting intestinal phosphate absorption through NPT2b and further defending against phosphate excess. However, suppression of calcitriol may have an adverse impact on cardiovascular and kidney

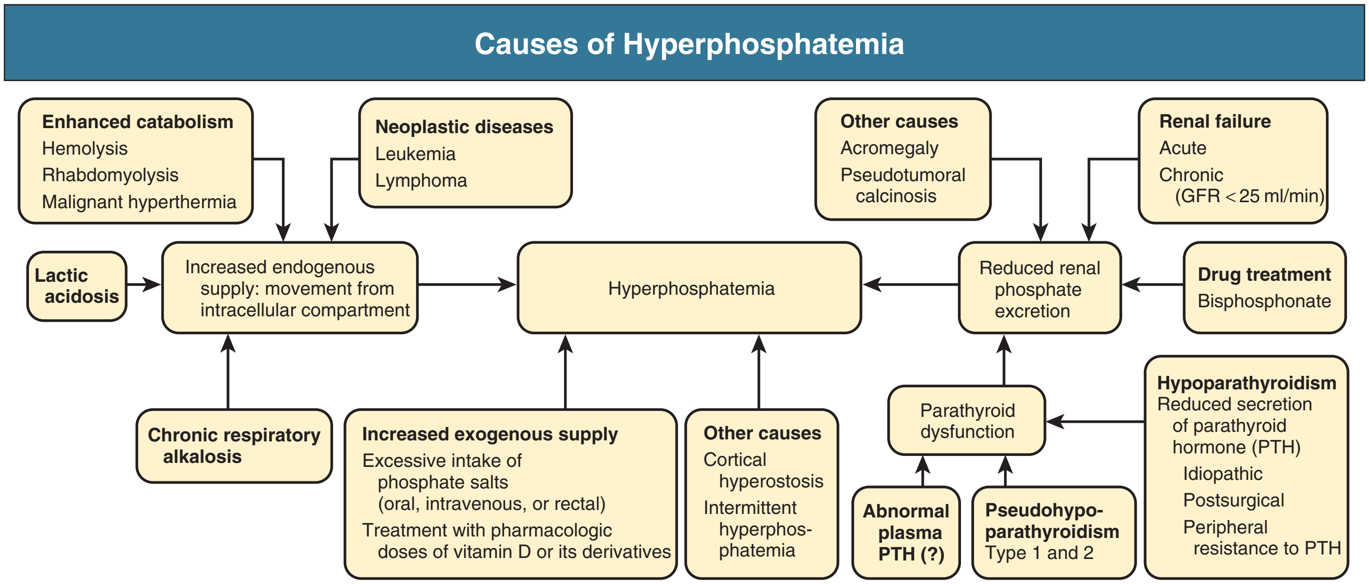
Causes of Hyperphosphatemia
Enhanced catabolism
Hemolysis
Rhabdomyolysis
Malignant hyperthermia
Neoplastic diseases
Leukemia
Lymphoma
Other causes
Acromegaly
Pseudotumoral calcinosis
Renal failure
Acute
Chronic (GFR < 25 ml/min)
Lactic acidosis
Increased endogenous supply: movement from intracellular compartment
Hyperphosphatemia
Reduced renal phosphate excretion
Drug treatment
Bisphosphonate
Hypoparathyroidism
Reduced secretion of parathyroid hormone (PTH)
Idiopathic
Postsurgical
Peripheral resistance to PTH
Parathyroid dysfunction
Chronic respiratory alkalosis
Increased exogenous supply
Excessive intake of phosphate salts (oral, intravenous, or rectal)
Treatment with pharmacologic doses of vitamin D or its derivatives
Other causes
Cortical hyperostosis
Intermittent hyperphosphatemia
Abnormal plasma PTH (?)
Pseudohypoparathyroidism
Type 1 and 2

Fig.10.16 Causes of hyperphosphatemia.

health because of biologic activities of calcitriol in downregulating renin expression, reducing inflammatory cytokines, and moderating ventricular hypertrophy. FGF-23 excess may have direct cardiovascular toxicity through stimulation of cardiac hypertrophy, as seen in animal models. A randomized controlled trial of phosphate binders in nondialysis CKD patients assessed the hormonal impact of phosphate binders in the setting of normal or only modestly elevated phosphate levels.[30] Compared with placebo, intensive therapy with phosphate binders over a median 8 months of follow-up lowered serum phosphate by a mean of 0.3 mg/dl, reduced mean 24-hour urine phosphate by 22%, and prevented an increase in PTH. However, phosphate binder treatment did not have an impact on serum FGF-23 levels.

Lytic States

Exaggerated phosphate loss by tissues is seen in states of extreme cell lysis, particularly rhabdomyolysis (crush injury), and in patients with malignancies, especially lymphoma and leukemia, and with their treatment. The hyperphosphatemia of rhabdomyolysis is typically accompanied by hypocalcemia, myoglobinuria, and AKI. Severe hypercatabolic states during severe infection or in diabetic ketoacidosis also can cause hyperphosphatemia through increased cellular release of phosphate, usually accompanied by an acute reduction in GFR.

Treatment-Induced Hyperphosphatemia

A massive supply of phosphate (e.g., phosphate-based laxatives or enemas) can lead to hyperphosphatemia. Oral sodium phosphate solutions used to prepare for colonoscopy contain massive quantities of phosphate and can cause precipitation of calcium phosphate crystals within the renal tubules and AKI. Recovery from this condition is slow and often incomplete, with some cases resulting in end-stage renal disease. Patients who have CKD should therefore receive alternative bowel preparations. Bisphosphonates, in particular etidronate in Paget disease, can increase serum phosphate levels, possibly through increased liberation of tissue phosphate or an increase in renal tubular reabsorption.

Hypoparathyroidism

Parathyroid hormone is a major phosphaturic hormone. In states of reduced PTH secretion (idiopathic or postsurgical hypoparathyroidism) or resistance to its peripheral action (pseudohypoparathyroidism), tubular excretion of phosphate is diminished. The resulting increase in plasma phosphate leads to an increase in the ultrafiltered load. This results in regulation of plasma phosphate at a new steady-state level.

Chronic Hypocalcemia

Hyperphosphatemia may be observed in association with chronic hypocalcemia with normal or high plasma PTH levels. In the absence of characteristic abnormalities of pseudohypoparathyroidism, the existence of an abnormal form of plasma PTH may be responsible, perhaps caused by abnormal conversion of the prohormone to its secreted form.

Acromegaly

In acromegaly, hyperphosphatemia results from an increase in tubular reabsorption of phosphate caused by stimulation by growth hormone and IGF-1.

Familial Tumoral Calcinosis

This rare autosomal recessive disorder seen primarily in people of Middle Eastern or African ancestry is caused by an inactivating mutation in *GALNT3*, *FGF23*, or klotho gene. The glycosyltransferase encoded by *GALNT3* is necessary for FGF-23 activity, thus resulting in a shared phenotype.[31] The lack of functional FGF-23 results in an exaggerated tubular phosphate reabsorption and uninhibited vitamin D activation, leading to hyperphosphatemia and hypercalcemia, high circulating levels of calcitriol, and metastatic soft tissue calcifications. The most common finding is densely calcified masses surrounding major joints that recur after removal. Circulating PTH is not decreased.

Respiratory Alkalosis With Prolonged Hyperventilation

Respiratory alkalosis resulting from prolonged hyperventilation is characterized by resistance to the renal action of PTH, hyperphosphatemia, and hypocalcemia. There also may be functional pseudohypoparathyroidism because renal phosphate clearance is diminished, whereas plasma PTH is normal, despite hypocalcemia. There is no decrease in urinary calcium excretion.

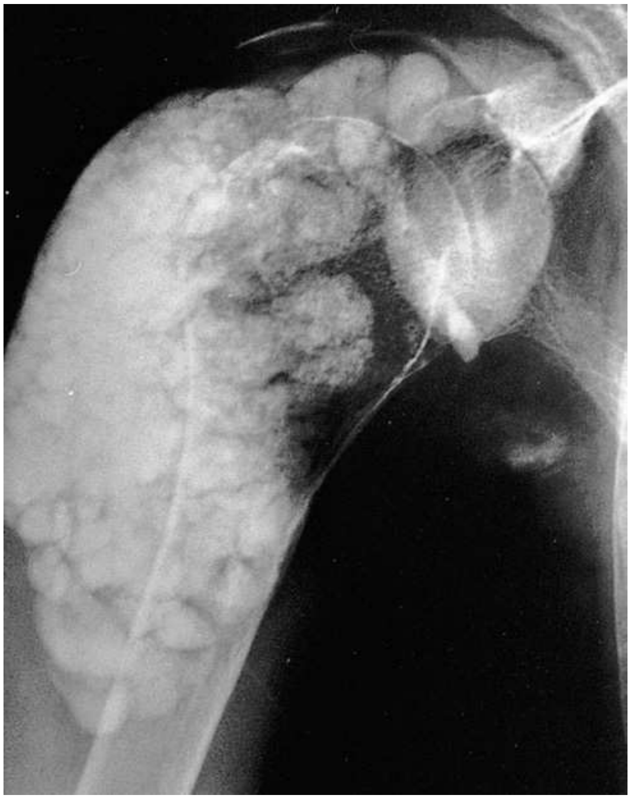

Fig. 10.17 Tumor-like extraskeletal calcification in the shoulder.

Clinical Manifestations

The major clinical implication of profound hyperphosphatemia is deposition of phosphate and calcium in soft tissues and in the renal tubules. Chronic hyperphosphatemia may contribute to cardiovascular calcification, particularly in CKD (see Chapter 81). In extreme cases, hyperphosphatemia can induce tumor-like soft tissue calcium phosphate deposits (Fig. 10.17) or extensive vascular calcification within the arteries of the skin (calciphylaxis or calcific uremic arteriolopathy; see Chapter 87). Hyperphosphatemia also blocks the conversion of 25-hydroxyvitamin D to calcitriol, leading to concomitant hypocalcemia and the stimulation of PTH.

Treatment

Treatment of acute hyperphosphatemia is usually targeted at improving phosphate excretion by intravenous fluids or by renal replacement therapy in patients with severe AKI. Intravenous dextrose and insulin can shift phosphate into cells, similar to treatment of hyperkalemia.

Treatment of chronic hyperphosphatemia in patients with CKD and those receiving dialysis remains a major component of CKD clinical care. Higher serum phosphate concentrations are *associated* with vascular calcification, cardiovascular events, and mortality in CKD,[32] but evidence that treatment improves hard outcomes is lacking. In patients on chronic dialysis, dietary phosphate restriction and phosphate binders lower the serum phosphate concentration. (see Chapter 84). Nicotinamide is an intriguing possible alternative to phosphate binding agents due to its ease of administration (once daily) and novel mechanism of action (inhibition of NPT2b in small intestine, blocking phosphate absorption).[33] However, nicotinamide may cause significant side effects and is unproven for treating hyperphosphatemia clinically.[34]

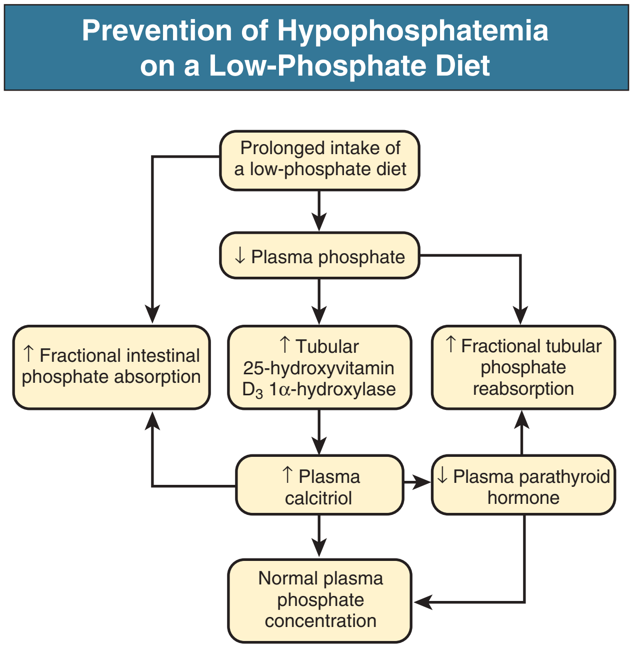
Prevention of Hypophosphatemia on a Low-Phosphate Diet
Prolonged intake of a low-phosphate diet
↓ Plasma phosphate
↑ Fractional intestinal phosphate absorption
↑ Tubular 25-hydroxyvitamin D_3 1α-hydroxylase
↑ Fractional tubular phosphate reabsorption
↑ Plasma calcitriol
↓ Plasma parathyroid hormone
Normal plasma phosphate concentration

Fig. 10.18 **Prevention of hypophosphatemia.** Compensatory mechanisms during prolonged intake of a phosphate-poor diet help to prevent hypophosphatemia.

HYPOPHOSPHATEMIA

Decreased plasma phosphate levels may reflect phosphate deficiency, which in theory could be due to a prolonged decrease in phosphate intake. However, several defense mechanisms counter a decrease in plasma phosphate resulting from low intake (Fig. 10.18). Moderately reduced plasma phosphate levels also may accompany maldistribution between the ICF and ECF compartments during acute respiratory alkalosis.

Causes of Hypophosphatemia

Moderate hypophosphatemia can be caused by genetic or acquired conditions (Fig. 10.19). The main acquired condition is malnutrition because of low food intake or anorexia during severe disease or alcoholism. Another cause is a shift of phosphate into cells, which can occur through various mechanisms, but especially with insulin administration. Although there are many genetic diseases and syndromes that can cause hypophosphatemia, overall these are rare. Severe forms of hypophosphatemia are all acquired conditions.

Inherited Forms of Hypophosphatemia

Inherited diseases associated with chronic hypophosphatemia are generally diagnosed in childhood.[35] Persistently low plasma phosphate usually leads to rickets or osteomalacia. Inherited hypophosphatemia results from primary defects, which are isolated or associated with proximal tubular disorders (Fanconi syndrome) or defects secondary to another genetically transmitted disease, mainly metabolic disorders or disturbances in vitamin D activity.

Autosomal dominant hypophosphatemic rickets. Children with this phosphate wasting disorder present with skeletal defects, including bowing of the long bones and widening of costochondral joints. Autosomal dominant hypophosphatemic rickets is linked to mutations in *FGF23,* in which an aberrant form of the molecule is resistant to proteolytic cleavage.[36] Excess FGF-23 causes phosphate wasting by downregulating NPT2a in the proximal renal tubule.

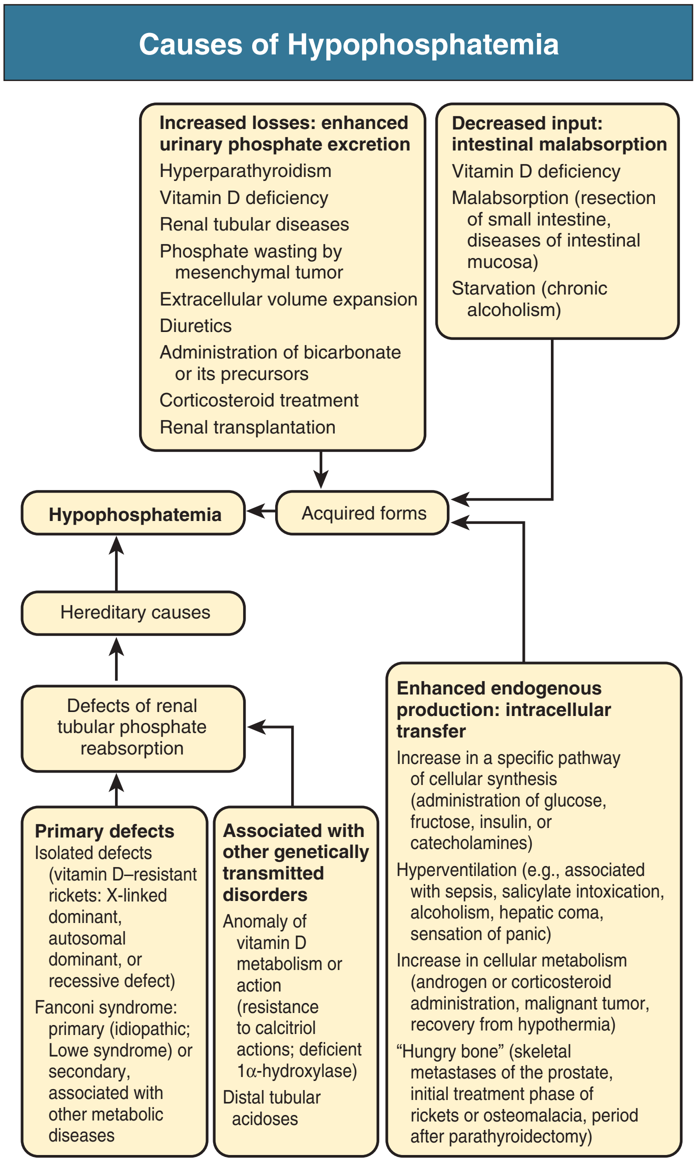
Causes of Hypophosphatemia
Increased losses: enhanced urinary phosphate excretion
Hyperparathyroidism
Vitamin D deficiency
Renal tubular diseases
Phosphate wasting by mesenchymal tumor
Extracellular volume expansion
Diuretics
Administration of bicarbonate or its precursors
Corticosteroid treatment
Renal transplantation
Decreased input: intestinal malabsorption
Vitamin D deficiency
Malabsorption (resection of small intestine, diseases of intestinal mucosa)
Starvation (chronic alcoholism)
Hypophosphatemia
Acquired forms
Hereditary causes
Defects of renal tubular phosphate reabsorption
Enhanced endogenous production: intracellular transfer
Increase in a specific pathway of cellular synthesis (administration of glucose, fructose, insulin, or catecholamines)
Hyperventilation (e.g., associated with sepsis, salicylate intoxication, alcoholism, hepatic coma, sensation of panic)
Increase in cellular metabolism (androgen or corticosteroid administration, malignant tumor, recovery from hypothermia)
"Hungry bone" (skeletal metastases of the prostate, initial treatment phase of rickets or osteomalacia, period after parathyroidectomy)
Primary defects
Isolated defects (vitamin D–resistant rickets: X-linked dominant, autosomal dominant, or recessive defect)
Fanconi syndrome: primary (idiopathic; Lowe syndrome) or secondary, associated with other metabolic diseases
Associated with other genetically transmitted disorders
Anomaly of vitamin D metabolism or action (resistance to calcitriol actions; deficient 1α-hydroxylase)
Distal tubular acidoses

Fig.10.19 Causes of hypophosphatemia.

X-linked hypophosphatemic rickets. The rare phosphate wasting syndrome X-linked hypophosphatemic rickets is characterized by skeletal deformities, short stature, and osteomalacia. X-linked hypophosphatemic rickets has been associated with various mutations in the *PHEX* gene (phosphate-regulating endopeptidase on X chromosome). *PHEX* likely plays a role in the proteolysis of FGF-23.[37] *PHEX* mutations result in high circulating FGF-23 concentrations, renal phosphate wasting, and hypophosphatemia. Serum calcium, calcitriol, and PTH levels are normal, and alkaline phosphatase level is elevated.

Autosomal recessive hypophosphatemic rickets. Inherited autosomal recessive hypophosphatemic rickets is caused by mutations in dentin matrix protein 1 gene *(DMP1),* which is believed to suppress FGF-23 secretion by bone.

Fanconi syndrome and proximal renal tubular acidosis. Fanconi syndrome is characterized by a complex transport defect of the proximal tubule that results in decreased reabsorption of glucose, amino acids, bicarbonate, and phosphate. Because 70% of the filtered phosphate load is typically reabsorbed in the proximal tubule, Fanconi syndrome leads to renal phosphate wasting and hypophosphatemia. A fractional urinary phosphate excretion greater than 15% in the setting of overt hypophosphatemia is helpful for suggesting renal phosphate wasting. Causes and management of Fanconi syndrome are discussed in Chapter 48.

In addition to a tubular defect causing phosphate wasting, the activity of renal 1α-25-OH-vitamin D hydroxylase may be insufficient, resulting in decreased circulating calcitriol levels and bone disease such as rickets and osteomalacia. Functional disorders associated with the Fanconi syndrome, such as polyuria and ECF volume contraction, lead to hyperaldosteronism with hypokalemia and eventually to renal failure.

Vitamin D–dependent rickets. Several rare inherited diseases are associated with hypophosphatemia and include vitamin D–dependent rickets type 1, caused by a defect of renal 25-OH-vitamin D hydroxylase, and type 2, caused by peripheral resistance to the action of calcitriol. Clinical signs are similar to those of vitamin D–deficient rickets, but alopecia also occurs in 50% of patients. In type 1, calcitriol levels are low, whereas in type 2 there is normal circulating 25-hydroxyvitamin D and high calcitriol. Treatment with low doses of calcitriol is sufficient to treat type 1, whereas extremely high doses of calcitriol, alfacalcidol, or calcidiol are required for type 2 vitamin D–dependent rickets.

Distal renal tubular acidosis (type 1). Distal renal tubular acidosis (type 1 RTA) is associated with hypercalciuria and sometimes nephrocalcinosis. Chronic acidosis enhances the reabsorption of citrate in the proximal tubule, preventing it from forming soluble calcium-citrate complexes in the urine (see Chapter 12). Chronic acidosis also causes increased calcium and phosphate release from bone. Hypophosphatemia is inconstant, possibly resulting only from concomitant vitamin D deficiency.

Acquired Forms of Hypophosphatemia

The number of acquired diseases that can be associated with hypophosphatemia is even greater than inherited diseases and includes hyperparathyroidism and vitamin D deficiency (see Fig. 10.19). True phosphate deficiency associated with total body depletion must be distinguished from enhanced influx of phosphate into cells or increased skeletal mineralization.

Alcoholism. Alcoholism is the most common cause of severe hypophosphatemia in Western countries. The multiple causes include prolonged poor food intake, excessive phosphate loss in urine secondary to hypomagnesemia, and phosphate transfer from the ECF to ICF compartment caused by hyperventilation or glucose infusion in patients with postalcoholic cirrhosis or in acute abstinence.

Hyperparathyroidism. PTH enhances urinary phosphate excretion by downregulating the NPT2a cotransporter. Patients with primary hyperparathyroidism typically present with mild hypercalcemia and hypophosphatemia.

Post-transplant hypophosphatemia. Renal phosphate wasting is exceedingly common in renal transplant recipients. At some point in their post-transplant course, most patients develop hypophosphatemia, which may be prolonged. Proposed explanations include residual hyperparathyroidism from CKD, but the best evidence implicates persistently high circulating levels of FGF-23 as the key factor.

Acute respiratory alkalosis. In intense and short-term hyperventilation, plasma phosphate can decrease to values as low as 0.1 mmol/l (0.3 mg/dl). Such a decrease is never observed in metabolic alkalosis. Hypophosphatemia after acute and intense hyperventilation is probably the result of muscle sequestration of extracellular phosphate. However, prolonged chronic hyperventilation leads to hyperphosphatemia (see previous discussion).

Diabetic ketoacidosis. During decompensated diabetes associated with acidosis provoked by accumulation of ketone bodies, glycosuria, and polyuria, plasma phosphate can be normal or high, even in the presence of hyperphosphaturia. Correction of this complication by administering insulin and refilling the ECF compartment leads to massive transfer of phosphate into the intracellular compartment, hypophosphatemia, and subsequently less urinary loss of phosphate. In general, plasma phosphate does not decrease to less than 0.3 mmol/l (0.9 mg/dl) unless there is preexisting phosphate deficiency.

Total parenteral nutrition. Hyperalimentation can be associated with severe hypophosphatemia through the insulin-mediated shift of phosphate into cells, particularly if phosphate is omitted from the parenteral nutrition solution. Severe hypophosphatemia also can occur with acute feeding after starvation.

Oncogenic hypophosphatemic osteomalacia. Hypophosphatemia associated with tumor-induced osteomalacia results from renal phosphate wasting in patients with mesenchymal tumors (hemangiopericytoma, fibroma, angiosarcoma). The mechanism of hypophosphatemia is tumor secretion of phosphatonins (FGF-23, sFRP-4, matrix extracellular phosphoglycoprotein [MEPE], FGF-7).[38] The condition resolves after tumor resection.

Drug-induced hypophosphatemia. Imatinib mesylate, a tyrosine kinase inhibitor, has been reported to cause hypophosphatemia and elevated PTH levels. The mechanism of action likely associates dysfunction of the renal proximal tubule and increased osteoformation.[39]

Clinical Manifestations

Clinical manifestations depend more on the rate of onset of hypophosphatemia than on its severity or the total body phosphate deficit. In practice, it is not clinically evident when serum phosphate is greater than 0.65 mmol/l (2.0 mg/dl). Manifestations include metabolic encephalopathy, red and white blood cell dysfunction, sometimes hemolysis, and thrombocytopenia. Reduced muscle strength (e.g., diaphragmatic strength) and decreased myocardial contractility, with occasional rhabdomyolysis and cardiomyopathy, respectively, may occur, motivating clinical practice to replete low serum phosphate concentration in intensive care settings.

Treatment

In general, phosphate deficiency is not an emergency. First, the mechanism involved should be defined to determine the most appropriate treatment. When phosphate deficiency is diagnosed, oral treatment by milk products or phosphate salts always should be tried first whenever possible, except in the presence of nephrocalcinosis or nephrolithiasis with urinary phosphate wasting. In severe symptomatic deficiency, phosphate also can be infused intravenously, in divided doses over 24 hours. In patients undergoing parenteral nutrition, 10 to 25 mmol potassium phosphate should be given for each 1000 kcal, taking care to avoid hyperphosphatemia because of the risk for inducing soft tissue calcifications. Dipyridamole may reduce the urinary excretion of phosphate in patients with a low renal phosphate threshold.

MAGNESIUM HOMEOSTASIS AND DISORDERS OF MAGNESIUM METABOLISM

Distribution of Magnesium in the Organism

Magnesium (Mg^{2+}) is the second most abundant cation in the ICF in living organisms and the fourth most abundant cation in the body. Mg^{2+} is involved in most metabolic processes and contributes to DNA and protein synthesis. Magnesium is involved in the regulation of mitochondrial function, inflammatory processes and immune defense, allergy, growth, and stress and in the control of neuronal activity, cardiac excitability, neuromuscular transmission, vasomotor tone, and blood pressure. Fig. 10.20 shows the distribution of Mg^{2+} within the intracellular and extracellular spaces. Fig. 10.21 shows the balance of ingestion, body distribution, and excretion of Mg^{2+} in healthy humans. Cell influx and efflux are linked to carbohydrate-dependent active transport systems; stimulation of β-adrenoceptors favors Mg^{2+} exit, whereas insulin, calcitriol, and vitamin B_6 favor Mg^{2+} entry into cells.

Intestinal and Renal Handling of Magnesium

The intestinal absorption of dietary Mg^{2+} occurs by both saturable and passive transport processes, the major part being absorbed in the distal

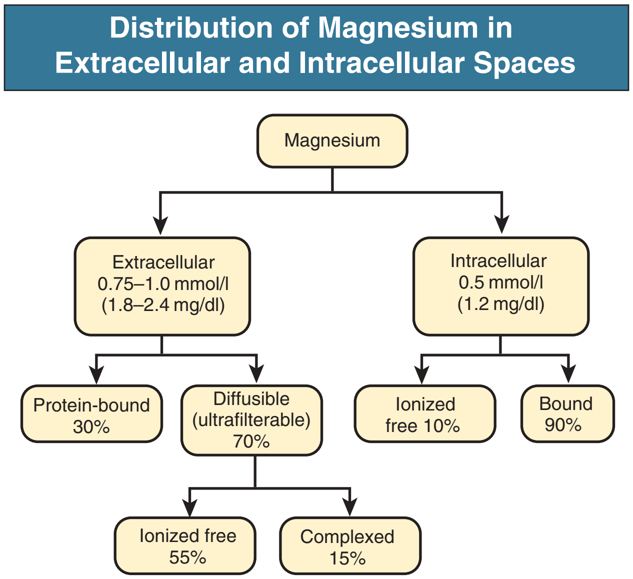
Distribution of Magnesium in Extracellular and Intracellular Spaces
Magnesium
Extracellular 0.75–1.0 mmol/l (1.8–2.4 mg/dl)
Intracellular 0.5 mmol/l (1.2 mg/dl)
Protein-bound 30%
Diffusible (ultrafilterable) 70%
Ionized free 10%
Bound 90%
Ionized free 55%
Complexed 15%

Fig.10.20 Magnesium distribution in extracellular and intracellular spaces. Intracellular magnesium concentration is that of free, not total, magnesium.

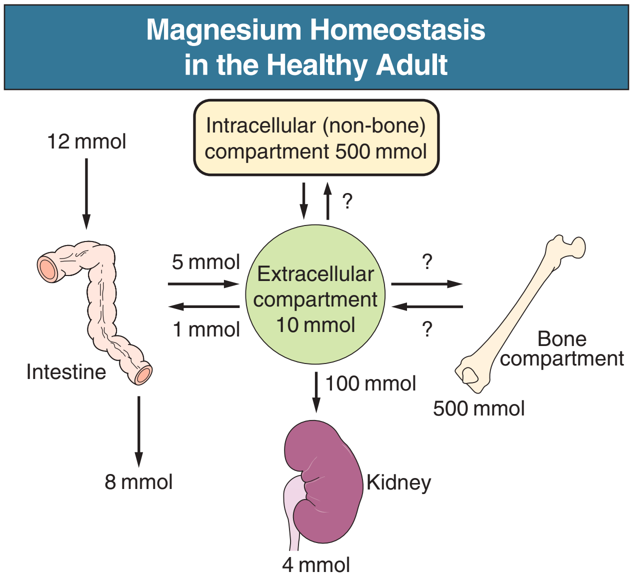
Magnesium Homeostasis in the Healthy Adult
Intracellular (non-bone) compartment 500 mmol
?
12 mmol
5 mmol
1 mmol
Extracellular compartment 10 mmol
?
?
Intestine
Bone compartment
500 mmol
100 mmol
8 mmol
Kidney
4 mmol

Fig.10.21 Magnesium homeostasis in healthy adults. Net zero balance results from net intestinal uptake (absorption minus secretion) equaling urinary loss. After its passage into the extracellular fluid, Mg^{2+} enters the intracellular space, is deposited in bone or soft tissue, or is eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also of identical magnitude; however, precise values of exchange are still debated.

small intestine and the colon. Paracellular Mg^{2+} absorption is responsible for 80% to 90% of intestinal Mg^{2+} uptake. It seems restricted primarily to areas that lack tightening claudins. Transcellular Mg^{2+} transport is mediated by transient receptor potential channel melastatin member 6 (TRPM6) and TRPM7 Mg^{2+} channels.[4] Mg^{2+} absorption can vary by as much as 25% to 60%, mainly depending on magnesium intake, with a mean absorption of approximately 30%. When magnesium intake is low, intestinal transport can rise up to 80%.[40,41]

Various factors modify intestinal Mg^{2+} absorption. In addition to high magnesium intake, high dietary phosphate intake is inhibitory, as is high phytate consumption. The effect of dietary calcium is complex, and calcitriol has an enhancing effect. Growth hormone slightly increases Mg^{2+} absorption, whereas aldosterone and calcitonin appear to reduce it. Vitamin B_6 has been reported to enhance absorption.

Magnesium is mainly eliminated by the kidney. Losses through intestinal secretion and sweat are negligible under normal conditions. With a normal plasma magnesium concentration (0.70 to 0.95 mmol/L [1.7 to 2.3 mg/dl]), of which 80% is ultrafilterable, the filtered load of magnesium amounts to approximately 104 mmol (or 2500 mg) daily. The urine output represents approximately 5% of the filtered load (4 to 5 mmol, or 100 mg daily). The major portion of filtered magnesium is reabsorbed by the renal tubules: 25% in proximal tubule, 65% in the TAL, and 5% in distal tubule (Fig. 10.22).[42,43]

Transport of Mg^{2+} in the TAL is primarily passive via the paracellular route. However, two conditions are necessary for normal Mg^{2+} reabsorption: (1) generation of an electrical, lumen-positive gradient induced by NaCl reabsorption that creates the driving force required for the reabsorption of divalent cations and (2) expression of Claudins-16 and -19, which form a cation-selective tight junction, facilitating paracellular Mg^{2+} transport. Different anomalies associated with either NaCl reabsorption or with Claudin-16 or -19 expression result in hypermagnesuria, such as Bartter syndrome, which is defined by genetic defects related to NaCl transport in the TAL.[44,45]

In the distal nephron (i.e., distal convoluted tubule and connecting tubule), Mg^{2+} is reabsorbed via the transcellular route against an uphill electrochemical gradient. The gatekeeper channel that controls Mg^{2+} entry into the tubular epithelium across the apical membrane is TRPM6.[4] Its activity is regulated by epidermal growth factor (EGF) and estrogen, but not by calcitriol or PTH.

Tubular Mg^{2+} transport is modulated by serum Mg^{2+} and Ca^{2+} and ECF volume. An increase in plasma Mg^{2+} or Ca^{2+} concentration results in impaired magnesium transport. ECF volume expansion produces a decrease in proximal tubular Mg^{2+} reabsorption, in parallel with that of Na^{+} and Ca^{2+}. Dietary phosphate restriction results in marked hypercalciuria and hypermagnesuria and thus leads to overt hypomagnesemia. PTH, vasopressin, calcitonin, and glucagon increase tubular Mg^{2+} reabsorption, probably by the paracellular pathway, whereas acetylcholine, bradykinin, and atrial natriuretic peptide stimulate urinary Mg^{2+} excretion.

Several drugs have also been shown to increase renal Mg^{2+} excretion, including the loop diuretics (furosemide, bumetanide), distal diuretics (thiazides), and osmotic diuretics (mannitol, urea). Thiazide diuretics increase sodium delivery to the cortical collecting duct, dissipating the

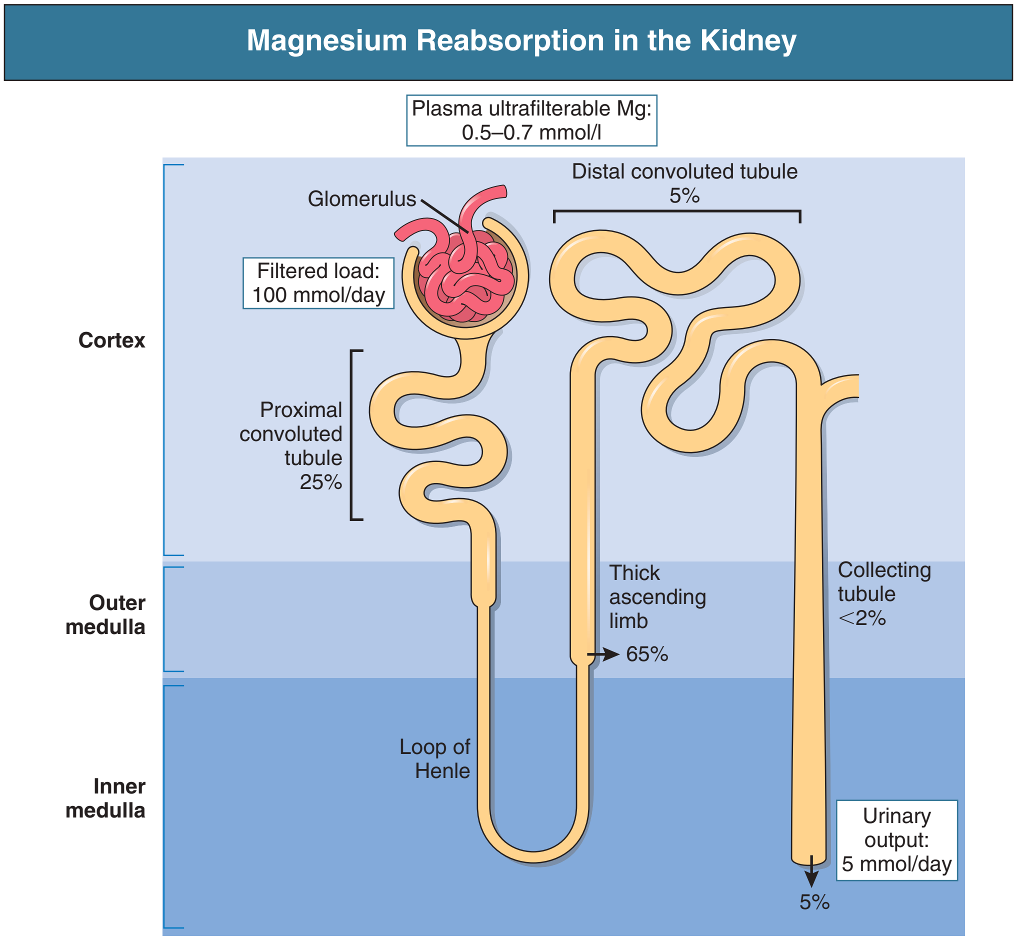
Magnesium Reabsorption in the Kidney
Plasma ultrafilterable Mg: 0.5–0.7 mmol/l
Glomerulus
Filtered load: 100 mmol/day
Distal convoluted tubule 5%
Cortex
Proximal convoluted tubule 25%
Outer medulla
Thick ascending limb
65%
Collecting tubule <2%
Inner medulla
Loop of Henle
Urinary output: 5 mmol/day
5%

Fig.10.22 Sites of magnesium reabsorption in various segments. Percentage absorbed in various segments of the renal tubule from the glomerular ultrafiltrate. (Redrawn from reference 42.)

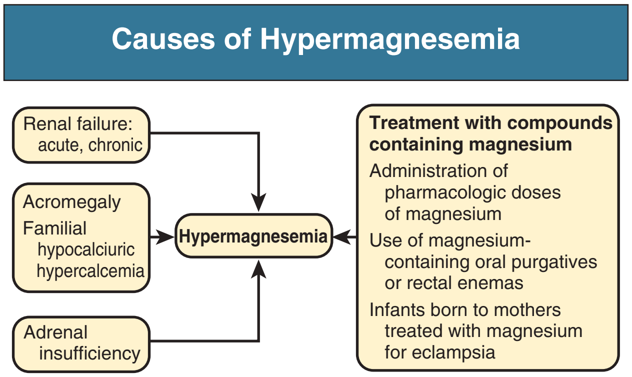
Causes of Hypermagnesemia
Renal failure: acute, chronic
Acromegaly
Familial hypocalciuric hypercalcemia
Adrenal insufficiency
Hypermagnesemia
Treatment with compounds containing magnesium
Administration of pharmacologic doses of magnesium
Use of magnesium-containing oral purgatives or rectal enemas
Infants born to mothers treated with magnesium for eclampsia

Fig.10.23 Causes of hypermagnesemia.

favorable electrochemical gradient for magnesium entry at this site. Thiazides also reduce TRPM6 expression in the distal convoluted tubule. Furthermore, renal Mg^{2+} wasting syndromes have been observed in patients treated with antibiotics such as gentamicin, antineoplastic agents such as cisplatin, and the calcineurin inhibitors cyclosporine and tacrolimus. The precise mechanisms of action of most of these agents are not well understood.

Hypermagnesemia

Elevated plasma Mg^{2+} is seen in patients with AKI and CKD, during the administration of pharmacologic doses of magnesium, in some infants born to mothers who received magnesium for eclampsia, and with the use of oral laxatives or rectal enemas containing magnesium (Fig. 10.23). Mild hypermagnesemia also may be present in patients with adrenal insufficiency, acromegaly, or FHH.

Clinical Manifestations

Symptoms and signs result from the effects of increased $[Mg^{2+}]$ on the nervous and cardiovascular systems. At $[Mg^{2+}]$ up to 1.5 mmol/l (3.6 mg/dl), hypermagnesemia is asymptomatic. Deep tendon reflexes are usually lost when plasma $[Mg^{2+}]$ is greater than 3 mmol/l (7.2 mg/dl). Respiratory paralysis, hypotension, and loss of consciousness may occur as plasma levels of magnesium approach 5 mmol/l (12 mg/dl).

Treatment

Treatment consists of cessation of magnesium administration and intravenous infusion of calcium salts, which is thought to counteract Mg blockade of calcium channels at the neuromuscular junction. For the management of symptomatic hypermagnesemia, calcium gluconate may be given, 1 to 2 g in 10 to 20 ml D5W IV over 5 to 10 minutes (each gram of calcium gluconate is approximately 90 mg elemental calcium).

HYPOMAGNESEMIA AND MAGNESIUM DEFICIENCY

Magnesium deficiency is defined as a decrease in total body magnesium content. Poor dietary intake of magnesium is usually not typically associated with marked magnesium deficiency because of the ability of the intestine to increase Mg^{2+} absorption and the kidney to conserve Mg^{2+}. However, prolonged and severe dietary magnesium restriction of less than 0.5 mmol/day can produce symptomatic magnesium deficiency. Severe hypomagnesemia is usually associated with magnesium deficiency. About 10% of patients admitted to a large U.S. city hospital were hypomagnesemic. The incidence may be as high as 65% in medical intensive care units.

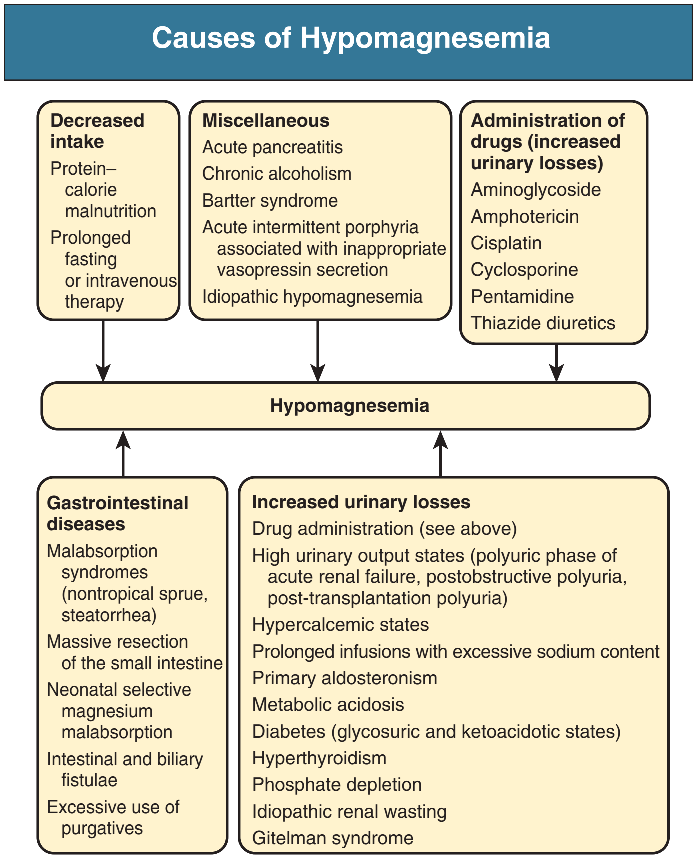
Causes of Hypomagnesemia
Decreased intake
Protein–calorie malnutrition
Prolonged fasting or intravenous therapy
Miscellaneous
Acute pancreatitis
Chronic alcoholism
Bartter syndrome
Acute intermittent porphyria associated with inappropriate vasopressin secretion
Idiopathic hypomagnesemia
Administration of drugs (increased urinary losses)
Aminoglycoside
Amphotericin
Cisplatin
Cyclosporine
Pentamidine
Thiazide diuretics
Hypomagnesemia
Gastrointestinal diseases
Malabsorption syndromes (nontropical sprue, steatorrhea)
Massive resection of the small intestine
Neonatal selective magnesium malabsorption
Intestinal and biliary fistulae
Excessive use of purgatives
Increased urinary losses
Drug administration (see above)
High urinary output states (polyuric phase of acute renal failure, postobstructive polyuria, post-transplantation polyuria)
Hypercalcemic states
Prolonged infusions with excessive sodium content
Primary aldosteronism
Metabolic acidosis
Diabetes (glycosuric and ketoacidotic states)
Hyperthyroidism
Phosphate depletion
Idiopathic renal wasting
Gitelman syndrome

Fig.10.24 Causes of hypomagnesemia.

Underlying causes are usually GI diseases, in particular malabsorption syndromes such as nontropical sprue (celiac disease) and massive resection of the small intestine. Hypomagnesemia also can be induced by prolonged tube feeding without magnesium supplements and excessive use of non–magnesium-containing laxatives (Fig. 10.24). The widely used proton pump inhibitors can induce a selective impairment in intestinal magnesium absorption.[43]

Hypomagnesemia occurs in 25% to 35% of patients with acute pancreatitis, is frequently observed in chronic alcoholism, and can also occur in poorly controlled diabetes mellitus. Hypomagnesemia may be observed in patients with hypercalcemic disorders and primary aldosteronism, and magnesium deficiency can contribute to the metabolic syndrome.[45]

Excessive urinary loss of magnesium leads to hypomagnesemia and magnesium deficiency, even with normal dietary intake. It may result from the overzealous use of loop and thiazide diuretics, and therefore it is important to monitor plasma Mg^{2+} levels in patients with congestive heart failure who are treated with diuretic agents. Other drugs that may cause hypomagnesemia, as previously described, include gentamicin, cisplatin, cyclosporine, anti EGF receptor monoclonal antibodies and tacrolimus. A rise in blood alcohol level has been associated with renal magnesium wasting, which is one factor contributing to magnesium deficiency in chronic alcoholism.

Several familial diseases are associated with hypermagnesuria, with or without hypomagnesemia. Inactivating mutations of the genes of the Na^+-K^+-$2Cl^-$ cotransporter, rectifying K^+ channel (ROMK), or basolateral Cl^- channel in Bartter syndrome are responsible for the abolition of the driving force for Mg^{2+} reabsorption in the TAL or distal nephron. This results in hypermagnesuria, although not necessarily hypomagnesemia. Activating mutations of the *CaSR* gene, whose protein product is a key regulator of paracellular ion reabsorption in the TAL through extracellular [Ca^{2+}], lead to hypermagnesuria and hypomagnesemia. Mutation of the CLDN16 and CLDN19 genes induces recessive diseases characterized by hypomagnesemia, hypermagnesuria, hypercalciuria, and nephrocalcinosis.

In the distal convoluted tubule, mutations in the *TRPM6* gene induce profound hypomagnesemia from impaired intestinal Mg^{2+} absorption and renal Mg^{2+} wasting, with secondary hypocalcemia.[46] Inactivating mutations of the thiazide-sensitive, electroneutral NaCl cotransporter gene *(NCC)* in Gitelman syndrome are also responsible for selective renal magnesium wasting and hypomagnesemia.

Hypomagnesemia associated with inappropriate magnesuria has been reported in an autosomal-dominant, isolated familial hypomagnesemia syndrome, apparently caused by misrouting of the Na^+,K^+-ATPase γ subunit.

Clinical Manifestations

Specific clinical manifestations of hypomagnesemia may be difficult to appreciate because of concomitant hypocalcemia and hypokalemia. The main clinical manifestations of moderate to severe magnesium depletion include general weakness and neuromuscular hyperexcitability with hyperreflexia, carpopedal spasm, seizure, tremor, and, rarely, tetany. Cardiac findings include a prolonged QT interval and ST depression. There is a predisposition to ventricular arrhythmias and potentiation of digoxin toxicity. The role of magnesium deficiency in the clinical development of seizures and cardiac arrhythmias is demonstrated by the treatment of these conditions with magnesium. In mothers with pregnancy-related hypertension, intravenous magnesium is more effective than phenytoin for preventing eclamptic seizures. In patients with acute myocardial infarction and hypomagnesemia, magnesium repletion reduces the frequency of cardiac arrhythmias.

Magnesium deficiency also can be associated with hypocalcemia (decreased PTH release and end-organ responsiveness) and hypokalemia (urinary loss). In addition, intracellular K^+ is frequently decreased. Magnesium deficit constitutes a cardiovascular risk factor and also a risk factor in pregnancy for the mother and the fetus.

The diagnosis of moderate degrees of magnesium deficiency is not easy because clinical manifestations may be absent and serum Mg^{2+} levels may not reflect the state of body magnesium. Severe magnesium deficits, however, are associated with hypomagnesemia.

Treatment

Magnesium deficiency is managed with the administration of magnesium salts. Magnesium sulfate is generally used for parenteral therapy, 2400 to 4800 mg (480–960 mg elemental Mg) daily. A variety of magnesium salts are available for oral administration, including oxide, hydroxide, sulfate, lactate, chloride, carbonate, and pidolate. Oral magnesium salts often are not well tolerated, at least at high dosage. All may induce GI intolerance, in particular diarrhea.

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SELF-ASSESSMENT QUESTIONS

1. Which is the most common cause of hypercalcemia in patients with chronic kidney disease?
   A. Secondary hyperparathyroidism
   B. Cholecalciferol or ergocalciferol therapy
   C. Malignant neoplasias
   D. Familial hypocalciuric hypercalcemia
   E. Hypomagnesemia
2. Which of the following conditions are *not* associated with hypocalcemia in patients with chronic kidney disease?
   A. Primary hypoparathyroidism
   B. Secondary hyperparathyroidism
   C. Hyperphosphatemia
   D. Vitamin D overload
   E. Treatment by calcium-based phosphate binders
3. All the following factors are involved in the regulation of renal phosphate handling *except:*
   A. Parathyroid hormone
   B. Adrenocorticotropin hormone
   C. Fibroblast growth factor (FGF-23)
   D. Klotho
   E. Growth hormone
4. Based on current evidence, which of the following outcomes is *most likely* to result from untreated hyperparathyroidism in a patient with chronic kidney disease (CKD)?
   A. Premature death
   B. Heart failure
   C. Wrist fractures
   D. Progression to chronic dialysis
   E. Worsening of secondary hyperparathyroidism
5. Which of the following symptoms and signs is *not* induced by hypermagnesemia?
   A. Anemia
   B. Nausea
   C. Muscle weakness
   D. Hypotension
   E. Bradycardia

11

Normal Acid-Base Balance

Biff F. Palmer

DEFINITION

The acid-base status of the body is carefully regulated to maintain arterial pH between 7.35 and 7.45 and intracellular pH between 7.0 and 7.3. This regulation occurs in the setting of continuous production of acidic metabolites and is accomplished by intracellular and extracellular buffering processes with respiratory and renal regulatory mechanisms. This chapter reviews the normal physiology of acid-base homeostasis.

NET ACID PRODUCTION

Both acid and alkali are generated from diet. Lipid and carbohydrate metabolism results in production of carbon dioxide (CO_2), a volatile acid, at the rate of approximately 15,000 mmol/day. Protein metabolism yields amino acids, which can be metabolized to form nonvolatile acid and alkali. Amino acids such as lysine and arginine yield acid on metabolism, whereas the amino acids glutamate and aspartate and organic anions such as acetate and citrate generate alkali. Sulfur-containing amino acids (methionine, cysteine) are metabolized to sulfuric acid (H_2SO_4), and organophosphates are metabolized to phosphoric acid (H_3PO_4). In general, animal foods are high in proteins and organophosphates and provide a net acid diet; plant foods are higher in organic anions and provide a net alkaline load. In addition to acid and alkali generated from diet, there is a small daily production of organic acids, including acetic acid, lactic acid, and pyruvic acid. Also, a small amount of acid is generated by the excretion of alkali into the stool. Under normal circumstances, daily net nonvolatile acid production is approximately 1 millimole (mmol) of hydrogen ions (H^+) per kilogram (kg) of body weight (Fig. 11.1).

BUFFER SYSTEMS IN REGULATION OF PH

Intracellular and extracellular buffer systems minimize the change in pH during the addition of acid or base equivalents but do not remove acid or alkali from the body. The most important buffer system is bicarbonate ion and carbon dioxide (HCO_3^--CO_2). In this system, carbon dioxide concentration [CO_2] is maintained at a constant level set by respiratory control. Addition of acid (HA) leads to conversion of HCO_3^- to CO_2 according to the reaction $HA + NaHCO_3 \rightarrow NaA + H_2O + CO_2$. HCO_3^- is consumed, but [CO_2] does not change because this is maintained by respiration. The net result is that the acid load has been buffered and pH changes are minimal.

Whereas the HCO_3^--CO_2 buffer system is the most important of the buffers in extracellular fluid (ECF), other buffers such as plasma proteins and phosphate ions also participate in the maintenance of a stable pH. During metabolic acidosis, the skeleton becomes a major buffer source as acid-induced dissolution of bone apatite releases alkaline Ca^{2+} salts and HCO_3^- into the ECF. With chronic metabolic acidosis, this can result in osteomalacia and osteoporosis. The calcium released can result in hypercalciuria and an increased likelihood of renal stones. Within the intracellular fluid (ICF) compartment, pH is maintained by intracellular buffers such as hemoglobin, cellular proteins, organophosphate complexes, and HCO_3^- as well as by the H^+-HCO_3^- mechanisms that transport acid and alkali in and out of the cell.

RESPIRATORY SYSTEM IN REGULATION OF PH

Removal of acid or alkali from the body is accomplished by the lungs and kidneys. The lungs regulate CO_2 tension (Pco$_2$), and the kidneys regulate serum bicarbonate concentration, [HCO_3^-]. Although the HCO_3^--CO_2 buffer system is not the only buffer system, all extracellular buffer systems are in equilibrium. Because serum [HCO_3^-] is much greater than that of other buffers, changes in the HCO_3^--CO_2 buffer pair easily titrate other buffer systems and thus set pH. The Henderson-Hasselbalch equation explains how the lungs and kidneys function in concert:

$$\mathrm{pH} = 6.1 + \log \frac{\mathrm{HCO_3^-}}{(0.03 \times \mathrm{Paco_2})}$$

pH is determined by the ratio of HCO_3^- to CO_2. Conditions associated with similar fractional changes in [HCO_3^-] and [CO_2], such as when both are halved, will not change blood pH.

The lungs defend pH by altering alveolar ventilation, which alters the CO_2 excretion rate and thereby controls the arterial CO_2 tension (Paco$_2$) of body fluids. Systemic acidosis stimulates the respiratory center, resulting in increased respiratory drive that lowers the Paco$_2$. As a result, the fall in blood pH is less than would have occurred in the absence of respiratory compensation. If the fractional change in Pco$_2$ were similar to that in serum [HCO_3^-], blood pH would not change. However, respiratory compensation rarely normalizes blood pH, and thus the fractional change in Pco$_2$ is less than the change in serum [HCO_3^-]. Quantitatively, the normal respiratory response in metabolic acidosis is a 1.2 mm Hg decrease in Paco$_2$ for every 1 mmol/l decrease in HCO_3^-; the increase in Paco$_2$ in response to metabolic alkalosis averages 0.7 mm Hg for every 1 mmol/l increase in HCO_3^- above baseline.[1]

RENAL REGULATION OF PH

Buffer systems and respiratory excretion of CO_2 help maintain normal acid-base balance, but the kidneys provide a critical role in acid-base homeostasis. The kidneys normally generate sufficient net acid excretion

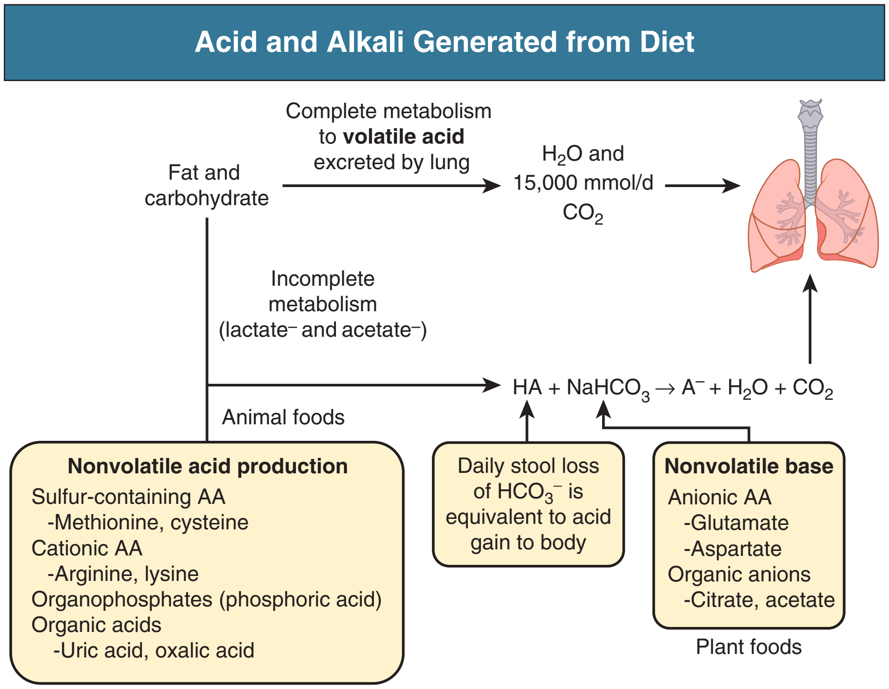
Acid and Alkali Generated from Diet
Fat and carbohydrate
Complete metabolism to **volatile acid** excreted by lung
H_2O and 15,000 mmol/d CO_2
Incomplete metabolism (lactate⁻ and acetate⁻)
$HA + NaHCO_3 \rightarrow A^- + H_2O + CO_2$
Animal foods
Nonvolatile acid production
Sulfur-containing AA
-Methionine, cysteine
Cationic AA
-Arginine, lysine
Organophosphates (phosphoric acid)
Organic acids
-Uric acid, oxalic acid
Daily stool loss of HCO_3^- is equivalent to acid gain to body
Nonvolatile base
Anionic AA
-Glutamate
-Aspartate
Organic anions
-Citrate, acetate
Plant foods

Fig. 11.1 Acid and alkali generated from the diet. A nonvolatile acid is an acid produced from sources other than CO_2 and is not excreted by the lungs. Nonvolatile acids are produced from incomplete metabolism of carbohydrates, fats, and proteins and from metabolism of animal foods. Plant foods tend to produce an alkali load. *AA,* Amino acids.

(NAE) to balance nonvolatile acid produced from normal metabolism. NAE has three components, titratable acids, ammonium (NH_4^+), and bicarbonate, and is calculated by the following formula:

$$\text{NAE} = V\,(U_{\text{Am}} + U_{\text{TA}} - U_{\text{HCO}_3^-})$$

where $U_{Am}V$ is the rate of NH_4^+ excretion, $U_{TA}V$ is the rate of titratable acid excretion, and $U_{HCO3^-}V$ is the rate of HCO_3^- excretion. Under basal conditions, approximately 40% of NAE is in the form of titratable acids and 60% is in the form of ammonia (NH_3); urinary bicarbonate concentrations and excretion are essentially zero under normal conditions.

Titratable acidity refers to weak acids filtered at the glomerulus that can act as buffers in the urine. These buffers are referred to as titratable because they are measured by determining the amount of alkali required to titrate the urine back to a pH of 7.4. To serve as a titratable buffer, a buffer must have a pK_a near the range of tubular fluid pH. The most important titratable buffer is phosphate ($HPO_4^{2-} \leftrightarrow H_2PO_4^-$) because it has a favorable pK_a of 6.80 and there is a relatively high rate of urinary excretion. However, when acid production increases, the increase in acid excretion is almost entirely caused by an increase in excretion of NH_4^+ because the ability to increase urinary phosphate is limited.

RENAL TRANSPORT MECHANISMS OF HYDROGEN AND BICARBONATE IONS

Glomerulus

The glomerulus is not normally considered as participating in acid-base regulation. However, the glomerulus filters an amount of HCO_3^- equivalent to serum [HCO_3^-] multiplied by the glomerular filtration rate (GFR). Under normal circumstances, the filtered load of HCO_3^- averages approximately 4000 mmol/day. Normal acid-base homeostasis requires both the reabsorption of this filtered bicarbonate and the generation of "new" bicarbonate; the latter replenishes bicarbonate and other alkaline buffers consumed in the process of titrating endogenous acid production. From the standpoint of prevention or correction of acidosis, GFR is not regulated by alterations in acid or base and therefore does not contribute to acid-base homeostasis.

Proximal Tubule

The proximal tubule reabsorbs approximately 80% of the filtered load of HCO_3^-. In addition, by titration of luminal pH from 7.4 down to approximately 6.7, the majority of phosphate, the major form of titratable acid, is titrated to its acid form. Finally, ammonia synthesis occurs in the proximal tubule.

Fig. 11.2 shows the acid-base transport mechanisms of the proximal tubule cell. HCO_3^- absorption from the tubular lumen is mediated by H^+ secretion across the membrane.[2] This H^+ secretion is active in that the electrochemical gradient favors H^+ movement from lumen to cell. Two mechanisms mediate active apical H^+ secretion. Approximately two thirds occurs through the apical membrane Na^+-H^+ antiporter NHE3.[3] This protein uses the inward Na^+ gradient to drive H^+ secretion. The Na^+-H^+ exchanger has a 1 : 1 stoichiometry and is electroneutral. In parallel with the Na^+-H^+ antiporter, there is an apical membrane H^+-ATPase that mediates approximately one third of basal proximal tubular HCO_3^- absorption.

Both these H^+ transporters generate base in the cell, which must exit across the basolateral membrane to effect transepithelial transport. This primarily occurs through a basolateral Na^+-HCO_3^--CO_3^{2-} cotransporter.[4] Because this protein transports the equivalent of two net negative charges, the negative cell voltage generated by the basolateral Na^+,K^+-ATPase provides a strong favorable driving force for base efflux. The Na^+ carried on this transporter is moved out of the cell without requiring ATP. The Na^+-$3HCO_3^-$ cotransporter NBCe1, encoded by the gene *SLC4A4,* mediates most of the exit of base from the proximal tubule.[5]

Carbonic anhydrase II is present in the proximal tubular cell cytoplasm, and carbonic anhydrase IV is on the apical and basolateral

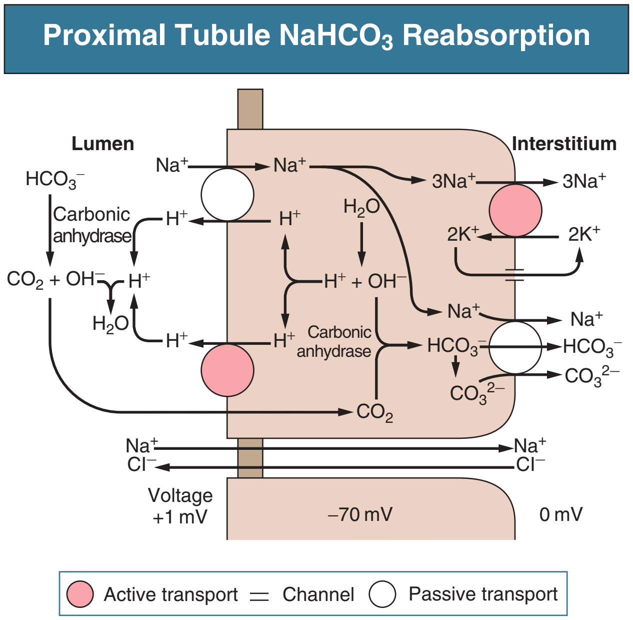

Fig. 11.2 Proximal tubule sodium bicarbonate ($NaHCO_3$) reabsorption. The secretion of H^+ into the proximal tubule lumen involves a Na^+-H^+ antiporter and an H^+-ATPase. Apical membrane H^+ secretion generates OH^-, which reacts with CO_2 to form HCO_3^- and CO_3^{2-}, and these exit with a Na^+ on the basolateral membrane Na^+-HCO_3^--CO_3^{2-} cotransporter. The Na^+ absorbed by the Na^+-H^+ antiporter exits the cell on the basolateral membrane Na^+,K^+-ATPase and the Na^+-HCO_3^--CO_3^{2-} cotransporter. The K^+ that enters the cell on the Na^+,K^+-ATPase exits on a basolateral membrane K^+ channel. Carbonic anhydrase catalyzes the conversion of HCO_3^- to CO_2 and OH^- in the lumen and the reverse reaction in the cell. Electrogenic H^+ secretion generates a small, lumen-positive voltage that generates a current flow across the paracellular pathway.

membranes. Carbonic anhydrase (carbonate dehydratase) has a number of functions in the proximal tubule. Apical membrane carbonic anhydrase allows secreted H^+ ions to react with luminal HCO_3^-, forming H_2CO_3, which rapidly dissociates to $CO_2 + H_2O$. This CO_2 diffuses across the apical plasma membrane into the cell. There the process is reversed, with use of cytoplasmic carbonic anhydrase, generating intracellular H^+ and HCO_3^-. This H^+ “replenishes” the H^+ secreted across the apical membrane, resulting in net movement of the HCO_3^- from the luminal solution to the cell cytoplasm. The intracellular HCO_3^- is then secreted across the basolateral plasma membrane, as described previously.

Thick Ascending Limb of the Loop of Henle

Tubular fluid arriving at the early distal tubule has a pH and serum [HCO_3^-] similar to that in the late proximal tubule. Because there is significant water extraction in the loop of Henle, maintenance of a constant serum HCO_3^- concentration requires reabsorption of HCO_3^-. The majority of this HCO_3^- absorption occurs in the thick ascending limb (TAL) through mechanisms similar to those present in the proximal tubule (Fig. 11.3). The majority of apical membrane H^+ secretion is mediated by the Na^+-H^+ antiporter NHE3. As in the proximal tubule, the low intracellular Na^+ concentration maintained by the basolateral Na^+,K^+-ATPase provides the primary driving force for the antiporter. Base efflux across the basolateral membrane is mediated by a Cl^--HCO_3^- exchanger (AE2) and K^+-HCO_3^- cotransport likely mediated by the K^+-Cl^- cotransporter KCC4.[6] These cells also possess an H^+-ATPase. The contribution of this pump to overall acidification in this segment is not clear.

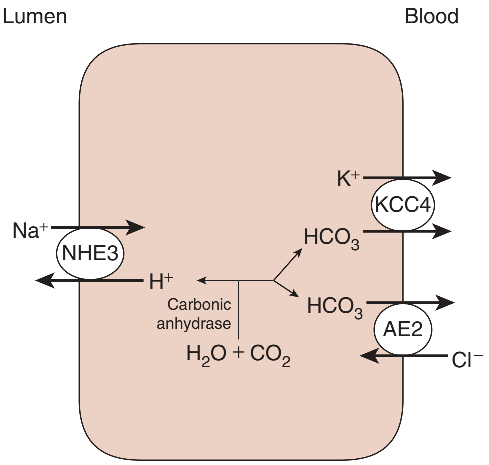

Fig. 11.3 Hydrogen (H^+) and bicarbonate (HCO_3^-) ion transport in thick ascending limb. Apical H^+ secretion is mediated by a Na^+-H^+ antiporter. The low intracellular Na^+ concentration, maintained by the basolateral Na^+,K^+-ATPase, provides the primary driving force for the antiporter. Both Cl^--HCO_3^- exchange and K^+-HCO_3^- cotransport mediate base exit across the basolateral membrane.

Distal Nephron

Approximately 80% of the filtered HCO_3^- is reabsorbed in the proximal tubule; most but not all of the remainder is absorbed in the TAL. One function of the distal nephron is to reabsorb the remaining 5% of filtered HCO_3^-. In addition, the distal nephron must secrete a quantity of H^+ equal to that generated systemically by metabolism to maintain acid-base balance.

The distal nephron is subdivided into several distinct portions that differ in their anatomy and acid secretory properties. Most of these segments transport H^+ and HCO_3^- into the luminal fluid, but the main segments appear to be in the collecting duct.[9] The segments of the collecting duct include the cortical collecting duct (CCD), the outer medullary collecting duct, and the inner medullary collecting duct. There are two distinct cell types in the CCD that can be distinguished histologically: the principal cell and the intercalated (IC) cell. The principal cell reabsorbs Na^+ and secretes K^+ and is discussed later. Depending on chronic acid-base status, the CCD is capable of either H^+ or HCO_3^- secretion. These functions are mediated by two types of IC cells: the acid-secreting α-IC cell and the base-secreting β-IC cell. Both IC cell types are rich in carbonic anhydrase II.

Reabsorption of HCO_3^- in the distal nephron is mediated by apical H^+ secretion by the α-IC cell. Two transporters secrete H^+: a vacuolar H^+-ATPase and an H^+-K^+-ATPase (Fig. 11.4). The vacuolar H^+-ATPase is an electrogenic pump related to the H^+ pump present within lysosomes, the Golgi apparatus, and endosomes. The H^+-K^+-ATPase uses the energy derived from adenosine triphosphate hydrolysis to secrete H^+ into the lumen and to reabsorb K^+ in an electroneutral fashion. The activity of the H^+-K^+-ATPase increases in K^+ depletion and thus provides a mechanism by which K^+ depletion enhances both collecting duct H^+ secretion and K^+ absorption.[7]

Active H^+ secretion by the apical membrane generates intracellular base that must exit the basolateral membrane. A basolateral Cl^--HCO_3^- exchanger (AE1) is the mechanism by which this base exit occurs. The Cl^- that enters the cell in exchange for HCO_3^- exits the cell through a basolateral membrane Cl^- conductance channel (see Fig. 11.4).

The HCO_3^--secreting β-IC cell is a mirror image of the α-IC cell (Fig. 11.5). It possesses an H^+-ATPase on the basolateral membrane, which mediates active H^+ extrusion. Alkali that is generated within the

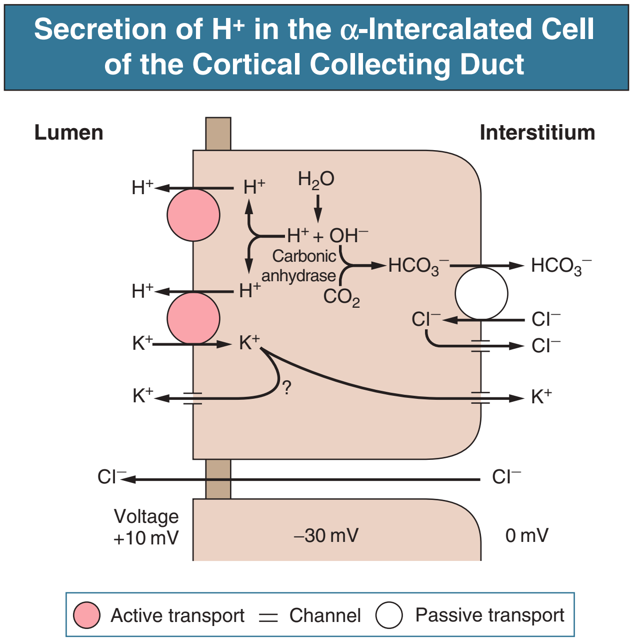
Secretion of H^+ in the α-Intercalated Cell of the Cortical Collecting Duct
Lumen
Interstitium
H^+
H^+
H_2O
$H^+ + OH^-$
Carbonic anhydrase
HCO_3^-
HCO_3^-
H^+
H^+
CO_2
Cl^-
Cl^-
Cl^-
K^+
K^+
K^+
?
K^+
Cl^-
Cl^-
Voltage +10 mV
−30 mV
0 mV
● Active transport = Channel ○ Passive transport

Fig. 11.4 H^+ secretion in cortical collecting duct α-intercalated cell. Secretion of hydrogen ions into the lumen by an H^+-ATPase and an H^+-K^+-ATPase. Apical membrane H^+ secretion generates OH^-, which reacts with CO_2 to form HCO_3^-. This bicarbonate exits across the basolateral membrane on a Cl^--HCO_3^- exchanger, a member of the anion exchanger-1 (AE1) family and a truncated form of the red blood cell AE1 Cl^--HCO_3^- exchanger. The Cl^- that enters the cell on the exchanger recycles across a basolateral membrane Cl^- channel. The K^+ that enters the cell on the H^+-K^+-ATPase appears to be able either to recycle across the apical membrane or exit across the basolateral membrane, depending on the potassium balance of the individual. Carbonic anhydrase catalyzes the conversion of CO_2 and OH^- to HCO_3^- in the cell. Electrogenic H^+ secretion generates a lumen-positive voltage that generates a current flow across the paracellular pathway.

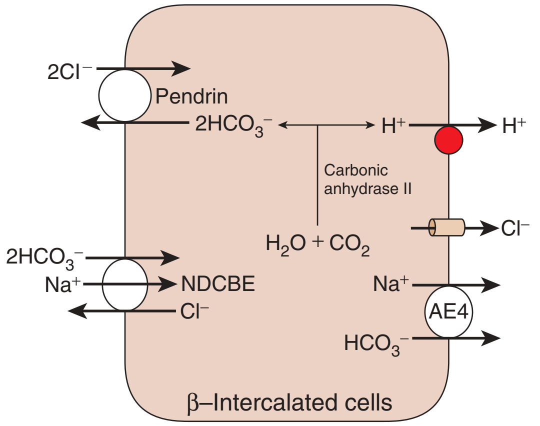
$2Cl^-$
Pendrin
$2HCO_3^-$
H^+
H^+
Carbonic anhydrase II
Cl^-
$H_2O + CO_2$
$2HCO_3^-$
Na^+
NDCBE
Cl^-
Na^+
AE4
HCO_3^-
β–Intercalated cells

Fig. 11.5 Bicarbonate secretion by cortical collecting duct β-intercalated cell. H^+ is secreted into the interstitium by an H^+-ATPase. The OH^- generated by basolateral membrane H^+ secretion reacts with CO_2 to form HCO_3^-, which exits across the apical membrane on a Cl^--HCO_3^- exchanger (pendrin). The Cl^- that enters the cell on the exchanger exits across a basolateral membrane Cl^- channel. Carbonic anhydrase catalyzes the conversion of CO_2 and OH^- to HCO_3^- in the cell. The Na^+-driven Cl^--HCO_3^- exchanger (NDCBE) colocalizes with pendrin on the apical membrane and mediates thiazide-sensitive electroneutral NaCl reabsorption in this segment.

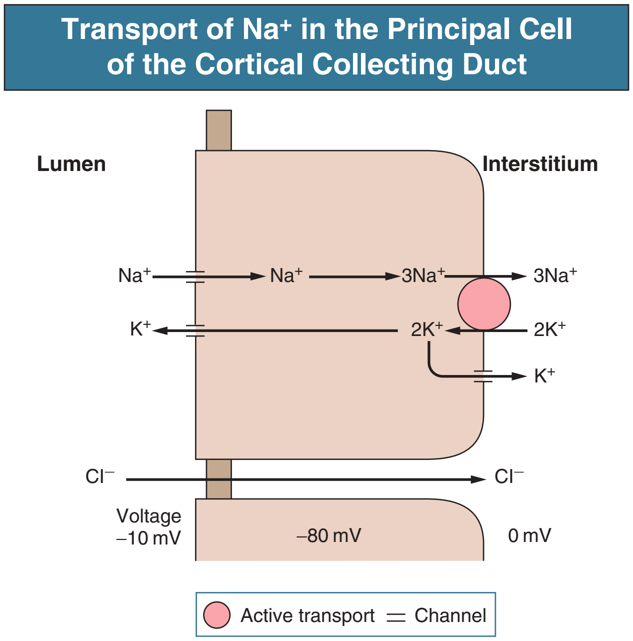
Transport of Na^+ in the Principal Cell of the Cortical Collecting Duct
Lumen
Interstitium
Na^+
Na^+
$3Na^+$
$3Na^+$
K^+
$2K^+$
$2K^+$
K^+
Cl^-
Cl^-
Voltage −10 mV
−80 mV
0 mV
● Active transport = Channel

Fig. 11.6 Sodium transport in cortical collecting duct principal cell. Electrogenic Na^+ absorption is mediated by the Na^+ channel. The Na^+ enters the cell across the apical membrane channel and exits the cell on the basolateral membrane Na^+,K^+-ATPase. The K^+ that enters the cell on the basolateral Na^+,K^+-ATPase can be secreted into the luminal fluid by an apical membrane K^+ channel. Electrogenic Na^+ absorption establishes a lumen-negative voltage that drives a paracellular current.

cell then exits on an apical membrane Cl^--HCO_3^- exchanger. This Cl^--HCO_3^- exchanger is distinct from the basolateral Cl^--HCO_3^- exchanger present in the α-IC cell and functions as an anion exchanger or Cl^- channel in the luminal membrane of epithelial cells.[10] The SLC26A4 protein (pendrin) is a family member that mediates apical Cl^--HCO_3^- exchange in the β-IC cell of the kidney. The Na^+-driven Cl^--HCO_3^- exchanger (NDCBE) colocalizes with pendrin on the apical membrane and together may explain a component of electroneutral NaCl reabsorption in the collecting duct that is thiazide sensitive.[8]

The other cortical collecting tubule cell type is the principal cell, which also regulates acid-base transport, although indirectly. Principal cells mediate electrogenic Na^+ reabsorption that results in a net negative luminal charge (Fig. 11.6). The greater this negative charge, the lesser is the electrochemical gradient for electrogenic proton secretion and therefore the greater the rate of net proton secretion. Thus factors that stimulate Na^+ reabsorption indirectly regulate the H^+ secretory rate.

The medullary collecting duct possesses mechanisms only for H^+ secretion. This H^+ secretion is mediated by α-IC cells but also by cells that appear morphologically distinct from IC cells but are functionally similar.

Net Acid Excretion

For the kidney to generate NAE, it must both reabsorb filtered HCO_3^- and excrete titratable acids and ammonia. Several weak acids, such as phosphate, creatinine, and uric acid, are filtered at the glomerulus and can buffer secreted protons. Of these, phosphate is the most important because of its favorable pK_a of 6.80 and its relatively high rate of urinary excretion (~25 to 30 mmol/day). However, the capacity of phosphate to buffer protons is maximized at a urine pH of 5.8, and acid-base disturbances generally do not induce substantial changes in urinary phosphate excretion. Other titratable acids, such as creatinine and uric acid, are limited by their lower excretion rate, which is not dramatically

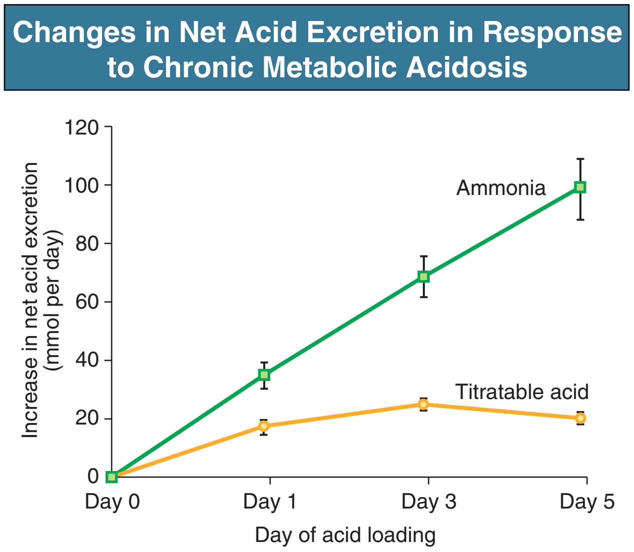

Fig. 11.7 Changes in net acid excretion. Chronic metabolic acidosis increases net acid excretion dramatically over several days; shown quantitatively are the increases in the two major components of net acid excretion, titratable acids and ammonia. Titratable acid excretion increases slightly and predominantly in the first 24 to 48 hours. In contrast, urinary ammonia excretion progressively increases over 7 days and is responsible for most of the increase in net acid excretion in chronic metabolic acidosis. (Plotted data redrawn from original data in reference 14.)

changed in response to acid-base disturbances. Titratable acid excretion is a minor component of the increase in NAE in response to metabolic acidosis (Fig. 11.7).

Ammonia Metabolism

Quantitatively, the most important component of NAE is the NH_3/NH_4^+ system.[11] Unlike for titratable acids, the rate of ammonia (NH_3) production and excretion varies according to physiologic needs. Under normal circumstances, ammonia excretion accounts for approximately 60% of total NAE, and in chronic metabolic acidosis, almost the entire increase in NAE is caused by increased NH_3 metabolism. Ammonia metabolism involves interplay among the proximal tubule, TAL, and collecting duct.

The proximal tubule is responsible for both ammonia production and luminal secretion. Ammonia is synthesized in the proximal tubule predominantly from glutamine metabolism through enzymatic processes in which phosphoenolpyruvate carboxykinase and phosphate-dependent glutaminase are the rate-limiting steps. This results in production of two ammonium (NH_4^+) and two HCO_3^- ions from each glutamine ion. Ammonia is then preferentially secreted into the lumen. The primary mechanism for this luminal secretion appears to be NH_4^+ transport by the apical Na^+-H^+ antiporter NHE3 (Fig. 11.8).

Metabolic acidosis increases the mobilization of glutamine from skeletal muscle and intestinal cells. Glutamine is preferentially taken up by the proximal tubular cell through the Na^+- and H^+-dependent glutamine transporter SNAT3. This transporter is a member of the *SCL38* gene family of Na^+-coupled neutral amino acid transporters. SNAT3 expression increases several-fold in metabolic acidosis, and it is preferentially expressed on the cell's basolateral surface, where it is poised for glutamine uptake.[12] The increase in plasma cortisol that typically accompanies metabolic acidosis plays a role in this transporter's upregulation.[13] Metabolic acidosis also causes increased expression and activity of phosphate-activated glutaminase and glutamate dehydrogenase.

Most of the ammonia that leaves the proximal tubule does not reach the distal tubule. Thus there is transport of ammonia out of the loop of Henle. This ammonia transport appears to occur predominantly in the TAL and is mediated by at least three mechanisms (Fig. 11.9). First, the lumen-positive voltage provides a driving force for passive paracellular NH_4^+ transport out of the TAL. Second, NH_4^+ can be transported out of the lumen by the furosemide-sensitive Na^+-K^+-$2Cl^-$ transporter. Third, NH_4^+ can leave the lumen across the apical membrane K^+ channel of the TAL cell. NH_4^+ exits the cell via the Na^+-H^+ exchanger NHE4, functioning in Na^+-NH_4^+ mode.

In addition, ammonia is secreted by the collecting duct. Although the traditional thought was that NH_3/NH_4^+ then enters the collecting duct by nonionic diffusion driven by the acid luminal pH, increasing evidence suggests that the nonerythroid glycoproteins Rhbg and Rhcg may be involved in collecting duct ammonia secretion.[15,16]

On the basis of the preceding discussion, it can be shown that ammonia excretion can be regulated by three mechanisms. First, ammonia synthesis in the proximal tubule can be regulated. Chronic acidosis and hypokalemia increase ammonia synthesis, whereas hyperkalemia suppresses ammonia synthesis. Second, ammonia delivery from the proximal tubule to the medullary interstitium can be regulated. In particular, chronic metabolic acidosis increases expression of both NHE3 and the loop of Henle Na^+-K^+-$2Cl^-$ cotransporter. Hyperkalemia can inhibit NH_4^+ reabsorption from the TAL. The combined effects of decreased NH_3 synthesis in the proximal tubule and interference in NH_4^+ reabsorption in the thick limb may explain the low urinary $[NH_4^+]$ found in hyperkalemic distal renal tubular acidosis. The reduced availability of ammonia to serve as a urinary buffer leads to a reduction in distal H^+ secretion and development of metabolic acidosis. Also, any interstitial renal disease that destroys renal medullary anatomy may decrease medullary interstitial $[NH_3/NH_4^+]$ transfer. Third, mechanisms that regulate collecting duct H^+ secretion or ammonia transporter expression can regulate ammonia entry into the collecting duct and ammonia excretion. Importantly, the primary mechanisms require synthesis of new proteins to increase both ammonia production and transport. Accordingly, changes in ammonia excretion may be delayed, and the maximal renal response to chronic metabolic acidosis requires 4 to 7 days.

REGULATION OF RENAL ACIDIFICATION

The regulation of acid-base balance requires an integrated system that precisely regulates proximal tubular H^+-HCO_3^- transport, distal nephron H^+-HCO_3^- transport, and ammonia synthesis and transport.

Blood pH

The regulation of acid-base balance requires that net H^+ excretion increase in states of acidosis and decrease in states of alkalosis. This form of regulation involves both acute and chronic mechanisms. In the proximal tubule, acute decreases in blood pH increase the rate of HCO_3^- absorption, and acute increases in blood pH inhibit HCO_3^- absorption. These alterations in the rate of HCO_3^- absorption occur whether the change in pH is the result of changes in $Pa{CO_2}$ or serum $[HCO_3^-]$. Similarly, in the collecting duct, acute changes in peritubular serum $[HCO_3^-]$ and pH regulate the rate of H^+ secretion.

In addition to acute regulation, mechanisms exist for chronic regulation. Chronic acidosis or alkalosis leads to parallel changes in the activities of the proximal tubule apical membrane Na^+-H^+ antiporter and basolateral membrane Na^+-HCO_3^--CO_3^{2-} cotransporter. Metabolic acidosis acutely increases the kinetic activity of NHE3 through direct pH effects and by phosphorylation; chronic acidosis increases the number of NHE3 transporters.[17,18] In addition, chronic acidosis increases proximal

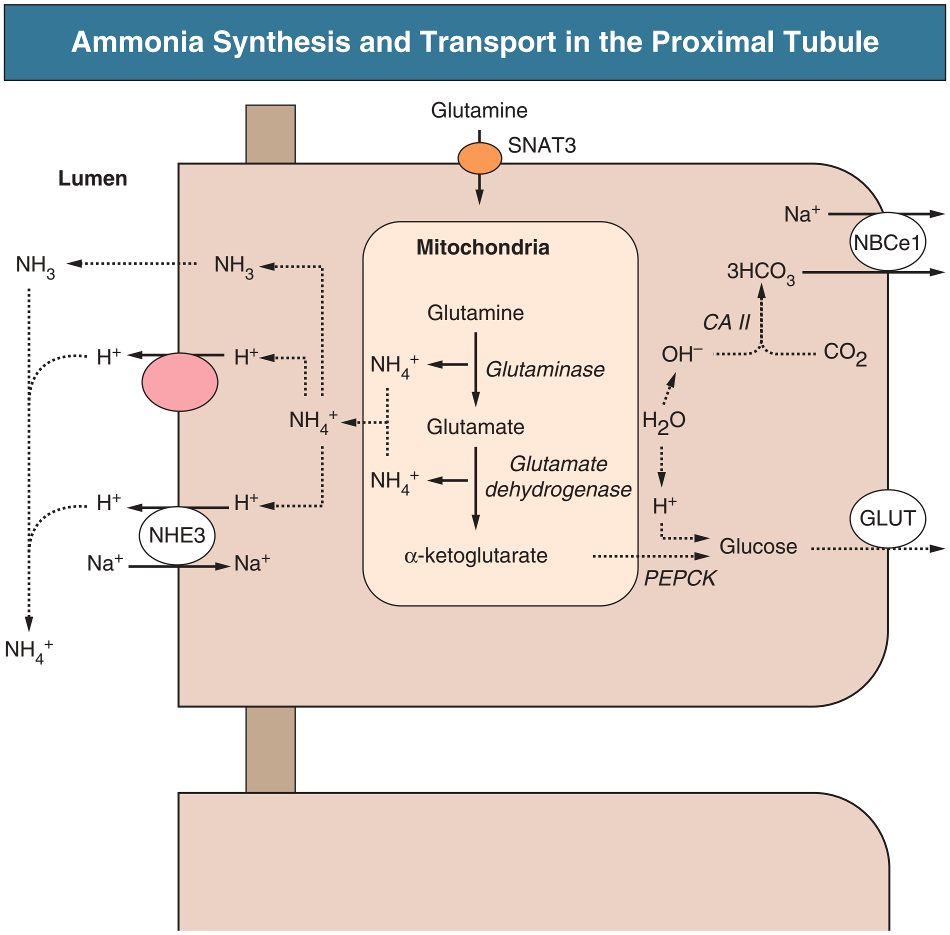
Ammonia Synthesis and Transport in the Proximal Tubule
Glutamine
SNAT3
Lumen
Mitochondria
NH_3
NH_3
H^+
H^+
NH_4^+
H^+
H^+
NHE3
Na^+
Na^+
NH_4^+
Glutamine
NH_4^+
Glutaminase
Glutamate
NH_4^+
Glutamate dehydrogenase
α-ketoglutarate
Na^+
NBCe1
$3HCO_3$
CA II
OH^-
CO_2
H_2O
H^+
GLUT
Glucose
PEPCK

Fig. 11.8 **Ammonia synthesis and transport in proximal tubule.** Metabolic acidosis and hypokalemia stimulate proximal ammonia synthesis by stimulating the uptake of glutamine through SNAT3.The generation of ammonia is the result of glutamine metabolism by enzymes closely linked to gluconeogenesis.

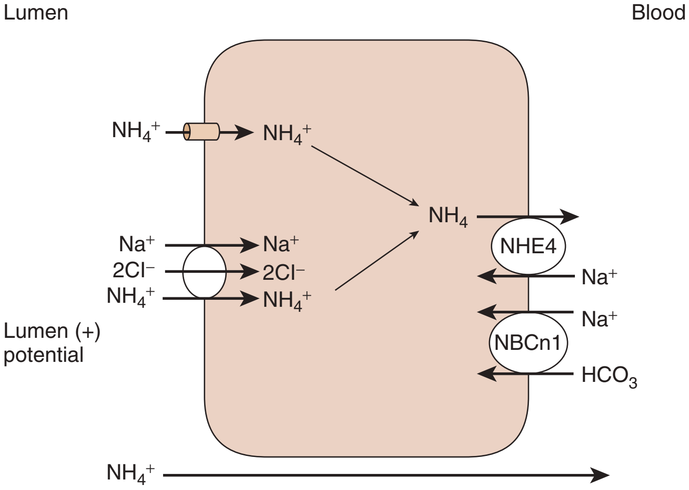
Lumen
Blood
NH_4^+
NH_4^+
NH_4
Na^+
$2Cl^-$
NH_4^+
Na^+
$2Cl^-$
NH_4^+
NHE4
Na^+
Na^+
NBCn1
HCO_3
Lumen (+) potential
NH_4^+

Fig. 11.9 **Ammonia transport in thick ascending limb of Henle loop.** In addition to reabsorption through the paracellular pathway driven by the lumen-positive potential, ammonium can substitute for K^+ on the Na^+-K^+-$2Cl^-$ transporter and the apical membrane K^+ channel (ROMK). NH_4^+ exits the cell via the Na^+-H^+ exchanger NHE4. The basolateral Na^+-HCO_3^- cotransporter (NBCn1) is thought to play a housekeeping role to maintain cell pH given the large transcellular ammonium flux.

tubular ammonia synthesis by increasing the activities of the enzymes involved in ammonia metabolism.

The CCD is also modified by chronic acid-base changes. Long-term increases in dietary acid lead to an increase in H^+ secretion, whereas long-term increases in dietary alkali lead to an increased capacity for HCO_3^- secretion.[19] This effect is mediated by changes in the relative number of α- and β-IC cells. For example, during metabolic acidosis the number of α-IC cells increases and the number of β-IC cells decreases, without a change in the total number of IC cells. Recent evidence suggests that the extracellular protein hensin may be involved in the switch between the predominant IC cell types.[20]

Mineralocorticoids, Distal Sodium Delivery, and Extracellular Fluid Volume

Mineralocorticoid hormones are key regulators of distal nephron and collecting duct H^+ secretion. Two mechanisms appear to be involved. First, mineralocorticoid hormone stimulates Na^+ absorption in principal cells of the CCD (see Fig. 11.6). This leads to a more lumen-negative voltage that then stimulates H^+ secretion. This mechanism is indirect in that it requires the presence of Na^+ and of Na^+ transport. The second mechanism is the direct activation of H^+ secretion by mineralocorticoids. This effect is chronic, requiring long exposure, and involves parallel increases in apical membrane H^+-ATPase and basolateral membrane Cl^--HCO_3^- exchanger activity.

Plasma Volume

Changes in plasma volume have important effects on acid-base homeostasis. This effect appears to be related to a number of factors. First, volume contraction is associated with a decreased GFR, which lowers the filtered load of HCO_3^- and decreases the load placed on the tubules, to maintain NAE. Volume contraction also acutely decreases the paracellular permeability of the proximal tubule. This will decrease HCO_3^- backleak around cells, thereby increasing net bicarbonate reabsorption by the proximal tubule. Third, chronic volume contraction is associated with an adaptive increase in the activity of the proximal tubule apical membrane Na^+-H^+ antiporter NHE3. Because this transporter contributes to both $NaHCO_3$ and NaCl absorption, both these capacities will be increased with chronic volume contraction. Further, volume contraction limits distal delivery of chloride. In the presence of chronic metabolic alkalosis, the CCD is poised for HCO_3^- secretion. However, collecting duct HCO_3^- secretion requires luminal Cl^- and is inhibited by Cl^- deficiency.

Potassium

Potassium deficiency is associated with an increase in renal NAE. This effect is multifactorial. First, chronic K^+ deficiency increases the proximal tubule apical membrane Na^+-H^+ antiporter and basolateral membrane Na^+-HCO_3^--CO_3^{2-} cotransporter activities. This effect is similar to that seen with chronic acidosis and may be caused by intracellular acidosis. Chronic K^+ deficiency also increases proximal tubular ammonia production. Finally, chronic K^+ deficiency leads to an increase in collecting duct H^+ secretion. This appears to be related to increased activity of the apical membrane H^+-K^+-ATPase. Such an effect increases the rate of H^+ secretion and the rate of K^+ reabsorption in the collecting duct. In addition, ammonia, whose production is stimulated by hypokalemia, has direct effects that stimulate collecting duct H^+ secretion. Counterbalancing these effects is that K^+ deficiency decreases aldosterone secretion, which can inhibit distal acidification. Thus, in normal individuals, the net effect of K^+ deficiency is typically a minor change in acid-base balance. However, in patients with nonsuppressible mineralocorticoid secretion (e.g., hyperaldosteronism, Cushing syndrome), K^+ deficiency can greatly stimulate renal acidification and cause profound metabolic alkalosis.

Hyperkalemia appears to have opposite effects on renal acidification. The most notable effect of hyperkalemia is inhibition of ammonia synthesis in the proximal tubule and ammonia absorption in the loop of Henle, resulting in inappropriately low levels of urinary ammonia excretion. This contributes to the metabolic acidosis seen in patients with hyperkalemic distal (type 4) renal tubular acidosis.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is *true* in regard to the effect of chronic K^+ deficiency on renal acidification?
   - **A.** Decreases basolateral membrane Na^+-HCO_3^--CO_3^{2-} cotransporter activity
   - **B.** Increases proximal tubular ammonia production
   - **C.** Decreases collecting duct H^+ secretion
   - **D.** Increases aldosterone secretion
2. Which one of the following is *true* with regard to ammonia handling in the kidney?
   - **A.** Ammonia synthesized in the proximal tubule is primarily reabsorbed in the cortical collecting duct.
   - **B.** Ammonia is reabsorbed passively in the thick ascending limb driven by the lumen-negative voltage.
   - **C.** NH_4^+ is transported into the lumen of the thick ascending limb by the Na^+-K^+-Cl^- transporter
   - **D.** Nonthyroid glycoproteins Rhbg and Rhcg are involved in collecting duct ammonia secretion.
3. Which of the following is *true* in regard to net acid production by the kidney?
   - **A.** Sulfur-containing amino acids are metabolized to CO_2.
   - **B.** Metabolism of lysine and arginine yield base on metabolism.
   - **C.** Animal foods are high in protein and organophosphates and provide a net acid diet.
   - **D.** Daily volatile acid production is approximately 1 mmol H^+.

12

Metabolic Acidosis

Biff F. Palmer

DEFINITION

Metabolic acidosis is defined as a low arterial blood pH in conjunction with a reduced serum bicarbonate concentration [HCO_3^-]. Respiratory compensation results in a decrease in arterial carbon dioxide tension ($Paco_2$). A low serum [HCO_3^-] alone is not diagnostic of metabolic acidosis because it also results from the renal compensation to chronic respiratory alkalosis. Measurement of the arterial pH differentiates between these two possibilities. Box 12.1 shows the expected compensatory responses for metabolic and respiratory acid-base disorders.[1]

After the diagnosis of metabolic acidosis is confirmed, the first step in the examination of the patient is to calculate the serum anion gap. The *anion gap* equals the difference between the serum concentrations of the major cation sodium ([Na^+]) and the major measured anions chloride and bicarbonate ([Cl^-] and [HCO_3^-]) and is given by the following formula:

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

In healthy individuals, the normal value of the anion gap is approximately 12 ± 2 mmol/l. Because many of the unmeasured anions consist of albumin, the normal anion gap is decreased by approximately 2.5 mmol/l for each 1 g/dl decrease in the serum albumin concentration below normal. The total number of cations must equal the total number of anions, so a decrease in the serum HCO_3^- concentration must be offset by an increase in the concentration of other anions. If the anion accompanying excess H^+ is Cl^-, the decrease in serum [HCO_3^-] is matched by an equal increase in serum [Cl^-]. This acidosis is classified as a "normal anion gap" or a "non–anion gap" or a hyperchloremic metabolic acidosis. By contrast, if excess H^+ is accompanied by an anion other than Cl^-, the decreased [HCO_3^-] is balanced by an increase in the concentration of the unmeasured anion. [Cl^-] remains the same. In this setting, the acidosis is said to be a "high anion gap" or "anion gap" metabolic acidosis.

The normal value for the anion gap has tended to fall over time because of changes in how serum Na^+ and Cl^- are measured.[2] Flame photometry for Na^+ measurement and a colorimetric assay for Cl^- have been replaced by the use of ion-selective electrodes, with which the serum Na^+ values have largely remained the same, whereas the serum Cl^- values have tended to be higher. As a result, the normal value for the anion gap has decreased to as low as 6 mmol/l in some reports. Recognizing this change, some laboratories have adjusted the calibration set point for Cl^- to return the normal value for the anion gap to the 12 ± 2 mmol/l range. The clinician needs to be aware that the average anion gap and range of normal values will vary across different facilities.

Fig. 12.1 provides a recommended approach to a patient with metabolic acidosis and lists the common causes of metabolic acidosis according to the anion gap.

NON–ANION GAP (NORMAL ANION GAP) METABOLIC ACIDOSIS

A non–anion gap metabolic acidosis can result from either renal or extrarenal causes. Renal causes of metabolic acidosis occur when renal bicarbonate generation, which results from net acid excretion, does not balance the loss of bicarbonate and other alkali buffers consumed in the buffering of normal endogenous acid production. This failure of net acid excretion is termed *renal tubular acidosis* (RTA). Extrarenal causes occur when exogenous acid loads, endogenous acid production, or endogenous bicarbonate losses are elevated and exceed renal net acid excretion. The most common extrarenal cause of non–anion gap metabolic acidosis is chronic diarrhea.

Renal and extrarenal causes of metabolic acidosis can be distinguished by measuring urinary ammonia excretion.[3] The primary response of the kidney to metabolic acidosis is to increase urinary ammonia excretion, each millimole of urinary ammonia excreted resulting in the generation of 1 mmol of "new" bicarbonate. Thus renal causes of metabolic acidosis are characterized by low urinary ammonia excretion rates. In contrast, in extrarenal metabolic acidosis, urinary ammonia excretion is elevated. Because most laboratories do not measure urinary ammonia, one can indirectly assess ammonia excretion by measuring the *urinary anion gap* (UAG):

$$UAG = (U_{Na^+} + U_{K^+}) - U_{Cl^-}$$

The UAG is normally a positive value, ranging from +30 to +50 mmol/l. A negative value for the UAG suggests increased renal excretion of an unmeasured cation (i.e., cation other than Na^+ or K^+). One such cation is NH_4^+. With chronic metabolic acidosis because of extrarenal causes, urinary ammonia concentrations, in the form of NH_4Cl, can reach 200 to 300 mmol/l. As a result, the measured cation concentration will be less than the measured anion concentration, which includes the increased urinary Cl^-, and the UAG will be less than zero and frequently less than −20 mmol/l.

The UAG only indirectly reflects the urinary ammonia concentration and, if other unmeasured ions are excreted, can give misleading results. Examples include diabetic ketoacidosis, associated with substantial urinary excretion of sodium ketoacid salts, and toluene exposure (discussed later), associated with increased urinary excretion of sodium hippurate and sodium benzoate. In these settings, the UAG value may remain positive despite an appropriate increase in urinary ammonia

BOX 12.1 Expected Compensatory Responses to Acid-Base Disorders

Acute respiratory acidosis

For every 10 mm Hg rise in P_{CO_2}, HCO_3^- increases by 1 mmol/l

Chronic respiratory acidosis

For every 10 mm Hg rise in P_{CO_2}, HCO_3^- increases by 3.5 mmol/l

Acute respiratory alkalosis

For every 10 mm Hg fall in P_{CO_2}, HCO_3^- decreases by 2 mmol/l

Chronic respiratory alkalosis

For every 10 mm Hg decrease in P_{CO_2}, HCO_3^- decreases by 5 mmol/l

Metabolic acidosis

1.2 mm Hg decrease in P_{CO_2} for each 1 mmol/l fall in HCO_3^-

$P_{CO_2} = HCO_3^- + 15$

P_{CO_2} = Last digits of pH

Metabolic alkalosis

P_{CO_2} increases by 0.7 for each mmol/l HCO_3^-

excretion because of the increased urinary excretion of Na^+ acid-anion salts. A similar situation occurs when urinary NH_4^+ is excreted with an anion other than Cl^-, such as β-hydroxybutyrate, acetoacetate, bicarbonate, or hippurate. In these settings, and even when NH_4^+ is excreted with Cl^{-}, the urine osmolal gap (UOG) can be used as a surrogate for NH_4^+ concentration. The UOG is the difference between the measured and the calculated urine osmolality.

$$\begin{aligned} \text{UOG} &= \text{Calculated urine osmolality (mOsmol/kg)} \\ &= (2\times[\text{Na}^+ + \text{K}^+]) + [\text{Urea nitrogen in mg/dL}]/2.8 \\ &\quad + [\text{Glucose in mg/dL}]/18 \end{aligned}$$

$$\begin{aligned} &\text{In SI units the formula is } 2\times[\text{Na}^+ + \text{K}^+]\ \text{mmol/L} \\ &\quad + [\text{Urea}]\ \text{in mmol/L} + [\text{Glucose}]\ \text{in mmol/L} \end{aligned}$$

The normal value of the UOG is approximately 10 to 100 mOsmol/kg. NH4$^+$ salts are generally the only other major urinary solute that contributes importantly to the urine osmolality, so values appreciably greater than 100 mOsmol/kg reflect increased excretion of NH_4^+ salts.

Urine pH, in contrast to the UAG or UOG, does not reliably differentiate acidosis of renal origin from that of extrarenal origin. For example, an acid urine pH does not necessarily indicate an appropriate increase in net acid excretion. If renal ammonia metabolism is inhibited, as occurs with chronic hyperkalemia, there is decreased ammonia available in the distal nephron to serve as a buffer, and small amounts of distal H^+ secretion can lead to significant urine acidification. In this setting, the urine pH is acid, but net acid excretion is low because of the low ammonia excretion. Similarly, alkaline urine does not necessarily imply a renal acidification defect. In conditions in which ammonia metabolism is stimulated, distal H^+ secretion can be massive and yet the urine remains relatively alkaline because of the buffering effects of ammonia.

Metabolic Acidosis of Renal Origin

An overall approach to patient assessment for workup of metabolic acidosis of renal origin is shown in Fig. 12.2.

Proximal Renal Tubular Acidosis (Type 2)

Normally, 80% to 90% of the filtered load of HCO_3^- is reabsorbed in the proximal tubule. In proximal (type 2) RTA, the proximal tubule has a decreased capacity to reabsorb filtered bicarbonate. When serum bicarbonate concentration is normal or nearly normal, the amount of bicarbonate filtered by the glomerulus exceeds proximal tubule bicarbonate reabsorptive capacity. When this happens, there is increased bicarbonate delivery to the loop of Henle and distal nephron that exceeds their capacity to reabsorb bicarbonate. As a result, some filtered bicarbonate appears in the urine. The net effect is that serum [HCO_3^-] decreases. Eventually, the filtered bicarbonate load decreases to the point at which the proximal tubule is able to reabsorb sufficient filtered bicarbonate that the bicarbonate load to the loop of Henle and the distal nephron is within their reabsorptive capacity. When this occurs, no further bicarbonate is lost in the urine, net acid excretion normalizes, and a new steady-state serum [HCO_3^-] develops, although at a lower-than-normal level.

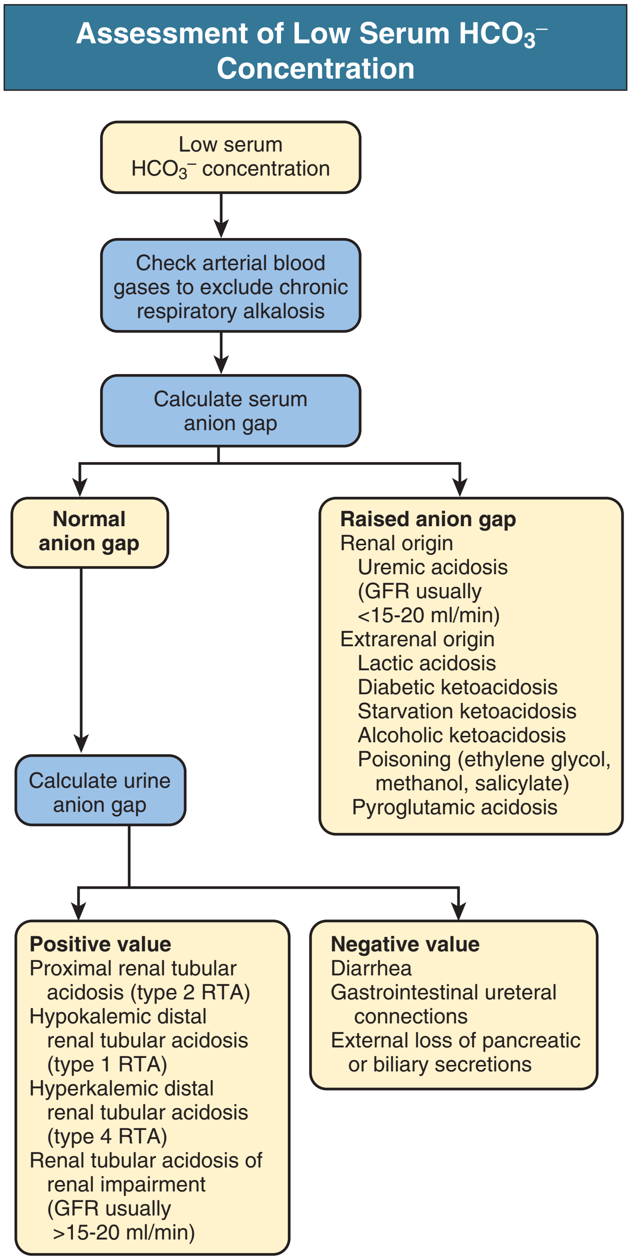
Assessment of Low Serum HCO3– Concentration
Low serum HCO3– concentration
Check arterial blood gases to exclude chronic respiratory alkalosis
Calculate serum anion gap
Normal anion gap
Raised anion gap
Renal origin
Uremic acidosis (GFR usually <15-20 ml/min)
Extrarenal origin
Lactic acidosis
Diabetic ketoacidosis
Starvation ketoacidosis
Alcoholic ketoacidosis
Poisoning (ethylene glycol, methanol, salicylate)
Pyroglutamic acidosis
Calculate urine anion gap
Positive value
Proximal renal tubular acidosis (type 2 RTA)
Hypokalemic distal renal tubular acidosis (type 1 RTA)
Hyperkalemic distal renal tubular acidosis (type 4 RTA)
Renal tubular acidosis of renal impairment (GFR usually >15-20 ml/min)
Negative value
Diarrhea
Gastrointestinal ureteral connections
External loss of pancreatic or biliary secretions

Fig. 12.1 Approach to the patient with low serum HCO_3^- concentration.

Hypokalemia is present in proximal RTA. Renal $NaHCO_3$ losses lead to intravascular volume depletion, which in turn activates the

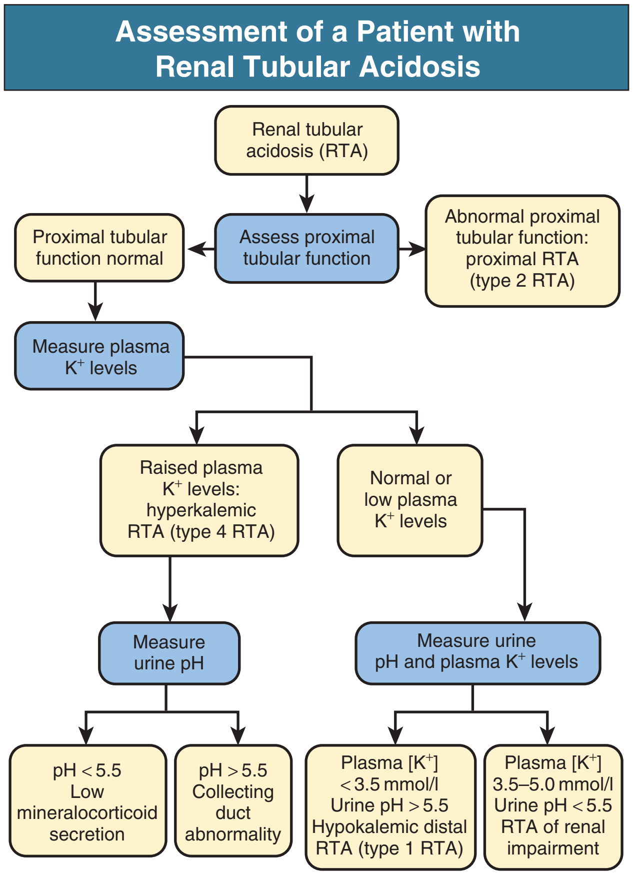
Assessment of a Patient with Renal Tubular Acidosis
Renal tubular acidosis (RTA)
Assess proximal tubular function
Proximal tubular function normal
Abnormal proximal tubular function: proximal RTA (type 2 RTA)
Measure plasma K+ levels
Raised plasma K+ levels: hyperkalemic RTA (type 4 RTA)
Normal or low plasma K+ levels
Measure urine pH
Measure urine pH and plasma K+ levels
pH < 5.5 Low mineralocorticoid secretion
pH > 5.5 Collecting duct abnormality
Plasma [K+] < 3.5 mmol/l Urine pH > 5.5 Hypokalemic distal RTA (type 1 RTA)
Plasma [K+] 3.5–5.0 mmol/l Urine pH < 5.5 RTA of renal impairment

Fig. 12.2 Approach to the patient with renal tubular acidosis.

renin-angiotensin-aldosterone system. Distal Na^+ delivery is increased as a result of the impaired proximal reabsorption of $NaHCO_3$. Because of the associated hyperaldosteronism and increased distal nephron Na^+ reabsorption, there is increased K^+ secretion. The net result is renal potassium wasting and the development of hypokalemia. In the steady state, when virtually all the filtered HCO_3^- is reabsorbed in the proximal and distal nephron, renal potassium wasting is less and the degree of hypokalemia tends to be mild.

Proximal RTA may occur as an isolated defect in acidification, but type 2 typically occurs in the setting of widespread proximal tubule dysfunction (Fanconi syndrome). In addition to decreased HCO_3^- reabsorption, patients with Fanconi syndrome have impaired reabsorption of glucose, phosphate, uric acid, amino acids, and low-molecular-weight proteins. Various inherited and acquired disorders have been associated with the development of Fanconi syndrome and proximal RTA (Box 12.2). The most common inherited cause in children is cystinosis (see Chapter 48). Most adults with Fanconi syndrome have an acquired condition that is related to an underlying dysproteinemic condition, such as multiple myeloma.

Skeletal abnormalities are common in these patients. Osteomalacia can develop from chronic hypophosphatemia caused by renal phosphate wasting if Fanconi syndrome is present. These patients also may have a deficiency in the active form of vitamin D because of an inability to convert 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D in the proximal tubule.

In contrast to distal RTA, proximal RTA is not associated with nephrolithiasis or nephrocalcinosis. One exception is the use of topiramate,[4,5] an antiepileptic drug that is increasingly used to treat a variety of neurologic and metabolic disorders. The drug exerts an inhibitory effect on renal carbonic anhydrase activity, resulting in a proximal acidification defect similar to that observed with acetazolamide. Topiramate also is associated with hypocitraturia, hypercalciuria, and elevated urine pH, leading to an increased risk for kidney stone disease.

BOX 12.2 Causes of Proximal (Type 2) Renal Tubular Acidosis

Not Associated With Fanconi Syndrome
- Sporadic
- Familial

Disorder of Carbonic Anhydrase
- Drugs: Acetazolamide, sulfanilamide, topiramate
- Carbonic anhydrase II deficiency

Associated With Fanconi Syndrome
- Selective (no systemic disease present)
- Sporadic

Familial
- Autosomal recessive proximal RTA with ocular abnormalities: Na^+-HCO_3^- cotransporter (NBCe1) defect
- Autosomal recessive proximal RTA with osteopetrosis and cerebral calcification: Carbonic anhydrase II defect
  - Generalized (systemic disorder present)
  - Genetic disorders
    - Cystinosis
    - Wilson disease
    - Hereditary fructose intolerance
    - Lowe syndrome
    - Metachromatic leukodystrophy

Dysproteinemic States
- Myeloma kidney
- Light-chain deposition disease

Hyperparathyroidism
- Primary
- Secondary

Drugs and Toxins
- Outdated tetracycline
- Ifosfamide
- Gentamicin
- Streptozocin
- Lead
- Cadmium
- Mercury

Tubulointerstitial Disease
- Post-transplantation rejection
- Balkan nephropathy
- Medullary cystic disease

Others
- Bone fibroma
- Osteopetrosis
- Paroxysmal nocturnal hemoglobinuria

HCO_3^-, bicarbonate ions; *P_{CO_2}*, carbon dioxide tension; *RTA*, renal tubular acidosis.

Proximal RTA should be suspected in a patient with a normal anion gap acidosis and hypokalemia who has an intact ability to acidify the urine to below 5.5 while in a steady state.[6] Proximal tubular dysfunction, such as euglycemic glycosuria, hypophosphatemia, hypouricemia, and mild proteinuria, helps support this diagnosis. The UAG is greater than zero, indicating the lack of increase in net acid excretion.

Treatment of proximal RTA is difficult. Administration of alkali increases serum [HCO_3^-], which increases urinary bicarbonate losses and thereby minimizes subsequent increases in the serum [HCO_3^-]. Moreover, the increased distal sodium load, in combination with increased circulating plasma aldosterone, results in increased renal potassium wasting and worsening hypokalemia. As a result, substantial amounts of alkali, often in the form of a potassium salt, such as potassium citrate, are required to prevent worsening hypokalemia. Children with proximal RTA should be aggressively treated to normalize their serum [HCO_3^-] to minimize growth retardation. These children may require large amounts of alkali therapy, typically 5 to 15 mmol/kg/day.

Adults with proximal RTA are frequently not treated as aggressively as children are because of the lack of systemic metabolic abnormalities or bone disease. Many clinicians administer alkali therapy if serum [HCO_3^-] is less than 18 mmol/l to prevent severe acidosis. Whether more aggressive therapy to normalize serum [HCO_3^-] is beneficial remains unknown. However, the large amounts of alkali required, about 700 to 1000 mmol/day for a 70-kg individual, make this approach problematic.

Hypokalemic Distal Renal Tubular Acidosis (Type 1)

In contrast to proximal RTA, patients with distal RTA are unable to acidify their urine, either under basal conditions or in response to metabolic acidosis.[7,8] Type 1 RTA results from a reduction in net H^+ secretion in the distal nephron and prevents urinary acidification, thereby minimizing titratable acid excretion and urinary ammonia excretion. As a result, these patients are unable to match net acid excretion to endogenous acid production, and acid accumulation ensues. The subsequent metabolic acidosis stimulates reabsorption of bone matrix to release the calcium alkali salts present in bone. During prolonged periods, this can result in progressive osteopenia in adults and in osteomalacia in children.

Distal RTA can be caused by either impaired H^+ secretion (secretory defect) or an abnormally permeable distal tubule, resulting in increased backleak of normally secreted H^+ (gradient defect); it may be genetic or acquired. Certain medications, especially amphotericin, result in increased backleak of protons across the apical plasma membrane, leading to a gradient defect form of distal RTA.

For patients with a secretory defect, the inability to acidify the urine below pH 5.5 results from abnormalities in any of the proteins involved in collecting duct H^+ secretion. Some patients may have an isolated defect in the H^+-K^+-ATPase that impairs H^+ secretion and K^+ reabsorption.[9] A defect confined to the vacuolar H^+-ATPase also results in renal potassium wasting.[10] The development of systemic acidosis tends to diminish net proximal fluid reabsorption with an increase in distal delivery, resulting in volume contraction and activation of the renin-aldosterone system. Increased distal Na^+ delivery coupled to increased circulating levels of aldosterone then leads to increased renal K^+ secretion.[11] Defects in the basolateral anion exchanger (AE1) also can cause distal RTA. In this case, the lack of basolateral HCO_3^- exit leads to intracellular alkalinization, which inhibits apical proton secretion.

Patients with distal RTA have low ammonia secretion rates. The decreased secretion is caused by the failure to trap ammonia in the tubular lumen of the collecting duct as a result of the inability to lower luminal fluid pH. In addition, there is often impaired medullary transfer of ammonia because of interstitial disease. Interstitial disease is frequently present in such patients through an associated underlying disease or as a result of nephrocalcinosis or hypokalemia-induced interstitial fibrosis.

In contrast to proximal RTA, nephrolithiasis and nephrocalcinosis are common.[12] Urinary Ca^{2+} excretion is high secondary to acidosis-induced bone mineral dissolution. Luminal alkalinization also inhibits calcium reabsorption, resulting in further increases in urinary calcium excretion.[13] Calcium phosphate solubility is also greatly lowered at alkaline pH, and calcium phosphate stone formation is accelerated. Stone formation is further enhanced as a result of low urinary citrate excretion. Citrate is metabolized to HCO_3^-, and its renal reabsorption is stimulated by metabolic acidosis, thereby minimizing the severity of metabolic acidosis. Urinary citrate also chelates urinary calcium, decreasing ionized calcium concentrations. Accordingly, the decreased citrate excretion that occurs in chronic metabolic acidosis as a result to distal RTA further contributes to both nephrolithiasis and nephrocalcinosis.

Distal RTA may be a primary disorder, either idiopathic or inherited, but it most often occurs in association with a systemic disease, one of the most common of which is Sjögren syndrome (Box 12.3). Hypergammaglobulinemic states as well as drugs and toxins also may cause this disorder.

A common cause of acquired distal RTA is glue sniffing. Inhalation of toluene from the fumes of model glue, spray paint, and paint thinners can give rise to hypokalemic normal anion gap acidosis through multiple mechanisms. First, toluene inhibits collecting duct proton secretion. Second, metabolism of toluene produces the organic acids hippuric and benzoic acid. These are buffered by sodium bicarbonate,

BOX 12.3 Causes of Hypokalemic Distal (Type 1) Renal Tubular Acidosis

Primary

- Idiopathic
- Familial

Secondary

Autoimmune Disorders

- Hypergammaglobulinemia
- Sjögren syndrome
- Primary biliary cirrhosis
- Systemic lupus erythematosus

Genetic Diseases

- Autosomal dominant RTA: Anion exchanger 1 defect
- Autosomal recessive RTA: H^+-ATPase A4 subunit
- Autosomal recessive with progressive nerve deafness: H^+-ATPase B1 subunit

Drugs and Toxins

- Amphotericin B
- Toluene

Disorders With Nephrocalcinosis

- Hyperparathyroidism
- Vitamin D intoxication
- Idiopathic hypercalciuria

Tubulointerstitial Disease

- Obstructive uropathy
- Renal transplantation

resulting in metabolic acidosis and the production of sodium hippurate and sodium benzoate. If plasma volume is normal, these salts are rapidly excreted in the urine, and a non–anion gap metabolic acidosis develops. If plasma volume is decreased, urinary excretion is limited, these salts accumulate, and an anion gap metabolic acidosis develops.

Distal RTA should be considered in all patients with a non–anion gap metabolic acidosis and hypokalemia who have an inability to lower the urine pH maximally. A urine pH above 5.5 in the patient with systemic acidosis suggests distal RTA, and a UAG value greater than zero or lack of an increase in the UOG is confirmatory. Depending on the duration of the distal RTA, the metabolic acidosis can be mild or very severe, with a serum [HCO_3^-] as low as 10 mmol/l. Urinary potassium losses lead to the development of hypokalemia. Severe hypokalemia (<2.5 mmol/l) may result in musculoskeletal weakness and nephrogenic diabetes insipidus. The latter occurs because hypokalemia decreases aquaporin 2 (AQP2) expression in the collecting duct, thereby minimizing the ability to concentrate urine. An abdominal ultrasound scan or radiograph may reveal nephrocalcinosis.

In patients with minimal disturbances in blood pH and plasma [HCO_3^-], a test of urinary acidification is required. Traditionally, such a test involved oral NH_4Cl administration to induce metabolic acidosis with assessment of the renal response by serial measurement of urine pH. Many patients poorly tolerate NH_4Cl ingestion because of gastric irritation, nausea, and vomiting. An alternative way to test the capacity for distal acidification is to administer furosemide and the mineralocorticoid fludrocortisone simultaneously.[14] The combination of both increased distal Na^+ delivery and mineralocorticoid effect will stimulate distal H^+ secretion by both an increase in the luminal electronegativity and a direct stimulatory effect on H^+ secretion. Normal individuals will lower urine pH to values below 5.5 with either maneuver.

Correction of the metabolic acidosis in distal RTA can be achieved by administration of alkali in an amount only slightly greater than daily acid production, usually 1 to 2 mmol/kg/day. In patients with severe K^+ deficits, correction of the acidosis with HCO_3^-, particularly if it is done with sodium alkali salts such as $NaHCO_3$, can lower serum potassium concentration to dangerous levels. In this setting, potassium replacement should begin before the acidosis is corrected. In general, a combination of sodium alkali and potassium alkali is required for long-term treatment of distal RTA. For the patient with recurrent renal stone disease caused by distal RTA, treatment of the acidosis increases urinary citrate excretion, which slows the rate of further stone formation and may even lead to stone dissolution.

Hyperkalemic Distal Renal Tubular Acidosis (Type 4)

Type 4 RTA is characterized by distal nephron dysfunction, resulting in impaired renal excretion of both H^+ and K^+ and causing hyperchloremic normal gap acidosis and hyperkalemia.[15] (It should be noted that type 3 RTA is most often applied to a rare autosomal recessive syndrome resulting from carbonic anhydrase II deficiency with features of both proximal and distal RTA.)

Type 4 RTA occurs most frequently with mild to moderate impairment in renal function; however, the magnitude of hyperkalemia and acidosis is disproportionately severe for the observed glomerular filtration rate (GFR). Whereas hypokalemic distal (type 1) RTA is also a disorder of distal nephron acidification, type 4 is distinguished from type 1 RTA on the basis of several important characteristics (Table 12.1). Type 4 RTA is also a much more common form of RTA, particularly in adults.

Hyperkalemic distal RTA results from deficient circulating aldosterone or abnormal cortical collecting duct (CCD) function, or it can be related to hyperkalemia. In either case, a defect in distal H^+ secretion develops. Impaired Na^+ reabsorption by the principal cell leads to a decrease in the luminal electronegativity of the CCD, which impairs distal acidification as a result of the decrease in driving force for H^+ secretion into the tubular lumen. The H^+ secretion is further impaired in this segment as well as in the medullary collecting duct as a result of either the loss of the direct stimulatory effect of aldosterone on H^+ secretion or an abnormality in the H^+-secreting cell.

TABLE 12.1 Differentiation of Renal Tubular Acidosis Types

Factor	Type 1	Type 2	Type 4
Serum K^+	Low	Low	High
Renal function	Normal or near normal	Normal or near normal	Stage 3, 4, or 5 chronic kidney disease
Urine pH during acidosis	High	Low	Low or high
Serum HCO_3^- (mmol/l)	10-20	16-18	16-22
Urine citrate	Low	High	Low
Fanconi syndrome	No	May be present	No

A consequence of the decrease in luminal electronegativity in the CCD is impaired renal K^+ excretion. In addition, a primary abnormality in CCD transport can also impair K^+ secretion. The development of hyperkalemia adds to the defect in distal acidification by decreasing the amount of ammonia available to act as a urinary buffer. Some studies suggest that hyperkalemia itself, through its effects on ammonia metabolism, is the primary mechanism by which metabolic acidosis develops in type 4 RTA.

The etiology of type 4 RTA includes disorders associated with decreased circulating levels of aldosterone and conditions associated with impaired CCD function. The most common disease associated with type 4 RTA in adults is diabetes mellitus. In these patients, primary NaCl retention leads to volume expansion and suppression and atrophy of the renin-secreting juxtaglomerular apparatus. Several common drugs, such as nonsteroidal antiinflammatory agents (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and high doses of heparin, as used for systemic anticoagulation, can lead to decreased mineralocorticoid synthesis. Impaired function of the CCD can be a feature of structural damage to the kidney, as in interstitial renal diseases such as sickle cell nephropathy, urinary tract obstruction, and lupus. CCD function also may be impaired from use of drugs such as amiloride, triamterene, and spironolactone.[16]

Type 4 RTA should be suspected in a patient with a normal gap metabolic acidosis associated with hyperkalemia. The typical patient is in the fifth to seventh decade of life with a long-standing history of diabetes mellitus with a moderate reduction in the GFR. Plasma [HCO_3^-] is usually 18 to 22 mmol/l and serum [K^+] between 5.5 and 6.5 mmol/l. Most patients are asymptomatic; however, the hyperkalemia may occasionally be severe enough to cause muscle weakness or cardiac arrhythmias. The UOG is not increased and the UAG value is slightly positive, indicating minimal ammonia excretion in the urine. When the disorder is caused by a defect in mineralocorticoid activity, patients typically have urine pH below 5.5, reflecting a more severe defect in ammonia availability than in H^+ secretion (Fig. 12.3). In patients with structural damage to the collecting duct, the urine pH may be alkaline, reflecting both impaired H^+ secretion and decreased urinary ammonia excretion.

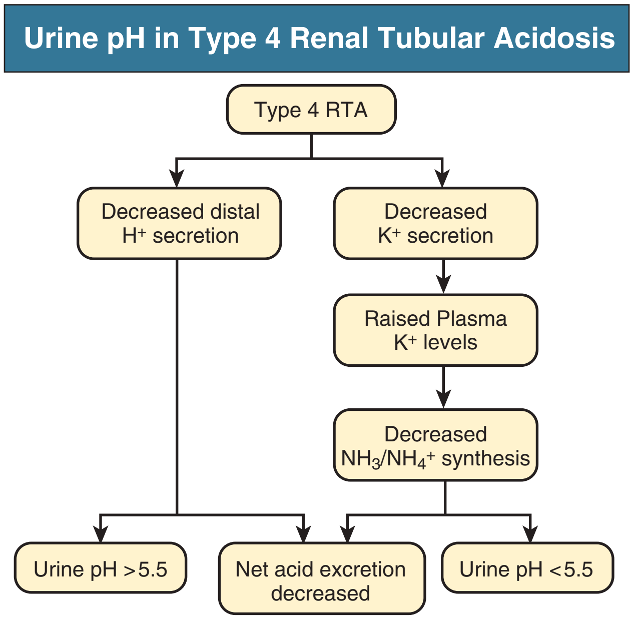
Urine pH in Type 4 Renal Tubular Acidosis
Type 4 RTA
Decreased distal H+ secretion
Decreased K+ secretion
Raised Plasma K+ levels
Decreased NH3/NH4+ synthesis
Urine pH >5.5
Net acid excretion decreased
Urine pH <5.5

Fig. 12.3 **Urine pH in hyperkalemic distal (Type 4) renal tubular acidosis.** Net acid excretion is always decreased; however, the urine pH can be variable. In structural disease of the kidney, the predominant defect is usually decreased distal H^+ secretion and the urine pH is above 5.5. In disorders associated with decreased mineralocorticoid activity, urine pH is usually below 5.5.

Treatment of patients with type 4 RTA is directed at both the hyperkalemia and the metabolic acidosis. In many patients, lowering serum $[K^+]$ will simultaneously correct the acidosis.[17] Correction of the hyperkalemia allows renal ammonia production to increase, thereby increasing the buffer supply for distal acidification. The first consideration in treatment is to discontinue any nonessential medication that might interfere in either the synthesis or activity of aldosterone or the ability of the kidneys to excrete potassium (Box 12.4). ACE inhibitors and angiotensin receptor blockers usually should be continued because of the beneficial effects on cardiovascular disease and their renoprotective benefits in patients with chronic kidney disease (CKD). In patients with aldosterone deficiency who are neither hypertensive nor fluid overloaded, administration of a synthetic mineralocorticoid such as fludrocortisone 0.1 mg/day can be effective. In patients with hypertension or volume overload, particularly in association with CKD, administration of either a thiazide or a loop diuretic is frequently effective. Loop diuretics are required in patients with estimated GFR below 30 ml/min. Loop and thiazide diuretics increase distal Na^+ delivery and thus stimulate K^+ and H^+ secretion in the collecting duct. Alkali therapy (e.g., $NaHCO_3$) also can be used to treat the acidosis and hyperkalemia, but the patient must be closely monitored to avoid volume overload and worsening hypertension.

BOX 12.4 Causes of Hyperkalemic Distal (Type 4) Renal Tubular Acidosis

Mineralocorticoid Deficiency

Low Renin, Low Aldosterone

- Diabetes mellitus
- Drugs
  - Nonsteroidal antiinflammatory drugs (NSAIDs)
  - Cyclosporine, tacrolimus
  - β-Blockers

High Renin, Low Aldosterone

- Adrenal destruction
- Congenital enzyme defects
- Drugs
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Angiotensin II receptor blockers (ARBs)
  - Heparin
  - Ketoconazole

Abnormal Cortical Collecting Duct

- Absent or defective mineralocorticoid receptor
- Drugs
  - Spironolactone, eplerenone
  - Triamterene
  - Amiloride
  - Trimethoprim
  - Pentamidine
- Chronic tubulointerstitial disease

Renal Tubular Acidosis in Chronic Kidney Disease

Metabolic acidosis in advanced CKD is caused by failure of the tubular acidification process to excrete the normal daily acid load. As functional renal mass is reduced by disease, there is an adaptive increase in ammonia production and H^+ secretion by the remaining nephrons. Despite increased production of ammonia from each remaining nephron, overall production may be decreased secondary to the decrease in total renal mass. In addition, less ammonia is delivered to the medullary interstitium secondary to a disrupted medullary anatomy.[18] The ability to lower the urinary pH remains intact, reflecting the fact that the impairment in distal nephron H^+ secretion is less than that in ammonia secretion. Quantitatively, however, the total amount of H^+ secretion is small, and the acidic urine pH is the consequence of very little buffer in the urine. The lack of ammonia in the urine is reflected by a positive value for the UAG and lack of an increase in the UOG. Differentiation of RTA from type 4 RTA can be difficult because it is based on the clinician's determination of whether the severity of metabolic acidosis is out of proportion to the degree of renal dysfunction.

Patients with CKD may develop a hyperchloremic normal gap metabolic acidosis associated with normokalemia or mild hyperkalemia as GFR decreases to less than 30 ml/min. With more advanced CKD (GFR <15 ml/min), the acidosis may change to an anion gap metabolic acidosis, reflecting a progressive inability to excrete phosphate, sulfate, and various organic acids. At this stage, the acidosis is commonly referred to as "uremic acidosis."

Correction of the metabolic acidosis in patients with CKD is achieved by treatment with $NaHCO_3$, 0.5 to 1.5 mmol/kg/day, beginning when the HCO_3^- level is less than 22 mmol/l. In some patients, non–sodium citrate formulations can be used. Loop diuretics are often used in conjunction with alkali therapy to prevent volume overload. If the acidosis becomes refractory to medical therapy, dialysis needs to be initiated. Recent evidence suggests that metabolic acidosis in the patient with CKD needs to be aggressively treated because chronic acidosis is associated with metabolic bone disease and may lead to an accelerated catabolic state in patients with CKD.[19,20]

Metabolic Acidosis of Extrarenal Origin

Diarrhea

Intestinal secretions from sites distal to the stomach are rich in HCO_3^-. Accelerated loss of this HCO_3^--rich solution can result in metabolic acidosis. The resultant volume loss signals the kidney to increase NaCl reabsorption; this combined with the intestinal $NaHCO_3$ losses generates a normal anion gap metabolic acidosis. The renal response is to increase net acid excretion by increasing urinary excretion of ammonia.[21] Hypokalemia, as a result of gastrointestinal losses, and the low serum pH both stimulate the synthesis of ammonia in the proximal tubule. The increase in availability of ammonia to act as a urinary buffer allows a maximal increase in H^+ secretion by the distal nephron.

The increase in urinary ammonia excretion associated with an extrarenal normal anion gap acidosis results in a negative UAG value and an increase in the UOG. Urine pH can be misleading and in chronic diarrhea may be above 6.0 because of substantial increases in renal ammonia metabolism that result in increased urine pH from the buffering ability of the ammonia. Although the clinical history should distinguish between these two possibilities, in a patient with surreptitious laxative abuse, this may not be helpful because diarrhea may not be reported. Colonoscopy may be required to demonstrate characteristic findings of laxative abuse (e.g., melanosis coli) if this diagnosis is being considered.

Treatment of diarrhea-associated metabolic acidosis is based on treatment of the underlying diarrhea. If this is not possible, alkali treatment, possibly including potassium alkali to treat hypokalemia and metabolic acidosis simultaneously, is indicated.

Ileal Conduits

Surgical diversion of the ureter into an ileal pouch is used in the treatment of the patient with neurogenic bladder or after cystectomy. The procedure may be associated rarely with development of a hyperchloremic normal anion gap metabolic acidosis. Acidosis in part is caused by reabsorption of urinary NH_4Cl by the intestine. The ammonia is transported through the portal circulation to the liver or is metabolized to urea to prevent hyperammonemic encephalopathy. This metabolic process consumes equimolar amounts of bicarbonate and therefore can result in the development of metabolic acidosis. Metabolic acidosis also may develop because urinary Cl^- can be exchanged for HCO_3^- through activation of a Cl^--HCO_3^- exchanger on the intestinal lumen. In some patients, a renal defect in acidification can develop and exacerbate the degree of acidosis. Such a defect may result from tubular damage caused by pyelonephritis or high colonic pressures, secondarily causing urinary obstruction.

The severity of acidosis relates to the length of time the urine is in contact with the bowel and the total surface area of bowel exposed to urine. In patients with a ureterosigmoid anastomosis, these factors are increased and the acidosis tends to be more common and more severe than in patients with an ileal conduit. The ileal conduit was designed to minimize the time and area of contact between urine and intestinal surface. Patients with surgical diversion of the ureter who develop metabolic acidosis should be evaluated for an ileal loop obstruction because this would lead to an increase in contact time between the urine and intestinal surface.

ANION GAP METABOLIC ACIDOSIS

Lactic Acidosis

Lactic acid is the end product in the anaerobic metabolism of glucose and is generated by the reversible reduction of pyruvic acid by lactic acid dehydrogenase and reduced nicotinamide adenine dinucleotide (NADH), as shown in the following formula:

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \leftrightarrow \text{Lactate} + \text{NAD}^+$$

Under normal conditions, the reaction is shifted toward the right and the normal lactate-to-pyruvate ratio is approximately 10:1. The reactants in this pathway are interrelated, as shown in the following equation:

$$\text{Lactate} = K[(\text{pyruvate})(\text{NADH})(\text{H}^+)]/(\text{NAD}^+)$$

where *K* is the equilibrium constant.

On the basis of this relationship, it is evident that lactate can increase for three reasons.[22] First, lactate can increase because of increased pyruvate production alone. In this situation, the normal 10:1 lactate-to-pyruvate ratio will be maintained. An isolated increase in pyruvate production can be seen in the setting of intravenous glucose infusions, intravenous administration of epinephrine, and respiratory alkalosis. Lactate levels in these conditions are minimally elevated, rarely exceeding 5 mmol/l. Second, lactate can increase as a result of an increased NADH-NAD^+ ratio. Under these conditions, the lactate-to-pyruvate ratio can increase to very high values. Third, lactate can increase with a combination of increased pyruvate production and increased NADH/NAD^+. This is common in severe lactic acidosis.

Lactic acidosis occurs when there is an imbalance between the production and the use of lactic acid. The net result is an accumulation of serum lactate and development of metabolic acidosis. The accumulation of the non–chloride anion lactate accounts for the increase in anion gap. Severe exercise and grand mal seizures are examples of lactic acidosis developing as a result of increased production. The short-lived nature of the acidosis in these conditions suggests that a concomitant defect in lactic acid use is present in most conditions of sustained and severe lactic acidosis.

Some of the disorders associated with the development of lactic acidosis are listed in Box 12.5. Type A lactic acidosis is characterized by underperfusion of tissue or acute hypoxia, such as hypotension, sepsis, acute tissue hypoperfusion, cardiopulmonary failure, severe anemia, hemorrhage, and carbon monoxide poisoning. Type B lactic acidosis occurs in the absence of overt hypoperfusion or hypoxia, such as with congenital defects in glucose or lactate metabolism, diabetes mellitus,

BOX 12.5 Causes of Lactic Acidosis

Type A (Tissue Underperfusion or Hypoxia)

- Cardiogenic shock
- Septic shock
- Hemorrhagic shock
- Acute hypoxia
- Carbon monoxide poisoning
- Anemia

Type B (Absence of Hypotension and Hypoxia)

- Hereditary enzyme deficiency (glucose 6-phosphatase)
- Drugs or toxins
  - Phenformin, metformin
  - Cyanide
  - Salicylate, ethylene glycol, methanol
  - Propylene glycol[26]
  - Linezolid[24]
  - Propofol[25]
  - Nucleoside reverse transcriptase inhibitors: Stavudine, didanosine[24]
  - Clenbuterol[27]
  - Isoniazid
- Thiamine deficiency
- Systemic disease
  - Liver failure
  - Malignancy

liver disease, effects of drugs and toxins, and neoplastic diseases.[23-28] Thiamine deficiency is being increasingly recognized as a cause of type B lactic acidosis in subjects with alcoholism, persistent vomiting and severe malnutrition. In clinical practice, many patients will often exhibit features of type A and type B lactic acidosis simultaneously.

Therapy is aimed at correction of the underlying disorder. Restoration of tissue perfusion and oxygenation is attempted if these are compromised. The role of alkali in the treatment of patients with lactic acidosis is controversial; some experimental models and clinical observations suggest that administration of HCO_3^- may depress cardiac function and exacerbate the acidemia. In addition, such therapy may be complicated by volume overload, hypernatremia, and rebound alkalosis after the acidosis has resolved.[29] In general, HCO_3^- should be given when the systemic pH decreases to below 7.1, because hemodynamic instability becomes much more likely with severe acidemia. In such patients, alkali therapy should be directed at increasing the pH above 7.1; attempts to normalize the pH or $[HCO_3^-]$ should be avoided. Acute hemodialysis is rarely beneficial for lactic acidosis induced by tissue hypoperfusion. The hemodynamic instability that can occur with hemodialysis in these critically ill patients may worsen the underlying difficulty in tissue oxygenation.

Diabetic Ketoacidosis

Diabetic ketoacidosis results from the accumulation of acetoacetic acid and β-hydroxybutyric acid. The development of ketoacidosis is the result of insulin deficiency and a relative or absolute increase in glucagon.[30] These hormonal changes lead to increased fatty acid mobilization from adipose tissue and alter the oxidative machinery of the liver such that delivered fatty acids are primarily metabolized into ketoacids. In addition, peripheral glucose use is impaired, and the gluconeogenic pathway in the liver is maximally stimulated. The resultant hyperglycemia causes an osmotic diuresis and volume depletion.

Ketoacidosis results when the rate of hepatic ketoacid generation exceeds renal excretion, causing increased blood ketoacid concentrations. The H^+ accumulation in the extracellular fluid (ECF) decreases HCO_3^- concentration, whereas the ketoacid anion concentration increases. An anion gap metabolic acidosis is the more common finding in the patient with diabetic ketoacidosis, but a normal gap metabolic acidosis also can be seen. In early stages of ketoacidosis, when the ECF volume is almost normal, ketoacid anions that are produced are rapidly excreted by the kidney as Na^+ and K^+ salts. Excretion of these salts is equivalent to the loss of potential HCO_3^-. This loss of potential HCO_3^- in the urine at the same time the kidney is retaining NaCl results in a normal gap metabolic acidosis. As volume depletion develops, renal ketoacid excretion cannot match production rates and ketoacid anions are retained within the body, thus increasing the anion gap.[31]

During treatment, the anion gap metabolic acidosis transforms once again into a normal gap acidosis. Treatment leads to a termination in ketoacid production. As the ECF volume is restored, there is increased renal excretion of the Na^+ salts of the ketoacid anions. The loss of this potential HCO_3^-, combined with the retention of administered NaCl, accounts for the redevelopment of the hyperchloremic normal gap acidosis. In addition, K^+ and Na^+ administered in solutions containing NaCl and KCl enter cells in exchange for H^+. The net effect is infusion of HCl into the ECF. The reversal of the hyperchloremic acidosis takes several days as the HCO_3^- deficit is corrected by the kidney.

Diabetic ketoacidosis can result in a severe metabolic acidosis with serum bicarbonate levels below 5 mmol/l. This diagnosis should be considered in patients with simultaneous metabolic acidosis and hyperglycemia. Diagnosis is confirmed by demonstration of retained ketoacids with nitroprusside tablets or reagent strips in the urine. However, these tests detect only acetone and acetoacetate and not β-hydroxybutyrate. In the patient with lactic acidosis or alcoholic ketoacidosis, acetoacetate may be converted to β-hydroxybutyrate to an extent that depends on the $NADH/NAD^+$ ratio. With treatment of the diabetic ketoacidosis, acetoacetate is generated as this ratio falls, and the nitroprusside test result may suddenly become strongly positive.

The limitations of the nitroprusside test can be prevented by direct measurement of β-hydroxybutyrate. With uncontrolled diabetes, a serum β-hydroxybutyrate level above 3.0 mmol/l in adults and above 3.8 mmol/l in children confirms diabetic ketoacidosis.[32] Compared with urinary ketone measurements, capillary blood levels of β-hydroxybutyrate better correlate with both the degree of acidosis and the response to therapy.[33]

Treatment consists of insulin and intravenous fluids to correct volume depletion. Deficiencies in K^+, Mg^{2+}, and phosphate are common; therefore these electrolytes are typically added to intravenous solutions. However, diabetic ketoacidosis typically manifests with hyperkalemia secondary to the insulin deficiency. Potassium should be administered only as hypokalemia develops, usually during insulin treatment of diabetic ketoacidosis. If there is significant hypokalemia at presentation, potassium supplementation may be needed before insulin administration to avoid life-threatening worsening of hypokalemia. Alkali therapy is generally not required because administration of insulin leads to the metabolic conversion of ketoacid anions to HCO_3^- and allows partial correction of the acidosis. However, HCO_3^- therapy may be indicated in patients who present with severe acidemia (pH <7.1).[34]

D-Lactic Acidosis

D-Lactic acidosis is a form of metabolic acidosis that can occur in the patient with small bowel resections or in patients with a jejunoileal bypass. Such short bowel syndromes create a situation in which carbohydrates that are normally extensively reabsorbed in the small intestine are delivered in large amounts to the colon. In the presence of colonic bacterial overgrowth, these substrates are metabolized into D-lactate and absorbed into the systemic circulation. Accumulation of D-lactate produces an anion gap metabolic acidosis in which the serum lactate concentration is normal because the standard test for lactate is specific for L-lactate. These patients typically present after ingestion of a large, high-carbohydrate meal, with neurologic abnormalities including confusion, slurred speech, and ataxia. Ingestion of low-carbohydrate meals and antimicrobial agents to decrease the degree of bacterial overgrowth are the principal treatments.

Starvation Ketosis

Abstinence from food can lead to a mild anion gap metabolic acidosis secondary to increased production of ketoacids. The pathogenesis of this disorder is similar to that of diabetic ketoacidosis in that starvation leads to relative insulin deficiency and glucagon excess. As a result, there is increased mobilization of fatty acids while the liver is set to oxidize fatty acids to ketoacids. With prolonged starvation, the blood ketoacid level can reach 5 to 6 mmol/l. The serum $[HCO_3^-]$ is rarely less than 18 mmol/l. More fulminant ketoacidosis is aborted because ketone bodies stimulate the pancreatic islets to release insulin and lipolysis is held in check. This break in the ketogenic process is notably absent in patients with insulin-dependent diabetes.[35] No specific therapy is indicated in starvation ketosis.

Alcoholic Ketoacidosis

Ketoacidosis develops in patients with a history of chronic ethanol abuse, decreased food intake, and often a history of nausea and vomiting. As with starvation ketosis, a decrease in the insulin-to-glucagon ratio leads to accelerated fatty acid mobilization and alters the enzymatic machinery of the liver to favor ketoacid production. However, features unique to this disorder differentiate alcoholic ketoacidosis from simple starvation ketosis. First, the alcohol withdrawal combined with volume depletion and starvation greatly increases the levels of circulating catecholamines. As a result, the peripheral mobilization of fatty acids is much greater than typically found with starvation alone. This sometimes massive mobilization of fatty acids can lead to marked ketoacid production and severe metabolic acidosis. Second, the metabolism of ethanol leads to accumulation of NADH. The increase in NADH/NAD$^+$ is reflected by a higher ratio of β-hydroxybutyrate to acetoacetate. As mentioned previously, the nitroprusside reaction may be diminished by this redox shift despite the presence of severe ketoacidosis. Treatment of patients with alcoholic ketoacidosis focuses on glucose administration, which leads to the rapid resolution of the acidosis; stimulation of insulin release leads to diminished fatty acid mobilization from adipose tissue, as well as decreased hepatic output of ketoacids.

Ethylene Glycol and Methanol Intoxications

Ethylene glycol and methanol intoxications are characteristically associated with the development of a severe anion gap metabolic acidosis. Metabolism of ethylene glycol by alcohol dehydrogenase generates various acids, including glycolic, oxalic, and formic acids. Ethylene glycol is present in antifreeze and solvents and is ingested by accident or as a suicide attempt. The initial effects of intoxication are neurologic and begin with drunkenness but can quickly progress to seizures and coma. If left untreated, cardiopulmonary symptoms such as tachypnea, noncardiogenic pulmonary edema, and cardiovascular collapse may appear. From 24 to 48 hours after ingestion, patients may develop flank pain and acute kidney injury, often accompanied by abundant calcium oxalate crystals in the urine (Box 12.6). A fatal dose of ethylene glycol is approximately 100 ml.

BOX 12.6 Ethylene Glycol and Methanol Poisoning

Time course of clinical symptoms and signs after ingestion

- Ethylene glycol
  - 0-12 hours: Inebriation progressing to coma
  - 12-24 hours: Tachypnea, noncardiogenic pulmonary edema
  - 24-36 hours: Flank pain, renal failure, urinary calcium oxalate crystals
- Methanol
  - 0-12 hours: Inebriation followed by asymptomatic period
  - 24-36 hours: Pancreatitis, retinal edema progressing to blindness, seizures
  - >48 hours: Putamen and white matter hemorrhage leading to Parkinson-like state

Increased anion gap metabolic acidosis

Increased osmolar gap

Treatment

Supportive care

Fomepizole (4-methylpyrazole) is agent of choice (competitor of alcohol dehydrogenase): 15 mg/kg IV loading dose, then 10 mg/kg every 12 hours for 48 hours. After 48 hours, increase dose to 15 mg/kg every 12 hours; increase frequency of dosing to EVERY 4 hours during hemodialysis.

Intravenous ethanol (5% or 10% solution) if fomepizole unavailable: Loading dose of 0.6 g/kg, followed by hourly maintenance dose of 66 mg/kg. Increase maintenance dose when the patient has history of chronic alcohol use and during hemodialysis.

Hemodialysis to accelerate removal of parent compound and metabolites

Bicarbonate therapy to treat acidosis

Methanol is also metabolized by alcohol dehydrogenase and forms formaldehyde, which is then converted to formic acid. Methanol is found in a variety of commercial preparations, such as shellac, varnish, and de-icing solutions, and is also known as wood alcohol. As with ethylene glycol, methanol can be ingested either by accident or as a suicide attempt. Clinically, methanol ingestion is associated with an acute inebriation followed by an asymptomatic period lasting 24 to 36 hours. Abdominal pain caused by pancreatitis, seizures, blindness, and coma may develop. The blindness is caused by direct toxicity of formic acid on the retina. Methanol intoxication is also associated with hemorrhage in the white matter and putamen, which can lead to the delayed onset of a Parkinsonian syndrome (see Box 12.6). The lethal dose of methanol is 60 to 250 ml.

Lactic acidosis is also a feature of methanol and ethylene glycol poisoning and contributes to the elevated anion gap. Together with an elevated anion gap, an osmolar gap is an important clue to the diagnosis of ethylene glycol and methanol poisoning. The osmolar gap is the difference between the measured and calculated osmolality. The formula for the calculated osmolality is as follows:

$$\begin{aligned}\text{Calculated osmolality} = {} & 2\times\text{Na}^+ + \text{BUN}/2.8\\ & + \text{glucose}/18 + \text{EtOH}/4.6\end{aligned}$$

where the blood urea nitrogen (BUN), glucose, and ethanol concentrations are in milligrams per deciliter. Inclusion of the ethanol concentration in this calculation is important because many patients ingest ethylene glycol or methanol while inebriated from ethanol ingestion. The normal value for the osmolar gap is less than 10 mOsm/kg. Each 100 mg/dl (161 mmol/l) of ethylene glycol will increase the osmolar gap by 16 mOsm/kg. Methanol contributes 32 mOsm/kg for each 100 mg/dl (312 mmol/l).

In addition to supportive measures, the patient with ethylene glycol and methanol poisoning is treated with fomepizole (4-methylpyrazole), which inhibits alcohol dehydrogenase and prevents formation of toxic metabolites[36] (see Box 12.6). If fomepizole is unavailable, intravenous ethanol can be used to prevent the formation of toxic metabolites. Ethanol has more than a 10-fold greater affinity for alcohol dehydrogenase than that of other alcohols. Ethanol has its greatest efficacy when levels of 100 to 200 mg/dl are obtained. In addition to both fomepizole and ethanol therapy, the patient should receive hemodialysis to remove both the parent compound and its metabolites. Correction of the acidosis is accomplished with an HCO_3^--containing dialysate or by intravenous infusion of $NaHCO_3$.

Salicylate

Aspirin (acetylsalicylic acid) is associated with a large number of accidental or intentional poisonings. At toxic concentrations, salicylate uncouples oxidative phosphorylation and, as a result, leads to increased lactic acid production. In children, ketoacid production also may be increased. The accumulation of lactic, salicylic, keto, and other organic acids leads to the development of an anion gap metabolic acidosis. At the same time, salicylate has a direct stimulatory effect on the respiratory center. Increased ventilation lowers the carbon dioxide tension ($P\text{CO}_2$), contributing to the development of a respiratory alkalosis. Children primarily manifest an anion gap metabolic acidosis with toxic salicylate levels; a respiratory alkalosis is most evident in adults.

In addition to conservative management, the initial goals of therapy for salicylate poisoning are to correct systemic acidemia and increase the urine pH. By increasing systemic pH, the ionized fraction of salicylic acid will increase, resulting in less accumulation of the drug in the central nervous system. Similarly, an alkaline urine pH favors increased

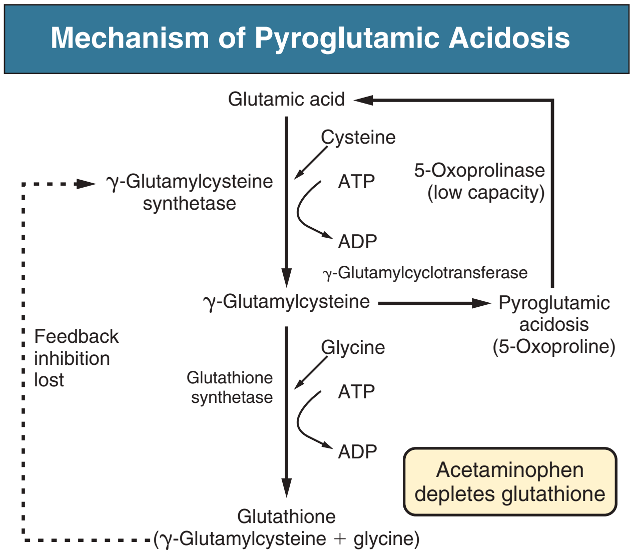
Mechanism of Pyroglutamic Acidosis
Glutamic acid
Cysteine
γ-Glutamylcysteine synthetase
ATP
ADP
5-Oxoprolinase (low capacity)
γ-Glutamylcyclotransferase
γ-Glutamylcysteine
Pyroglutamic acidosis (5-Oxoproline)
Feedback inhibition lost
Glycine
Glutathione synthetase
ATP
ADP
Acetaminophen depletes glutathione
Glutathione
(γ-Glutamylcysteine + glycine)

Fig. 12.4 Mechanism of pyroglutamic acidosis. Glutathione is formed from γ-glutamylcysteine and glycine in the presence of glutathione synthetase. Glutathione normally regulates the activity of γ-glutamylcysteine synthetase through feedback inhibition. Depletion of glutathione results in increased formation of γ-glutamylcysteine, which in turn is metabolized to pyroglutamic acid (5-oxoproline) and cystine through γ-glutamylcyclotransferase. Pyroglutamic acid accumulates because the enzyme responsible for its metabolism (5-oxoprolinase) is low capacity. *ADP,* ADENOSINE diphosphate; *ATP,* adenosine triphosphate.

TABLE 12.2 Alkali Treatment Options

Therapy	Route	Usual Dose per Unit	Comments
Sodium bicarbonate tablet	PO	650 mg = 8 mmol	May cause gastric gas
Sodium bicarbonate	IV	50 mmol in 50 ml	Hypertonic, may cause hypernatremia
5% Dextrose with water with $NaHCO_3$	IV	150 mmol/l	Useful for simultaneous intravascular volume expansion and alkali administration
Potassium citrate (tablet)	PO	5 and 10 mmol per tablet	Useful for simultaneous K^+ and alkali therapy
Citric acid/ potassium citrate/sodium citrate (liquid)	PO	1 mmol of Na^+ and K^+ and 2 mmol of citrate per milliliter	Avoid concomitant aluminum-containing medications such as antacids and sucralfate 1 mmol citrate equivalent to 3 mmol HCO_3^-
Potassium citrate (liquid)	PO	2 mmol of K^+ and 2 mmol of citrate per milliliter	Avoid concomitant aluminum-containing medications

IV, intravenous; *PO,* oral.

urinary excretion because the ionized fraction of the drug is poorly reabsorbed by the tubule. At serum concentrations above 80 mg/dl or in the setting of severe clinical toxicity, hemodialysis can be used to accelerate drug elimination.

Pyroglutamic Acidosis

Pyroglutamic acid, also known as 5-oxoproline, is an intermediate in glutathione metabolism. An anion gap acidosis caused by pyroglutamic acid has been described rarely in critically ill patients receiving therapeutic doses of acetaminophen[37,38] (Fig. 12.4). Patients present with severe anion gap metabolic acidosis accompanied by alterations in mental status ranging from confusion to coma. High concentrations of pyroglutamic acid are found in the blood and urine. In this setting, glutathione levels are reduced because of the oxidative stress associated with critical illness and by the metabolism of acetaminophen. The reduction in glutathione secondarily leads to increased production of pyroglutamic acid. The diagnosis of pyroglutamic acidosis should be considered in patients with unexplained anion gap metabolic acidosis and recent acetaminophen ingestion.

ALKALI TREATMENT OF METABOLIC ACIDOSIS

Treatment of metabolic acidosis usually involves either sodium bicarbonate or citrate[34] (Table 12.2). $NaHCO_3$ can be taken orally as tablets or powder or given intravenously as a hypertonic bolus or an isotonic infusion, which can be created by adding 150 mmol $NaHCO_3$ to 1 liter of 5% dextrose in water (D5W). This solution is useful if treatment requires both volume expansion and alkali administration.

Citrate may be taken orally as a liquid, as sodium citrate, potassium citrate, or citric acid, or a combination. Many patients find citrate-containing solutions more palatable than oral $NaHCO_3$ as a source of oral alkali therapy. Oral citrate therapy should not be combined with medications that include aluminum. Citrate, which has a −3 charge under normal conditions, can complex with aluminum (Al^{3+}) in the intestinal tract, resulting in an uncharged moiety that is rapidly absorbed across the intestinal tract and then can dissociate to release free aluminum. This can increase the rate of aluminum absorption dramatically and in some patients, particularly those with severe CKD, has resulted in acute aluminum encephalopathy.

The dose of alkali therapy administered is based on both the total body bicarbonate deficit and the desired rapidity of treatment. Under normal circumstances, the volume of distribution (V_D) for bicarbonate is approximately 0.5 l/kg total body weight. Thus the bicarbonate deficit, in millimoles, can be estimated from the following formula:

$$\text{Bicarbonate deficit} = (0.5 \times \text{LBW}_{\text{kg}}) \times (24 - \text{HCO}_3^-)$$

where LBW_{kg} is the lean body weight in kilograms and *24* is the desired resultant bicarbonate concentration.

Several caveats regarding this equation should be understood. First, edema fluid contributes to the volume of distribution of bicarbonate. Accordingly, an estimation of the amount of edema fluid should be included in this calculation. Second, the volume of distribution for bicarbonate increases as the severity of the metabolic acidosis worsens. When serum [HCO_3^-] is 5 mmol/l or less, the volume of distribution may increase to 1 l/kg or more.

When acute treatment is desired, 50% of the bicarbonate deficit should be replaced during the first 24 hours. If hypertonic $NaHCO_3$ is administered, the increase in serum [HCO_3^-] will be mirrored by an increase in serum [Na^+]. After the initial 24 hours of therapy, the response to therapy and the patient's current clinical condition are reevaluated before future therapy is decided. Acute hemodialysis solely for the treatment of metabolic acidosis, other than that associated with renal failure, is rarely beneficial.

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SELF-ASSESSMENT QUESTIONS

1. A 65-year-old man presents with the chief complaint of progressive weakness over the last several months. He is normotensive; physical examination is unremarkable with these laboratory results (mmol/l): Na^+ 135, Cl^- 105, K^+ 3.0, HCO_3^- 18, creatinine 1.8, blood urea nitrogen (BUN), glucose 110, PCO_2 28 mm Hg, pH 7.33, hematocrit 25%, WBCs 5600/mm^2, platelets 340,000/mm^3, and urinalysis: trace protein, 1+ glucose, normal sediment, and 4.8 protein g/24 h.

   Which of the following is characteristic of the renal lesion present in this patient?

   A. Nephrocalcinosis will be shown on kidney, ureter, bladder (KUB) film of the abdomen.
   B. Serum HCO_3^- concentration will increase after oral bicarbonate administration but then decrease to 18 mmol/l after therapy is discontinued.
   C. Bicarbonate therapy will cause the serum K^+ to decline slightly because of a shift into cells.
   D. Urine pH will be persistently alkaline.
   E. Urine anion gap will be negative.

2. A 35-year-old woman presents having ingested a large quantity of aspirin after breaking up with her boyfriend. Her medical history is unremarkable, and she is taking no medications. Physical examination shows blood pressure 130/80 mm Hg lying and 110/62 standing, pulse 102, and respiratory rate 24; the remainder of examination is normal. Laboratory tests on admission (millimoles per liter) are Na^+ 138; K^+ 3.2; Cl^- 100; HCO_3^- 13; pH 7.48; PCO_2 21 mm Hg; urinalysis: 1+ ketone, normal sediment; and urine chemistry (mmol/L): Na^+ 38, Cl^- <10, and K^+ 45.

   Which of the following statements is *true* regarding salicylate poisoning?

   A. A 5-year-old child who has accidentally swallowed an unknown quantity of his mother's aspirin is likely to present with similar acid-base findings.
   B. The cause of hyperkalemia is a shift of K^+ into cells because of respiratory alkalosis.
   C. Serum uric acid levels are likely to be low in this patient.
   D. The high urine Na^+ is caused by proximal tubular dysfunction as a result of salicylate nephrotoxicity.
   E. Measurement of serum lactic acid in this patient is likely to be normal.

3. A 65-year-old white man with an extensive smoking history and known chronic obstructive pulmonary disease is admitted to the hospital with hematemesis. On the day of admission, endoscopy shows a nonbleeding duodenal ulcer. The procedure was complicated by the development of aspiration pneumonia and respiratory failure. A continuous infusion of intravenous lorazepam was required to control agitation and minimize peak inspiratory pressures. Admission laboratory results (mmol/l): Na^+ 142, K^+ 4.3, Cl^- 105, HCO_3^- 22, creatinine 1.4 mg/dl, BUN 25 mg/dl, hematocrit 36, pH 7.35, PCO_2 45, and PO_2 75. On hospital day 4, gastrointestinal bleeding recurred, and the patient was taken to the operating room and underwent oversewing of a bleeding duodenal ulcer. The patient remained hemodynamically stable throughout the hospitalization but continued to require intravenous lorazepam for sedation. Laboratory results (mmol/l): Na^+ 138, K^+ 4.8, Cl^- 100, HCO_3^- 10, creatinine 1.8 mg/dl, BUN 28 mg/dl, glucose 120 mg/dl, serum osmolality 330 mOsm/l (osmolar gap = 37).

   Which of the following is the cause of this patient's anion gap metabolic acidosis and increased osmolar gap?

   A. Propylene glycol toxicity
   B. Diabetic ketoacidosis
   C. Lactic acidosis
   D. Uremic acidosis
   E. Isopropyl alcohol administration

13

Metabolic Alkalosis

Alan Segal, F. John Gennari

DEFINITION

Metabolic alkalosis is caused by retention of excess alkali and is defined by a venous [total CO_2] (a measured value) of greater than 30 mmol/l or an arterial [HCO_3^-] (a calculated value) greater than 28 mmol/l. The increase in pH that results from the elevation in [HCO_3^-] induces hypoventilation, producing a secondary increase in arterial P_{CO_2}. Thus the disorder is characterized by coexisting elevations in serum [HCO_3^-], arterial pH, and P_{CO_2}. Because the kidney normally responds to an increase in [HCO_3^-] by rapidly excreting excess alkali, sustained metabolic alkalosis occurs only when some additional factor impairs bicarbonate excretion. Three factors play key roles: chloride depletion, abnormal aldosterone secretion, and hypokalemia.

BICARBONATE TRANSPORT ALONG THE NEPHRON

Figs. 13.1 and 13.2 illustrate the epithelial transporters and channels that participate in HCO_3^- reabsorption and secretion. In the proximal tubule, where most of the filtered HCO_3^- is reabsorbed, H^+ is secreted into the tubule both by the Na^+/H^+ exchanger (NHE3) and by an H^+-ATPase. In the thick ascending limb of the loop of Henle, H^+ is secreted via NHE3; in the collecting duct, H^+ secretion is accomplished primarily via an apical membrane H^+-ATPase that is regulated by aldosterone in concert with Na^+ delivery to this site in the nephron. When body K^+ stores are low, an apical membrane H^+/K^+-ATPase is activated in the α-intercalated cells, further promoting H^+ secretion linked to K^+ reabsorption.[2] Excretion of excess bicarbonate is facilitated by its secretion into the tubule urine by pendrin in β-intercalated cells.[3] Pendrin is activated by alkalemia and requires Cl^- reabsorption in exchange for secreted HCO_3^-. The HCO_3^- secreted into the urine by this transporter can be recaptured again by H^+ secretion further along in the collecting duct, so that excretion of excess alkali requires both stimulation of pendrin and suppression of the collecting duct H^+-ATPase.

FACTORS AFFECTING BICARBONATE REABSORPTION AND SECRETION

Angiotensin II

Ang II stimulates H^+ secretion in the proximal tubule via the apical Na^+/H^+ exchanger (NHE3) and bicarbonate reabsorption via the basolateral Na^+-HCO_3^- cotransporter (NBC).[3] In the distal nephron, Ang II stimulates H^+ secretion via the apical H^+-ATPase in α-ICs, and bicarbonate secretion via the apical Cl^-/HCO_3^- exchanger (pendrin) in β-ICs.[2,4,5]

Aldosterone

Aldosterone normally regulates sodium and potassium homeostasis, as well as proton secretion, via signaling along the distal nephron (see Fig. 13.1).[6] When aldosterone secretion is abnormal (e.g., primary hyperaldosteronism), activation of apical amiloride-sensitive epithelial sodium channel (ENaC) and basolateral Na^+,K^+-ATPase stimulates Na^+ reabsorption coupled to K^+ secretion in principal cells, and activation of apical H^+-ATPase stimulates proton secretion in α-ICs, causing metabolic alkalosis and hypokalemia.[7]

Pendrin

This Cl^-/HCO_3^- exchanger secretes bicarbonate and is stimulated by both Ang II and aldosterone.[2] Under conditions of chloride depletion, however, the reabsorptive effects of Ang II and aldosterone prevail because collecting duct Na^+ reabsorption is secondarily stimulated, providing the driving force for recapturing all secreted bicarbonate.

Hypokalemia

Potassium depletion promotes abnormal retention of filtered bicarbonate via activation of the K^+/H^+-ATPase in the α-ICs. Secretion of H^+ via this apical transporter is accompanied by basolateral reabsorption of bicarbonate (see Fig. 13.1). Hypokalemia also accelerates ammoniagenesis, providing increased ammonia delivery to the collecting duct urine, where it is available to combine with secreted H^+, allowing for increased H^+ excretion at any given urine pH.

PATHOPHYSIOLOGY OF METABOLIC ALKALOSIS

Normally, excess bicarbonate is rapidly excreted by the kidney by (1) an increased filtered load, allowing additional bicarbonate to be delivered to the distal nephron; (2) chloride-dependent secretion of bicarbonate by pendrin, in the cortical collecting duct;[4] and (3) down-regulation of H^+ secretion in the cortical and medullary collecting duct.

Metabolic alkalosis occurs when abnormal H^+ loss or bicarbonate administration is coupled with (1) a reduced filtered load of bicarbonate (e.g., hypoperfusion of the kidney, advanced kidney disease); (2) enhanced bicarbonate reabsorption along the tubule (e.g., effects of angiotensin II, aldosterone, hypokalemia); (3) continued stimulation of H^+ secretion by the α-intercalated cells in the collecting duct (e.g., primary hyperaldosteronism, chloride depletion); and/or (4) impaired bicarbonate secretion by pendrin (e.g., chloride depletion; advanced kidney disease).

With the exception of alkali administration in the setting of severe impairment of kidney function (GFR <30 ml/min), sustained metabolic

Three Major Types of Collecting Duct Epithelial Cells and their Transporters

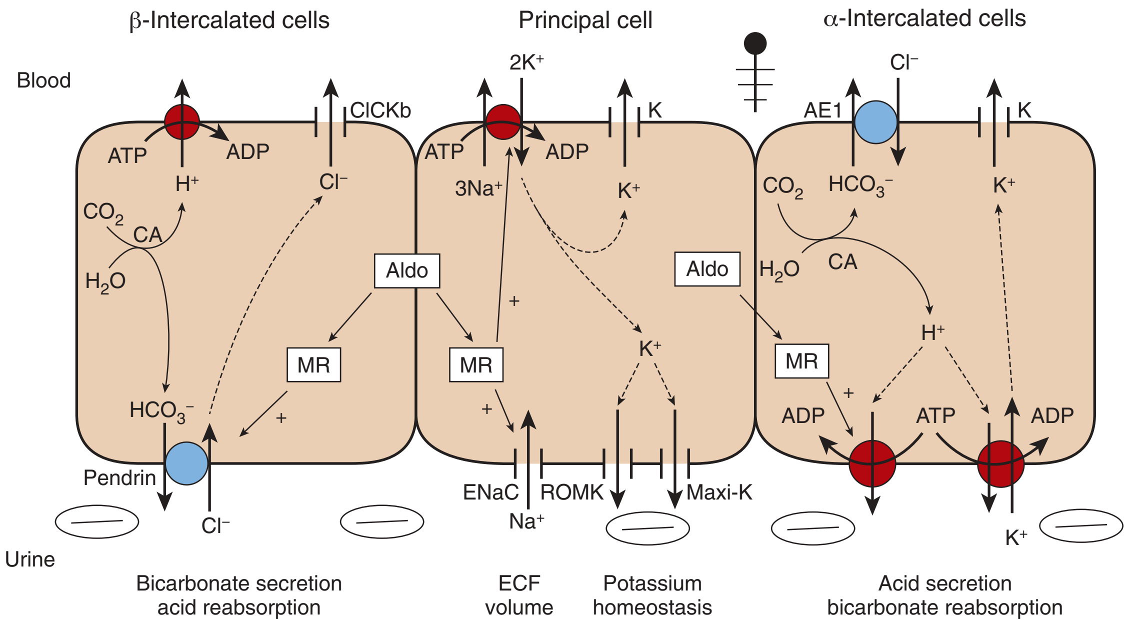

Fig. 13.1 Diagram of the three types of epithelial cells in the collecting duct and key transporters involved in Na^+, K^+, and H^+ reabsorption and secretion. By convention the blood side is electrical ground (⏚). Reabsorption of Na^+ by the principal cell *(middle)* via the epithelial Na^+ channel *(ENaC)* across the apical membrane and then via the Na^+,K^+-ATPase across the basolateral membrane renders the urinary lumen electronegative. This electronegativity (⊖) provides the driving force for K^+ secretion across the *ROMK* and maxi-K channels and facilitates H^+ secretion via the H^+-ATPase in the apical membrane of the α-intercalated cells *(right).* Proton secretion across the apical membrane is associated with bicarbonate reabsorption across the basolateral membrane via a Cl^-/HCO_3^- antiporter called *AE1.* A H^+-K^+-ATPase in the apical membrane of the α-intercalated cell becomes active under conditions of K^+ depletion. Bicarbonate secretion is accomplished by a Cl^-/HCO_3^- antiporter called *pendrin* in the apical membrane of the β-intercalated cell *(left).* Chloride exits the basolateral membrane via a Cl^- channel (ClCKb). Several of these processes are stimulated by aldosterone *(Aldo)* via the mineralocorticoid receptor *(MR). ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *CA,* carbonic anhydrase.

alkalosis is always the result of dysregulation of the transporters that control bicarbonate reabsorption and acid secretion by the kidney.

A key feature of this dysregulation is stimulation of collecting duct ion transport (Box 13.1).[9] Most commonly, stimulation of collecting duct ion transport is secondary to abnormalities in Na^+ and Cl^- reabsorption that occur before the urine reaches the collecting duct. Less frequently, metabolic alkalosis is the result of primary stimulation of collecting duct ion transport as a result of abnormal signaling via the mineralocorticoid receptor or because of genetic abnormalities. Fig. 13.3 summarizes the sites along the nephron and the key transport proteins involved in the pathophysiology of the main causes of metabolic alkalosis.

Secondary Stimulation of Collecting Duct Ion Transport

Chloride Depletion

The most common clinical presentations of metabolic alkalosis are generated by Cl^- depletion. The term *contraction alkalosis,* used as a synonym for Cl^- depletion alkalosis, is confusing because it implies that volume contraction itself is responsible for the disorder. The term refers specifically to the increase in serum [HCO_3^-] that follows only one type of extracellular fluid (ECF) volume contraction—that caused by selective Cl^- losses. Moreover, it is likely that volume contraction is neither necessary nor instrumental in inducing this change in serum [HCO_3^-].[10]

BOX 13.1 Pathophysiological Classification of Causes of Metabolic Alkalosis

Secondary Stimulation of Collecting Duct Ion Transport*

- Extrarenal Cl^- losses and secondary K^+ losses
- Renal Cl^- losses and secondary K^+ losses
  - Pharmacological (diuretics)
  - Inactivating gene mutations of Cl^- linked Na^+ cotransporters

Primary Stimulation of Collecting Duct Ion Transport*

- Mineralocorticoid excess
- Activating genetic mutations of ENaC or its signal pathway

Alkali Administration in Setting of Impaired HCO_3^- excretion (e.g. kidney failure)

ENaC, Epithelial sodium channel in collecting duct.
*Na^+ uptake, H^+ and K^+ secretion.

Cl^- depletion, induced by vomiting or nasogastric aspiration, increases serum [HCO_3^-].[11] The degree of alkalosis generated is greater when H^+ loss also occurs (Fig. 13.4), but it may occur even when H^+ loss is minimized by administration of a proton pump inhibitor. In either setting, maintenance of the disorder depends on sustained depletion

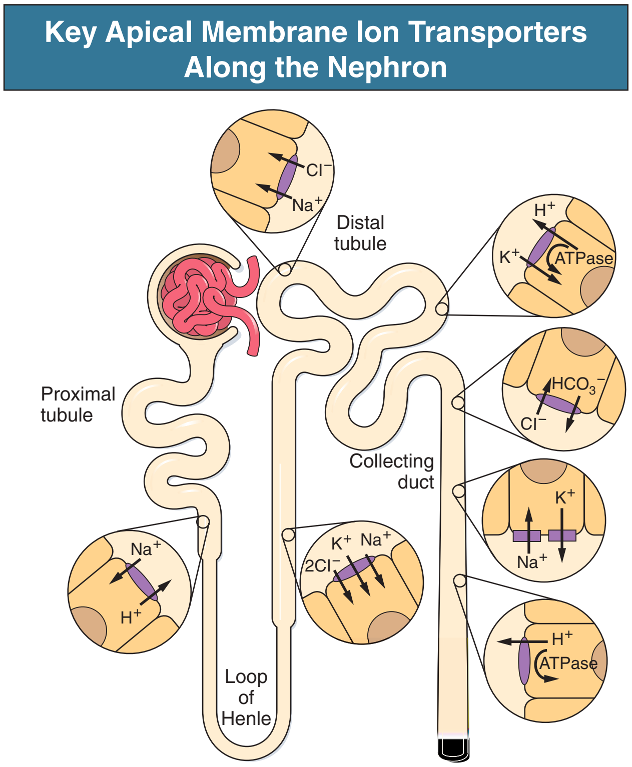

Fig. 13.2 Key apical membrane ion transporters along the nephron. Bicarbonate ions (HCO_3^-) are recaptured by H^+ secretion along the nephron. In the proximal tubule and loop of Henle, H^+ secretion is directly linked to Na^+ reabsorption through the Na^+/H^+ exchanger. In addition, H^+ secretion occurs in the proximal tubule through an apical membrane H^+-ATPase (not shown). In the collecting duct, H^+ secretion is indirectly coupled to Na^+ uptake via ENaC in the principal cells increasing lumen electronegativity, which promotes transport via the H^+-ATPase in the α-intercalated cells. Chloride-linked Na^+ reabsorption in the loop of Henle and early distal tubule affects H^+ secretion by determining Na^+ delivery to the collecting duct. Bicarbonate secretion occurs in the distal tubule and cortical collecting duct under conditions of alkalemia through a Cl^--linked exchanger (pendrin). Potassium reabsorption in states of K^+ depletion is linked to H^+ secretion through a H^+-K^+-ATPase.

of body Cl^- stores; serum [HCO_3^-] returns to normal when sufficient Cl^- is given to replenish losses.

Chloride-depletion metabolic alkalosis always causes concomitant K^+ depletion, but Cl^- administration can correct the alkalosis even if the K^+ deficit is deliberately maintained.[12] Despite this experimental finding, secondary K^+ depletion plays a key role in maintaining alkalosis. When K^+ depletion is sustained, much larger amounts of Cl^- are needed to fully correct the disorder.[13]

The metabolic alkalosis induced by gastrointestinal Cl^- losses can be very severe; serum [HCO_3^-] levels greater than 60 mmol/l have been reported.[14,15] A less severe metabolic alkalosis, without evident H^+ loss, is generated by the administration of loop or thiazide diuretics, and by two genetic abnormalities in Cl^- reabsorption, Bartter and Gitelman syndromes (see Chapter 47), which mimic the action of loop and thiazide diuretics, respectively.

When metabolic alkalosis is induced by Cl^- depletion and dietary Cl^- intake is restricted, a characteristic sequence of changes in electrolyte excretion occurs (see Fig. 13.4).[11] Sodium and HCO_3^- excretion increase transiently and then decrease rapidly to low levels, accompanied by abnormal K^+ excretion. The increase in K^+ excretion is also transient but nonetheless produces K^+ depletion. In the new steady state, urinary K^+ excretion matches intake despite K^+ depletion (see Fig. 13.4). As a result, hypokalemia is a cardinal feature of chloride-depletion metabolic alkalosis.

Maintenance of systemic alkalemia in the steady state (i.e., when the net acid excretion rate matches net acid production rate) indicates a failure to downregulate H^+ secretion in the collecting duct. The contributions of Cl^- and K^+ depletion to the maintenance of metabolic alkalosis is shown diagrammatically in Fig. 13.5.

Potassium Depletion

Potassium depletion downregulates both the Na^+-K^+-$2Cl^-$ cotransporter and the Na^+-Cl^- cotransporter,[16] increasing Na^+ delivery to the collecting duct and further stimulating collecting duct H^+ secretion (see Fig. 13.5). When K^+ deficiency is severe, this effect results in abnormal Cl^- excretion despite Cl^- depletion and sustained metabolic alkalosis even when NaCl is administered.[17] Finally, K^+ depletion stimulates renal NH_4^+ production, facilitating the acid excretion needed to sustain metabolic alkalosis (see Fig. 13.5). Although the apical Cl^-/HCO_3^- exchanger (pendrin) is activated by metabolic alkalosis, its activation in turn stimulates collecting duct H^+ secretion, resulting in reabsorption of all the secreted HCO_3^- and continued acid excretion.[18]

Induction of net K^+ loss by severe restriction of dietary K^+ intake produces a small increase in serum [HCO_3^-].[13] When dietary Cl^- intake is concomitantly restricted, however, the resultant alkalosis is four times as great, illustrating the synergistic and complementary roles of Cl^- and K^+ in regulating renal HCO_3^- reabsorption. Depletion of body K^+ stores is probably the most important factor in producing and sustaining the rarer forms of metabolic alkalosis, discussed below.

Primary Stimulation of Collecting Duct Ion Transport

Primary stimulation of collecting duct ion transport accounts for less than 5% of the causes of metabolic alkalosis, of which the most common cause is primary hyperaldosteronism.[19] This disorder is characterized by persistently high and unregulated aldosterone secretion. As discussed earlier, aldosterone activates ENaC in the principal cell, and H^+-ATPase in the α-IC (see Figs. 13.1 and 13.3). Thus the effect of sustained aldosterone secretion is to increase Na^+ reabsorption and H^+ secretion in the collecting duct by a direct effect, leading to an increase in K^+ secretion and depletion of body K^+ stores. Sodium retention leads to hypertension and also ensures continued Na^+ delivery to the collecting duct, sustaining the cycle of increased Na^+ reabsorption and increased K^+ and H^+ secretion. Aldosterone also stimulates bicarbonate secretion via pendrin. This would act to mitigate the alkalosis, so the resultant bicarbonate level is determined by the stimulation of pendrin relative to ENaC stimulation.

As a result of all these events, metabolic alkalosis is sustained despite dietary Cl^- intake.

Exogenous Alkali

Normally the kidney responds rapidly to excess alkali by increasing HCO_3^- excretion, so sustained metabolic alkalosis does not occur unless massive amounts of alkali are administered. When lesser amounts of $NaHCO_3$ are ingested on a daily basis, serum [HCO_3^-] does not increase unless dietary Cl^- intake is severely restricted[20] or a second process associated with metabolic alkalosis (e.g., vomiting) is present.[21]

In contrast, if HCO_3^- excretion is impaired as a result of kidney failure, even minimal daily alkali administration can cause a sustained metabolic alkalosis independent of Cl^- intake.[22] End-stage renal disease results in impaired HCO_3^- excretion. Any added alkali remains in the body until it is consumed in buffering strong acids produced by protein metabolism or excreted via the gastrointestinal tract.

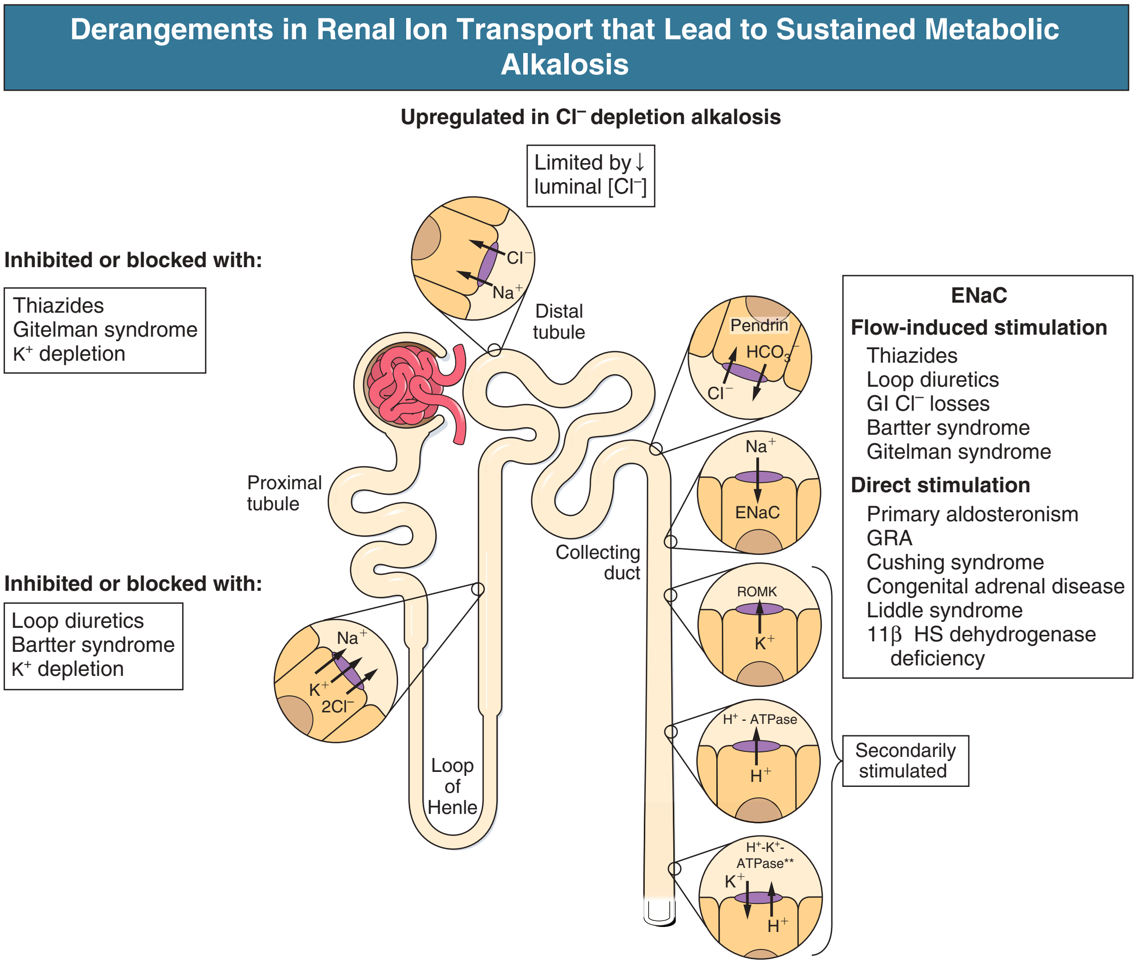
Derangements in Renal Ion Transport that Lead to Sustained Metabolic Alkalosis
Upregulated in Cl^- depletion alkalosis
Limited by ↓ luminal [Cl^-]
Inhibited or blocked with:
Thiazides
Gitelman syndrome
K^+ depletion
Cl^-
Na^+
Distal tubule
Pendrin
HCO_3^-
Cl^-
ENaC
Flow-induced stimulation
Thiazides
Loop diuretics
GI Cl^- losses
Bartter syndrome
Gitelman syndrome
Direct stimulation
Primary aldosteronism
GRA
Cushing syndrome
Congenital adrenal disease
Liddle syndrome
11β HS dehydrogenase deficiency
Proximal tubule
Na^+
ENaC
Collecting duct
Inhibited or blocked with:
Loop diuretics
Bartter syndrome
K^+ depletion
ROMK
K^+
Na^+
K^+
$2Cl^-$
H^+ - ATPase
H^+
Secondarily stimulated
Loop of Henle
H^+-K^+-ATPase**
K^+
H^+

Fig. 13.3 Derangements in renal ion transport that lead to sustained metabolic alkalosis. Schematic depiction of key apical membrane transport proteins in the loop of Henle and distal nephron and the ways in which their function is altered to impair renal HCO_3^- excretion and sustain K^+ excretion in the face of K^+ depletion. Bartter and Gitelman syndromes are caused by genetic abnormalities that impede the activity of or inactivate Cl^--linked Na^+ reabsorption in the loop and early distal tubule, respectively. The epithelial Na^+ channel in the collecting duct is stimulated directly in primary hyperaldosteronism and in several genetic abnormalities. One of these causes aldosterone secretion to respond to adrenocorticotropic hormone rather than to angiotensin II (GRA); one blocks downregulation of the channel (Liddle syndrome), and one allows cortisol to act as a mineralocorticoid (11β-hydroxysteroid dehydrogenase type 2 deficiency). *ENaC,* Amiloride-sensitive epithelial sodium channel; *GI,* gastrointestinal; *GRA,* Glucocorticoid remediable aldosteronism; *HS,* hydroxysteroid.

Secondary Response to the Alkalemia Induced by HCO_3^- Retention

Regardless of cause, body pH increases in metabolic alkalosis and elicits secondary hypoventilation, increasing arterial P_{CO_2}. The response is a potent one, occurring despite the concomitant development of hypoxemia. On average, P_{CO_2} increases by 0.7 mm Hg (0.1 kilopascal [kPa]) for each 1 mmol/l increase in serum [HCO_3^-]. Assuming a normal [HCO_3^-] of 24 mmol/l and normal P_{CO_2} of 40 mm Hg (5.5 kPa), the predicted P_{CO_2} for any given serum [HCO_3^-] in metabolic alkalosis can be calculated as follows:

$$P_{CO_2}(\text{mm Hg}) = 40 + 0.7 \times ([HCO_3^-]\,(\text{mmol/l}) - 24)$$

Although this formula is helpful in determining whether the ventilatory response to metabolic alkalosis is appropriate, it implies a precision that does not exist in nature. Variations of up to 5 to 7 mm Hg between the observed and calculated P_{CO_2} may occur. Moreover, when serum [HCO_3^-] exceeds 60 mmol/l, the formula is not a reliable predictor of the respiratory response. Even when metabolic alkalosis is severe (serum [HCO_3^-] >50 mmol/l), however, the P_{CO_2} (in mm Hg) virtually always exceeds the value for the serum [HCO_3^-] (in mmol/l).[14]

Fig. 13.6 illustrates the ameliorating effect of increasing P_{CO_2} on pH in metabolic alkalosis. While it mitigates the alkalemia, the increase in P_{CO_2}, when sustained, directly stimulates renal HCO_3^- reabsorption, increasing serum [HCO_3^-] further.[23] This effect is small and unimportant in the clinical setting.

ETIOLOGY

The major causes of metabolic alkalosis are subdivided into three groups based on pathophysiology (see Box 13.1).[9] The first group (secondary stimulation) is manifested by chloride and potassium depletion. The second group (primary stimulation) includes the metabolic alkaloses

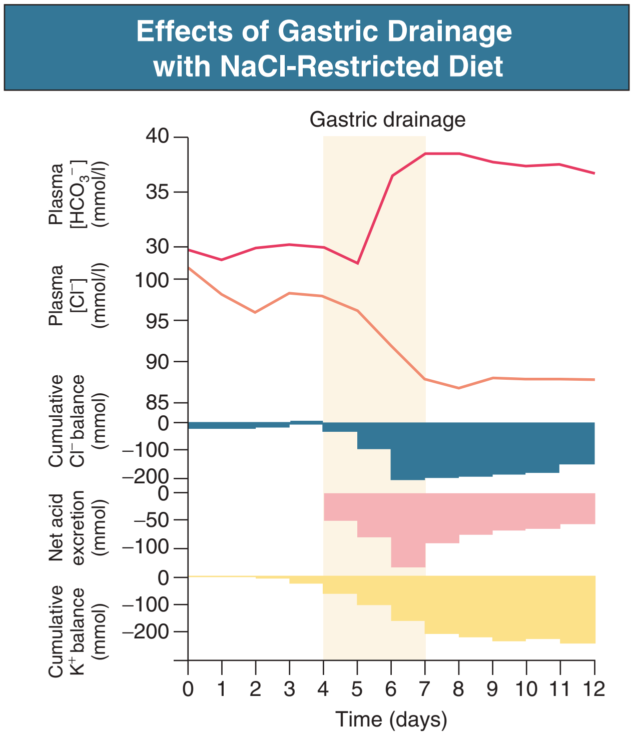

Fig. 13.4 Effect of gastric drainage on plasma [HCO_3^-] and [Cl^-] and on the net balance of [Cl^-] and [K^+] in the body in a normal individual ingesting a NaCl-restricted diet. Changes in net acid excretion are also shown. Gastric drainage on three consecutive nights in this subject increased plasma [HCO_3^-] by 9 mmol/l, a change that persisted after gastric drainage was stopped. Potassium depletion occurs as a result of renal K^+ losses during the period of gastric drainage. These losses are not regained, however, after the drainage is discontinued despite the continued daily ingestion of 70 mmol of K^+. Net acid excretion decreases transiently during the period of drainage but then returns to control levels despite sustained metabolic alkalosis. Chloride depletion is maintained by the low dietary intake of this ion.

induced and sustained by excess adrenal corticosteroids, or by collecting duct transport abnormalities that mimic excess mineralocorticoid activity. The third subgroup is caused by alkali administration or ingestion.

This new classification replaces the traditional separation of causes based on treatment response (i.e., chloride-responsive and chloride-resistant).

Secondary Stimulation of Collecting Duct Ion Transport

Box 13.2 lists the causes of metabolic alkalosis caused by stimulation of collecting duct ion transport by abnormal transport events occurring earlier in the nephron.

Vomiting or Nasogastric Drainage

Loss of chloride from the upper gastrointestinal tract, often accompanied by concomitant H^+ losses, produces a metabolic alkalosis that is sustained until body Cl^- stores are replenished (see previous discussion and Fig. 13.4). With continued emesis or nasogastric suction, serum [HCO_3^-] may rise to very high levels.[14,15]

Diuretic Administration

Diuretics that inhibit Cl^- transport proteins in the kidney are the most common cause of metabolic alkalosis (see Box 13.2). The loop diuretics inhibit the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle while thiazides and metolazone inhibit the Na^+-Cl^- cotransporter in the early distal tubule (see Fig. 13.3). These agents all impair Cl^- reabsorption, causing selective Cl^- depletion, and stimulate K^+ excretion by increasing Na^+ delivery to the collecting duct. The alkalosis produced is typically mild (serum [HCO_3^-] <38 mmol/l), except in patients who continue to ingest excess salt and have extreme renal Na^+ avidity. Hypokalemia due to K^+ depletion is prominent and a major management problem.[24]

Genetic Impairment of Cl^--Linked Na^+ Transport

Bartter and Gitelman syndromes are hereditary disorders manifested by metabolic alkalosis and hypokalemia without hypertension (see Chapter

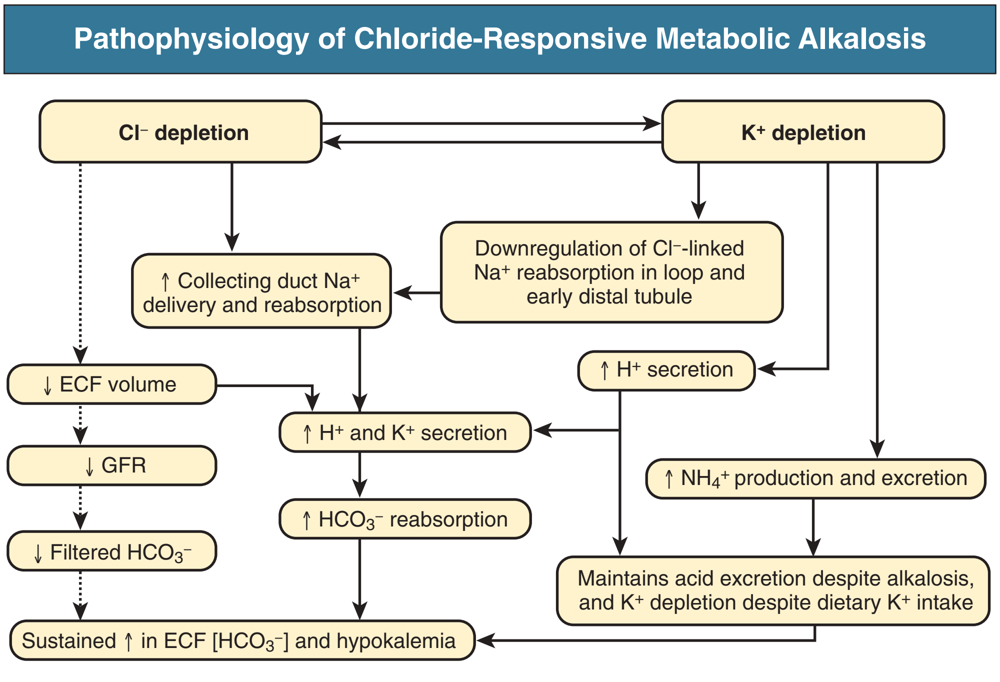
Pathophysiology of Chloride-Responsive Metabolic Alkalosis
Cl− depletion
K+ depletion
↑ Collecting duct Na+ delivery and reabsorption
Downregulation of Cl−-linked Na+ reabsorption in loop and early distal tubule
↓ ECF volume
↑ H+ secretion
↑ H+ and K+ secretion
↓ GFR
↑ NH4+ production and excretion
↑ HCO3− reabsorption
↓ Filtered HCO3−
Maintains acid excretion despite alkalosis, and K+ depletion despite dietary K+ intake
Sustained ↑ in ECF [HCO3−] and hypokalemia

Fig. 13.5 Pathophysiology of metabolic alkalosis caused by depletion of body chloride stores. Chloride depletion stimulates H^+ and K^+ secretion into the collecting duct as a result of disproportionate distal Na^+ delivery and reabsorption. The resultant K^+ depletion further stimulates H^+ secretion and promotes ammonium (NH_4^+) production and excretion as well as downregulating Na^+ reabsorption in the loop of Henle. These events contribute to a sustained increase in serum [HCO_3^-]. Chloride depletion also reduces the glomerular filtration rate and therefore HCO_3^- filtration, reducing potential alkali losses. As indicated by the *dashed lines,* the role of this effect in sustaining metabolic alkalosis remains controversial.

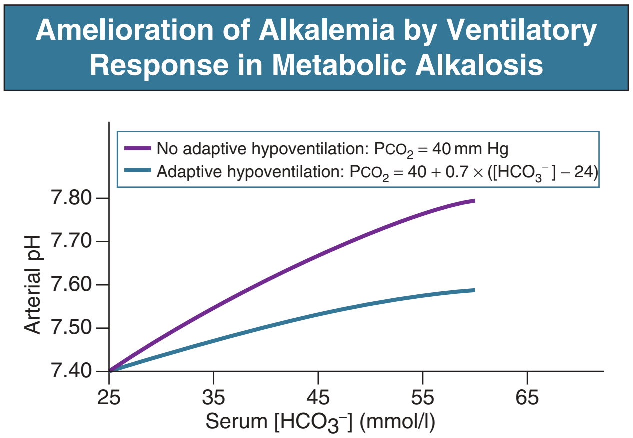

Fig. 13.6 Amelioration of alkalemia by the normal ventilatory response to the increase in serum $[HCO_3^-]$ in metabolic alkalosis. The *red (upper) line* in the graph illustrates the relationship between arterial pH and serum $[HCO_3^-]$ in the absence of adaptive hypoventilation (P_{CO_2} maintained at 40 mm Hg), and the *green (lower) line,* the relationship when P_{CO_2} is increased by the expected level of hypoventilation.

BOX 13.2 Causes of Metabolic Resulting From Secondary Stimulation of Collecting Duct Ion Transport

Chloride loss from the stomach (common)
- Vomiting
- Nasogastric suction

Chloride-depleting diarrheas (rare)
- Congenital chloridorrhea
- Some villous adenomas of the colon
- High-volume ileostomy losses

Diuretic administration (common)
- Thiazides
- Metolazone
- Loop diuretics: furosemide, bumetanide, torsemide, ethacrynic acid

Impaired chloride-linked sodium transport (rare)
- Bartter syndrome
- Gitelman syndrome

Rare causes
- Recovery from chronic hypercapnia
- Gastrocystoplasty
- Cystic fibrosis
- Severe potassium deficiency

47). Bartter syndrome is due to loss of function mutations in one of the transport elements in the thick ascending loop of Henle resulting in impaired function of the Na^+-K^+-$2Cl^-$ cotransporter. Clinically, the phenotype mimics the effect of loop diuretics (see Fig. 13.3).[25]

Patients with this syndrome usually become ill early in life with metabolic alkalosis and volume depletion, features similar to those seen in individuals abusing loop diuretic agents.

Gitelman syndrome is caused by genetic mutations that decrease the activity of the thiazide-sensitive Na^+-Cl^- cotransporter in the early distal tubule (see Fig. 13.3), leading to hypokalemia and metabolic alkalosis similar to that caused by thiazide diuretics. Gitelman syndrome becomes clinically apparent later in life and differs from Bartter syndrome in that hypomagnesemia and hypocalciuria are prominent features.[26,27]

Recovery From Chronic Hypercapnia

Sustained hypercapnia results in an increase in HCO_3^- reabsorption and a decrease in Cl^- reabsorption by the kidney (see Chapter 14). As a result, serum $[HCO_3^-]$ increases and body Cl^- stores are reduced. When P_{CO_2} is restored to normal, renal excretion of excess HCO_3^- requires repletion of the Cl^- losses incurred during adaptation. If these Cl^- losses are not replaced, recovery from hypercapnia can result in persistent metabolic alkalosis.

Congenital Chloridorrhea

This rare form of diarrhea is caused by an inactivating mutation in the “downregulated in adenoma” *(DRA)* gene, an apical membrane Cl^-/HCO_3^- exchanger in the small intestine. The result is a large-volume diarrhea that is rich in Cl^-, causing selective loss of this ion as well as H^+ and K^+ losses. The resultant metabolic alkalosis is ameliorated by K^+ and Cl^- administration, but correction is difficult because of continuing losses. The volume of diarrhea can be reduced by proton pump inhibition, which reduces gastric Cl^- secretion and presumably reduces Cl^- delivery to the small intestine.[28]

Other Causes of Excessive Chloride Losses

Villous adenomas occur in the distal colon and typically secrete 1 to 3 liters of fluid a day that is rich in Na^+, Cl^-, and K^+. Because the volume of secreted fluid is relatively low, these tumors are only occasionally associated with metabolic alkalosis, and it is usually mild if present.[29] Cystic fibrosis is characterized by high sweat $[Cl^-]$ and, with excessive sweating, Cl^- losses can be large enough to cause metabolic alkalosis. In children and adolescents, this acid-base disorder can be the presenting symptom.[30] Patients with high-volume chloride-rich ileostomy losses can sometimes develop severe metabolic alkalosis.[31] The use of gastric tissue to augment bladder size (gastrocystoplasty) can occasionally lead to transient metabolic alkalosis as a result of gastrin-induced Cl^- secretion into the urine.[32]

Severe K^+ Deficiency

In patients with severe K^+ depletion (serum $[K^+]$ <2 mmol/l), metabolic alkalosis can be sustained despite Cl^- administration.[17] Chloride resistance in this setting is probably due to the impairment of renal Cl^- reabsorption induced by K^+ depletion and activation of the K^+-H^+-ATPase in the α-ICs (see earlier discussion). Partial repletion of K^+ stores rapidly reverses this problem and renders the alkalosis Cl^- responsive.

Primary Stimulation of Collecting Duct Ion Transport

Box 13.3 lists the causes of metabolic alkalosis secondary to primary stimulation of collecting duct ion transport.

Mineralocorticoid Excess

The metabolic alkalosis induced by aldosterone and other mineralocorticoids is typically mild (serum $[HCO_3^-]$ 30 to 35 mmol/l) and is associated with more severe hypokalemia (K^+ often <3 mmol/l) than is observed with Cl^- depletion alkalosis.[16,19] Primary hyperaldosteronism is the most common cause of this form of metabolic alkalosis (see Chapter 38), but it also can occur with rarer hereditary defects in cortisol synthesis or in the regulation of aldosterone secretion (see Box 13.3). Glucocorticoid-remediable aldosteronism (Chapter 47) is caused by a mutation that results in aldosterone secretion falling under the control of adrenocorticotropic hormone (ACTH) rather than angiotensin. Fludrocortisone, an oral mineralocorticoid drug, as well as inhaled 9α-fluoro-prednisolone can induce metabolic alkalosis if used inappropriately. Corticosteroids, when administered in very high doses, increase renal K^+ excretion nonspecifically and produce a mild increase

BOX 13.3 Causes of Metabolic Alkalosis Resulting From Primary Stimulation of Collecting Duct Ion Transport

Mineralocorticoid Excess

- Primary hyperaldosteronism: Adenoma, hyperplasia
- Cushing syndrome
- Corticotropin-secreting tumor
- Renin-secreting tumor
- Glucocorticoid-remediable aldosteronism
- Adrenogenital syndromes
- Fludrocortisone treatment
- 9α-Fluoro-prednisolone (inhaled)

Apparent Mineralocorticoid Excess

- Licorice
- Carbenoxolone
- Liddle syndrome
- 11β-Hydroxysteroid dehydrogenase deficiency

Glucocorticoids (High Dose)

- Methylprednisolone

in serum [HCO_3^-]. High aldosterone levels induced by hyperreninemia in renovascular or malignant hypertension are associated with hypokalemia and, occasionally, with very minor increases in serum [HCO_3^-].

Apparent Mineralocorticoid Excess Syndromes

Several inherited abnormalities produce a metabolic alkalosis that is clinically indistinguishable from hyperaldosteronism but without measurable aldosterone (see Chapter 47). Liddle syndrome results from a genetic mutation that prevents the removal of ENaC from the urinary membrane of collecting duct epithelial cells (see Fig. 13.3). As a result, hyperreabsorption of Na^+ via ENaC cannot be downregulated, causing the same cascade of events seen in hyperaldosteronism. Because continuous stimulation of Na^+ reabsorption expands ECF volume and decreases ECF [K], aldosterone levels are vanishingly low. This condition is also called *pseudohyperaldosteronism* because the phenotype makes it appear that aldosterone levels are high when in fact aldosterone (and renin) levels are negligible.

In another rare familial disorder, the syndrome of apparent mineralocorticoid excess, a mutation inactivates 11β-hydroxysteroid dehydrogenase type 2, an enzyme adjacent to the mineralocorticoid receptor that rapidly converts cortisol to cortisone, minimizing cortisol binding.[34] When the enzyme is inactivated, cortisol activates the receptor, stimulating Na^+ reabsorption and K^+ secretion and producing metabolic alkalosis and hypertension. Glycyrrhizic acid (a component of black licorice), carbenoxolone, and gossypol (an agent that retards spermatogenesis) all inhibit the activity of 11β-hydroxysteroid dehydrogenase type 2 and can cause the same clinical picture.[16] Just as in Liddle syndrome, aldosterone and renin levels are negligible, so this is another form of pseudohyperaldosteronism.

Alkali Administration

Table 13.1 lists the causes of metabolic alkalosis induced by alkali administration. Unless given in massive amounts, exogenous alkali produces metabolic alkalosis in individuals with normal kidney function only when body K^+ or Cl^- stores are deficient (see earlier discussion and Fig. 13.3).[20] In acute or chronic kidney disease, alkali administration or ingestion can produce metabolic alkalosis independent of K^+ and Cl^- stores.[22]

TABLE 13.1 Causes of Metabolic Alkalosis Associated with Alkali Administration

Renal Status	Causes
Normal kidney function*	$NaHCO_3$, citrate, acetate, lactate, amino acid anions
Kidney failure	$NaHCO_3$, citrate, acetate, lactate, amino acid anions Milk alkali syndrome Aluminum hydroxide with K^+ exchange resin

*Only in presence of K^+ depletion or very low NaCl intake

TABLE 13.2 Potential Sources of Alkali

Alkali or Alkali Precursors	Source
Bicarbonate	$NaHCO_3$: Pills, intravenous solutions Proprietary preparations (e.g., Alka-Seltzer), baking soda $KHCO_3$: Pills, oral solutions
Lactate	Ringer solutions Peritoneal dialysis solutions
Acetate, glutamate, propionate	Parenteral nutrition solutions
Citrate	Blood products Plasma exchange, K^+ supplements Alkalinizing agents
Calcium compounds*	Calcium supplements and phosphate binders ($CaCO_3$, calcium acetate, calcium citrate)

*Alkalinizing effect minimal when given orally.

Milk-alkali syndrome is characterized by the concomitant presence of metabolic alkalosis and kidney damage, brought on by the ingestion of $NaHCO_3$ in combination with excess calcium (either in milk or as $CaCO_3$).[35,36] Kidney damage is caused by calcium deposition (facilitated by an alkaline urine). Metabolic alkalosis is maintained because HCO_3^- excretion is limited in the face of continued ingestion. Metabolic alkalosis is usually relatively mild in these patients unless they develop concomitant vomiting.[21] In hospitalized patients with kidney failure, a wide variety of alkali sources or alkali precursors can cause metabolic alkalosis (Table 13.2). A common offender is acetate used to replace chloride in parenteral nutrition solutions. Although aluminum hydroxide is only rarely administered now, its use in combination with sodium polystyrene sulfonate (Kayexalate) can cause metabolic alkalosis because aluminum binds to the resin in exchange for Na^+. As a result, the HCO_3^- normally secreted into the duodenum is not titrated by H^+ (which was neutralized by the aluminum hydroxide), nor does it form an insoluble salt with aluminum. Instead, it is completely reabsorbed from the gut, increasing serum [HCO_3^-].[37]

Other Causes

Citrate, an organic anion used as an anticoagulant in blood products, can produce metabolic alkalosis because full metabolism of sodium citrate ($C_6H_5O_7Na_3$) yields 3 molecules of $NaHCO_3$. Metabolic alkalosis can occur after (1) massive blood transfusions resulting from the large amount of new HCO_3^- generated acutely; (2) in patients with impaired kidney function treated with plasma exchange using fresh frozen plasma because this solution contains a high concentration of sodium citrate[38]; and (3) when using regional citrate anticoagulation during continuous dialysis procedures.[39]

Refeeding after starvation causes an abrupt increase in serum [HCO_3^-] from the low levels characteristic of the fasting state. In some instances, serum [HCO_3^-] increases transiently above normal, causing mild metabolic alkalosis. The mechanisms are multiple, including HCO_3^- generation from metabolism of accumulated organic anions and K^+ and Cl^- depletion.

Administration of either vitamin D or parathyroid hormone causes a small increase in serum [HCO_3^-].[40,41] Despite this experimental finding, hyperparathyroidism is not associated with clinically significant metabolic alkalosis. Hypercalcemia and vitamin D intoxication have been associated with metabolic alkalosis, but in most instances, the alkalosis can be explained by the vomiting that accompanies these disorders.

CLINICAL MANIFESTATIONS

Mild to moderate metabolic alkalosis is well tolerated, with few clinically important adverse effects. Patients with serum [HCO_3^-] levels as high as 40 mmol/l are usually asymptomatic. The adverse effect of most concern is hypokalemia, which increases the likelihood of cardiac arrhythmias in patients with underlying cardiac dysfunction.[41] With more severe metabolic alkalosis (serum [HCO_3^-] >45 mmol/l), arterial Po_2 often falls to less than 50 mm Hg (<6.6 kPa) secondary to hypoventilation, and ionized calcium decreases (due to alkalemia). Patients with serum [HCO_3^-] greater than 50 mmol/l may develop seizures, tetany, delirium, or stupor. Changes in mental status and cardiac irritability also can occur and are probably multifactorial in origin, as a result of alkalemia, hypokalemia, hypocalcemia, and/or hypoxemia.

DIAGNOSIS

Diagnosis of metabolic alkalosis involves three steps (Fig. 13.7). The first step, detection, is most often based on the finding of elevated venous [total CO_2]. The second step is evaluation of the secondary response (hypoventilation), excluding the possibility that a respiratory acid-base abnormality is also present. This step requires measurement of arterial pH and Pco_2. The third step is determination of the cause.

Serum [total CO_2] levels above 30 mmol/l in association with hypokalemia are virtually pathognomonic of metabolic alkalosis. The only other cause of an elevated value is chronic respiratory acidosis, and hypokalemia is not a feature of this disorder (see Chapter 14). Because the diagnosis is usually evident and the disorder is almost always uncomplicated, one need not measure pH and Pco_2 in most patients. If the alkalosis is severe (serum [HCO_3^-] >38 mmol/l), if the cause of the elevated [HCO_3^-] is unclear, or if a mixed acid-base disorder is suspected, however, one should always fully characterize the disorder to confirm the presence of alkalosis and allow an estimation of whether the degree of hypoventilation is appropriate for the elevation in serum [HCO_3^-] (see Fig. 13.7 and earlier equation). A major deviation in Pco_2 from the expected value indicates the presence of a complicating respiratory acid-base disorder (either respiratory acidosis or alkalosis; see Chapter 14). The anion gap is not increased in mild to moderate metabolic alkalosis, but it can be increased by as much as 3 to 5 mmol/l when alkalosis is severe. If the anion gap is greater than 20 mmol/l, the disorder is most likely complicated by superimposed metabolic acidosis (see Chapter 12).

In most instances, the third step, elucidation of the cause, is straightforward. In more than 95% of cases, metabolic alkalosis is caused either by diuretic use or by Cl^- losses from the gastrointestinal tract. This information is easily obtained from the history, and attention can be directed toward appropriate treatment. If the cause is unclear, measurement of urine [Cl^-] may help. Unless the patient has recently taken a diuretic agent, urine [Cl^-] should be less than 10 mmol/l if the metabolic alkalosis is due to Cl^- depletion. Urine Cl^- excretion is also usually low in bulimic patients, but may be elevated if measured shortly after a vomiting episode (see earlier in discussion of pathophysiology). In this setting or with surreptitious diuretic use, urine [Cl^-] may be high, causing a diagnostic dilemma that may lead to an extensive workup for rarer forms of metabolic alkalosis. Urinary screens for specific diuretic compounds may be necessary to establish the correct diagnosis. If the cause is not apparent from this analysis, rarer forms of metabolic alkalosis caused by tubule transport abnormalities should be considered. In these forms of metabolic alkalosis, urine [Cl^-] is typically greater than 30 mmol/l.

In the patient with hypertension and adequate chloride intake who is not taking any diuretic agents, the most common cause of metabolic alkalosis is primary hyperaldosteronism. Measurement of serum renin and serum or urine aldosterone levels can distinguish mineralocorticoid excess syndromes from the rarer syndromes of pseudohyperaldosteronism (Fig. 13.7, see Chapter 38). In the normotensive or hypotensive patient who is not taking any diuretic agents and has metabolic alkalosis *despite adequate chloride intake,* Bartter or Gitelman syndrome should be considered. Aldosterone and renin levels are not helpful in making these diagnoses because the levels can be low or high, depending on the patient's ECF volume at the time of measurement. Familial genetic studies can establish these diagnoses with high specificity.

TREATMENT

Chloride Depletion Metabolic Alkalosis

In the patient with metabolic alkalosis secondary to nasogastric drainage or vomiting, some degree of ECF volume depletion is virtually always a concomitant feature and treatment is straightforward. Administration of intravenous NaCl will correct both the alkalosis and volume depletion. Potassium losses also should be replaced by oral or intravenous KCl. Typically the K^+ deficit is 200 to 400 mmol. When nasogastric drainage must be continued, H^+ and Cl^- losses can be reduced by administration of drugs that inhibit gastric acid secretion.

In contrast to patients with gastrointestinal losses, NaCl administration is not indicated in patients with metabolic alkalosis caused by diuretics unless clinical signs of volume depletion are present. Potassium chloride supplements should be given to minimize K^+ depletion and mitigate the severity of the metabolic alkalosis. The addition of a potassium-sparing diuretic, such as amiloride, triamterene, spironolactone, or eplerenone, can assist in minimizing these abnormalities. Complete repair of diuretic-induced metabolic alkalosis is often difficult because of continued Cl^- and K^+ losses. Fortunately, such a therapeutic goal is not necessary in most instances.

The metabolic alkalosis and hypokalemia seen in Bartter and Gitelman syndromes is the most difficult to manage. In addition to oral KCl supplements (and magnesium supplements in Gitelman syndrome), nonsteroidal antiinflammatory drugs have been used with moderate success. These drugs help minimize renal Cl^- losses.

Mineralocorticoid and Apparent Mineralocorticoid-Induced Metabolic Alkalosis

Management of metabolic alkalosis caused by mineralocorticoids or tubule transport abnormalities that mimic mineralocorticoid excess depends on the underlying cause. If the alkalosis is caused by an adrenal adenoma, the disorder may be corrected by surgical removal (see Chapter 38) but often can be managed medically using spironolactone or

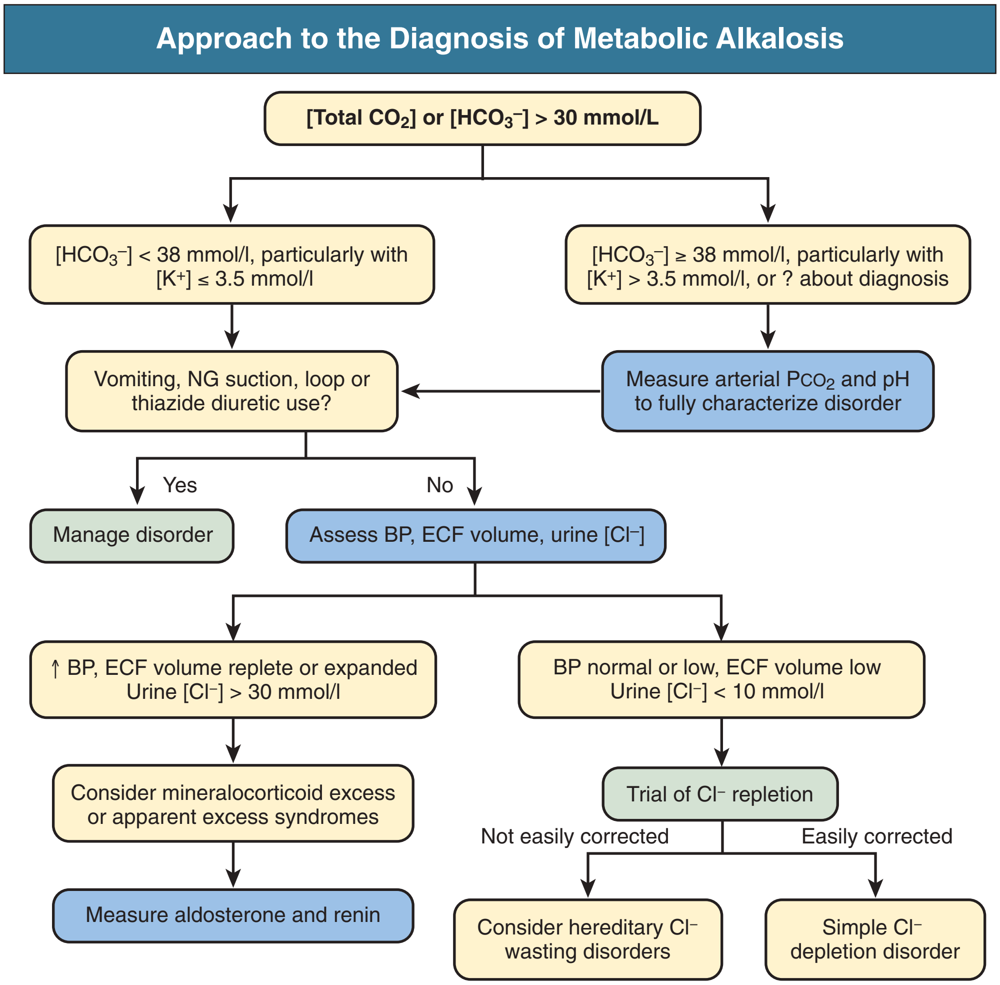
Approach to the Diagnosis of Metabolic Alkalosis
[Total CO_2] or [HCO_3^-] > 30 mmol/L
[HCO_3^-] < 38 mmol/l, particularly with [K^+] ≤ 3.5 mmol/l
[HCO_3^-] ≥ 38 mmol/l, particularly with [K^+] > 3.5 mmol/l, or ? about diagnosis
Vomiting, NG suction, loop or thiazide diuretic use?
Measure arterial P_{CO_2} and pH to fully characterize disorder
Yes
No
Manage disorder
Assess BP, ECF volume, urine [Cl^-]
↑ BP, ECF volume replete or expanded Urine [Cl^-] > 30 mmol/l
BP normal or low, ECF volume low Urine [Cl^-] < 10 mmol/l
Consider mineralocorticoid excess or apparent excess syndromes
Trial of Cl^- repletion
Not easily corrected
Easily corrected
Measure aldosterone and renin
Consider hereditary Cl^- wasting disorders
Simple Cl^- depletion disorder

Fig. 13.7 **Approach to diagnosis of metabolic alkalosis.** If the increase in [total CO_2] (or serum [HCO_3^-]) is mild and hypokalemia is present, arterial gas measurements are usually not necessary, and a simple algorithm can be used to diagnose the cause of the metabolic alkalosis. If hypokalemia is not present, if the increase in serum [total CO_2] is severe, or if there is a question about the diagnosis, arterial measurement of pH and P_{CO_2} is recommended to determine whether the condition is due to metabolic alkalosis, respiratory acidosis, or a mixed disorder. *BP,* Blood pressure; *ECF,* extracellular fluid; *NG,* nasogastric.

eplerenone. In other forms of primary hyperaldosteronism, the alkalosis can be minimized by dietary NaCl restriction and aggressive replacement of body K^+ stores. Spironolactone or eplerenone can also correct the disorder. In glucocorticoid-remediable aldosteronism, the disorder is corrected by dexamethasone administration, which suppresses ACTH secretion and thereby reduces aldosterone secretion. In Liddle syndrome, amiloride is the most effective treatment. Amiloride is not as effective for 11β-hydroxysteroid dehydrogenase deficiency; eplerenone may be the best treatment, especially in children, because it specifically blocks the mineralocorticoid receptor and unlike spironolactone does not bind to estrogen and androgen receptors.[42,43]

Alkali Ingestion

Identification and discontinuation of the offending alkali (Table 13.2) is the first approach to treatment. In the intensive care unit, care should be taken to look for sources of exogenous alkali.

SPECIAL PROBLEMS IN MANAGEMENT

Management of metabolic alkalosis is a more difficult undertaking in patients with severe congestive heart failure or kidney failure. In patients with heart failure and fluid overload who still have adequate kidney function, acetazolamide can be used to reduce serum [HCO_3^-]. This carbonic anhydrase inhibitor impairs H^+-linked Na^+ reabsorption, causing excretion of both Na^+ and HCO_3^-. Acetazolamide decreases extracellular volume and serum [HCO_3^-], but it also promotes K^+ excretion, exacerbating hypokalemia. Its use should be accompanied by aggressive K^+ replacement therapy.

In patients with kidney failure, serum [HCO_3^-] can be reduced in a timely fashion by renal replacement therapy. Continuous venovenous hemofiltration can remove as much as 30 l/day of an ultrafiltrate of plasma, and a bicarbonate-free replacement solution can be used to reduce serum [HCO_3^-] and increase serum [Cl^-]. Serum [HCO_3^-] also can be lowered by continuous slow low-efficiency dialysis, with the dialysate [HCO_3^-] adjusted to 23 mmol/l. Standard hemodialysis or peritoneal dialysis is less useful because these treatments are designed to add alkali to the blood. However, hemodialysis machines allow adjustment of the dialysate [HCO_3^-] to as low as 30 mmol/l, and this has been used to treat severe metabolic alkalosis successfully.[14]

If renal replacement therapy is unavailable, titration with HCl is an alternative therapy. This approach is limited by the concentration of HCl that can be administered without producing hemolysis or venous coagulation. Although some investigators have used higher concentrations, the recommended safe level of H^+ should not exceed 100 mmol/l (0.1 N HCl). Even at this concentration, HCl must be administered through a central vein. Because the apparent space of distribution of HCO_3^- is approximately 50% of body weight, 350 mmol of H^+ is required to reduce serum $[HCO_3^-]$ by 10 mmol/l in a 70-kg patient. The volume of fluid required for this titration using HCl, unfortunately, is 3.5 liters. Ammonium chloride (NH_4Cl) and arginine monohydrochloride are not recommended for the treatment of metabolic alkalosis because of the life-threatening complications of ammonia intoxication and severe hyperkalemia, respectively.[44]

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SELF-ASSESSMENT QUESTIONS

1. Sustained metabolic alkalosis is always due to:
   A. Impaired renal excretion of excess bicarbonate
   B. Depletion of body chloride stores
   C. Depletion of body potassium stores
   D. Increased production of mineralocorticoids
2. You are asked to see a 45-year-old woman with the following venous blood laboratory results:

Na^+	138 mmol/l
K^+	3.2 mmol/l
Cl^-	88 mmol/
Total CO_2	37 mmol/l
Creatinine	1.3 mg/dl

   The most useful information for diagnosing the cause of these abnormal laboratory values will come from which of the following data?
   A. Arterial pH and Pco_2 measurements
   B. Urine chloride concentration
   C. Aldosterone and renin measurements
   D. History and physical examination
3. Which of the following ion transporters appears to play a central role in the pathogenesis of all causes of metabolic alkalosis:
   A. The $Na^+/K^+/2Cl^-$ cotransporter
   B. The sodium channel ENaC
   C. The potassium channel ROMK
   D. The H^+-ATPase hydrogen secretory transporter
4. You see a patient with hypertension (BP 150/95) and the following laboratory values. She is asymptomatic, save for some constipation. She has no edema. She has a normal appetite and her BMI is 26. She was adopted, so no family history is available.

Na^+	143 mmol/l
K^+	2.8 mmol/l
Cl^-	102 mmol/
Total CO_2	34 mmol/l
Creatinine	0.9 mg/dl

   Which of the following laboratory tests will provide you with the most helpful data in seeking the cause of her problem?
   A. Urine chloride concentration
   B. Abdominal CT scan
   C. Arterial pH and Pco_2
   D. Serum aldosterone and renin levels

14

Respiratory Acidosis, Respiratory Alkalosis, and Mixed Disorders

Horacio J. Adrogué, Nicolaos E. Madias

Deviations of systemic acidity in either direction can have adverse consequences and, when severe, can be life-threatening to the patient. Therefore it is essential for the clinician to recognize and properly diagnose acid-base disorders, understand their impact on organ function, and be familiar with their treatment and the potential complications of treatment.[1,2]

RESPIRATORY ACIDOSIS (PRIMARY HYPERCAPNIA)

Definition

Respiratory acidosis is the acid-base disturbance initiated by an increase in CO_2 tension (Pco_2) of body fluids and whole-body CO_2 stores. The secondary increment in serum bicarbonate ion concentration (serum $[\text{HCO}_3^-]$) observed in acute and chronic hypercapnia is an integral part of respiratory acidosis.[3] The level of arterial CO_2 tension (Paco_2) is greater than 45 mm Hg in patients with simple respiratory acidosis, as measured at rest and at sea level. (To convert values from millimeters of mercury [mm Hg] to kilopascals [kP], multiply by 0.1333.) An element of respiratory acidosis may still occur with lower Paco_2 in patients residing at high altitude (i.e., above 4000 m or 13,000 ft) or with metabolic acidosis, in which a normal Paco_2 is inappropriately high for this condition.[4] Another special case of respiratory acidosis is the presence of arterial eucapnia, or even hypocapnia, occurring together with severe venous hypercapnia, in patients having an acute, profound decrease in cardiac output but relative preservation of respiratory function.[5,6] This disorder is known as pseudo–respiratory alkalosis and is examined in the discussion of respiratory alkalosis.

Etiology and Pathogenesis

The ventilatory system is responsible for eucapnia by adjustment of alveolar minute ventilation ($\dot{V}_A$) to match the rate of CO_2 production. Its main elements are the respiratory pump, which generates a pressure gradient responsible for airflow, and the loads that oppose such action.

CO_2 retention can occur from an imbalance between the strength of the respiratory pump and the extent of respiratory load (Fig. 14.1). When the respiratory pump is unable to balance the opposing load, respiratory acidosis develops. Respiratory acidosis may be acute or chronic (Tables 14.1 and 14.2). Certain causes of chronic respiratory acidosis (e.g., chronic obstructive pulmonary disease [COPD]) can superimpose an element of acute respiratory acidosis during periods of decompensation (e.g., pneumonia, major surgery, heart failure). Life-threatening acidemia of respiratory origin can occur during severe, acute respiratory acidosis or with respiratory decompensation in patients with chronic hypercapnia. A vital capacity less than 1 liter in patients with myasthenic crisis predicts impending acute respiratory failure with CO_2 retention.

A simplified form of the alveolar gas equation at sea level and on breathing of room air (Fio_2, 21%) is as follows:

$$P_{A}\text{O}_2 = 150 - 1.25\,\text{Paco}_2$$

where $P_{A}\text{O}_2$ is alveolar O_2 tension (millimeters of mercury). This equation demonstrates that patients breathing room air cannot reach Paco_2 levels much greater than 80 mm Hg (10.6 kP) because the hypoxemia that would occur at greater values is incompatible with life. Therefore extreme hypercapnia occurs only during O_2 therapy, and severe CO_2 retention is often the result of uncontrolled O_2 administration.

Secondary Physiologic Response

Adaptation to acute hypercapnia elicits an immediate increment in serum $[\text{HCO}_3^-]$ as a result of titration of non-HCO_3^- body buffers; such buffers generate HCO_3^- by combining with H^+ derived from the dissociation of carbonic acid, as follows:

$$\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+ \text{ and } \text{H}^+ + \text{B}^- \leftrightarrow \text{HB}$$

where B^- refers to the base component and HB refers to the acid component of non-HCO_3^- buffers. This adaptation is completed within 5 to 10 minutes from the increase in Paco_2, and, assuming a stable level of hypercapnia, no further change in acid-base equilibrium is detectable for a few hours.[7] Moderate hypoxemia does not alter the adaptive response to acute respiratory acidosis. However, preexisting hypobicarbonatemia (whether it is caused by metabolic acidosis or chronic respiratory alkalosis) enhances the magnitude of the HCO_3^- response to acute hypercapnia; this response is diminished in hyperbicarbonatemic states, whether caused by metabolic alkalosis or chronic respiratory acidosis).[8,9]

The adaptive increase in serum $[\text{HCO}_3^-]$ during chronic hypercapnia is larger than the corresponding increase in response to acute hypercapnia and is achieved by renal HCO_3^- generation.[10] In addition, the renal response to chronic hypercapnia includes a reduction in the rate of Cl^- reabsorption, resulting in depletion of body Cl^- stores. Complete adaptation to chronic hypercapnia requires 3 to 5 days.[7] Table 14.3 provides quantitative aspects of the secondary physiologic responses to acute and chronic hypercapnia. More recently, a substantially steeper slope for the change in serum $[\text{HCO}_3^-]$ in chronic respiratory acidosis was reported (0.51 mmol/l for each 1 mm Hg chronic increase in Paco_2), but this study was based on only 18 arterial blood gas (ABG) measurements and its findings should be viewed with caution.[11] The renal response to chronic hypercapnia is not altered appreciably by dietary Na^+ or Cl^- restriction, moderate K^+ depletion, alkali loading, or moderate hypoxemia. However, recovery from chronic hypercapnia is crippled

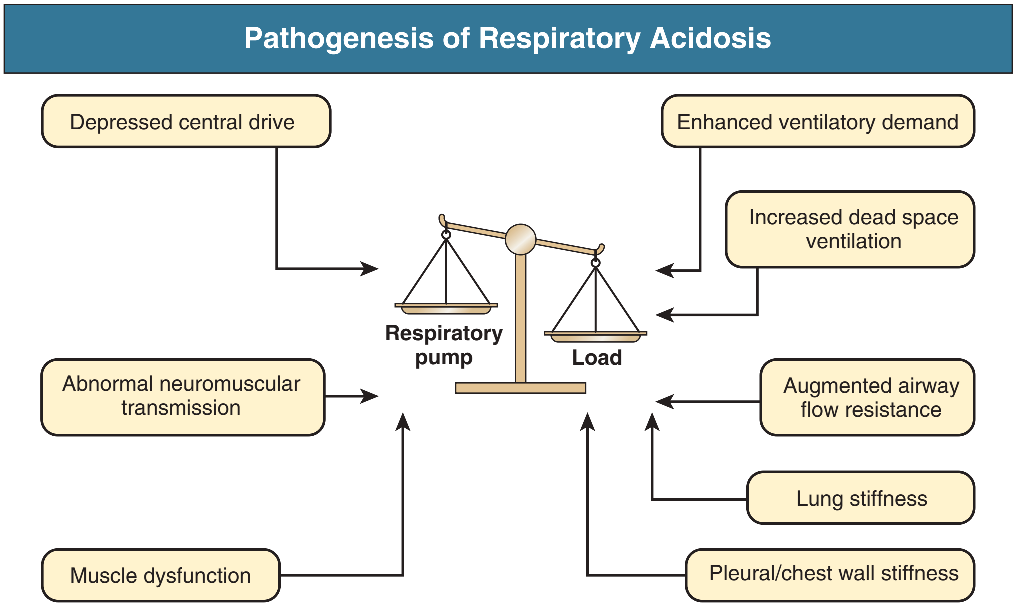
Pathogenesis of Respiratory Acidosis
Depressed central drive
Enhanced ventilatory demand
Increased dead space ventilation
Respiratory pump
Load
Abnormal neuromuscular transmission
Augmented airway flow resistance
Lung stiffness
Muscle dysfunction
Pleural/chest wall stiffness

Fig. 14.1 Pathogenesis of Respiratory Acidosis.

by a diet deficient in Cl^-; [HCO_3^-] remains elevated despite correction of the level of Paco$_2$, leading to posthypercapnic metabolic alkalosis.

Clinical Manifestations

Because clinical hypercapnia almost always occurs in association with hypoxemia, it is often difficult to determine whether a specific manifestation is the consequence of elevated Paco$_2$ or reduced Pao$_2$. Nevertheless, several characteristic manifestations of neurologic or cardiovascular dysfunction help diagnose the condition accurately and treat it effectively.[4,7]

Neurologic

Hypercapnia results in systemic vasodilatation via a direct action on vascular smooth muscle; this effect is most obvious in the cerebral circulation, where blood flow increases in direct relation to the level of Paco$_2$. Acute hypercapnia is often associated with marked anxiety, severe breathlessness, disorientation, confusion, incoherence, and combativeness. A narcotic-like effect can occur in patients with chronic hypercapnia, and drowsiness, inattention, memory loss, irritability, confusion, and somnolence may be observed. Motor disturbances, including tremor, myoclonic jerks, and asterixis, are frequently observed with both acute and chronic hypercapnia. Sustained myoclonus and seizure activity also can develop. Signs and symptoms of increased intracranial pressure (ICP) such as pseudotumor cerebri are occasionally evident in patients with either acute or chronic hypercapnia and are related to the vasodilating effects of CO_2 on cerebral blood vessels. Headache is a frequent complaint. Blurring of the optic discs and frank papilledema can be found when hypercapnia is severe. Hypercapnic coma characteristically occurs in patients with acute exacerbations of chronic respiratory insufficiency who are treated injudiciously with high-flow O_2.[12]

Cardiovascular

Acute hypercapnia of mild to moderate degree is usually characterized by warm and flushed skin, bounding pulse, sweating, increased cardiac output, and normal or increased blood pressure. By comparison, severe hypercapnia might be attended by decreases in both cardiac output and blood pressure. Cardiac arrhythmias occur frequently in patients with either acute or chronic hypercapnia, especially those receiving digoxin. CO_2 retention can produce vasoconstriction in the pulmonary circulation resulting in pulmonary hypertension and right heart failure (cor pulmonale).

Renal

Mild to moderate hypercapnia results in renal vasodilation, but acute increments in Paco$_2$ to levels above 70 mm Hg (9.3 kP) can induce renal vasoconstriction and hypoperfusion. Salt and water retention commonly attend sustained hypercapnia, especially in the presence of cor pulmonale. In addition to the effects of heart failure on the kidney, other factors include stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis, increased renal vascular resistance, and elevated levels of antidiuretic hormone (ADH) and cortisol.[12]

Diagnosis

Whenever CO_2 retention is suspected, ABG values should be obtained, which allow assessment of acid-base status and pulmonary gas exchange.[12] Venous blood sampling also can be used effectively to assess acid-base status and obtain information about tissue oxygenation. If the patient has hypercapnia in association with acidemia, at least an element of respiratory acidosis must be present. However, hypercapnia can be associated with a normal or even an alkaline pH if certain additional acid-base disorders are also present. Information from the patient history, physical examination, and ancillary laboratory data should be used to assess whether part or all of the increase in Paco$_2$ reflects an adaptive response to metabolic alkalosis rather than being primary in origin.

Treatment

CO_2 retention (whether acute or chronic) is always associated with hypoxemia in patients breathing room air. Consequently, O_2 administration represents a critical element in the management of respiratory acidosis.[1,13] However, supplemental O_2 may lead to worsening hypercapnia, especially in patients with chronic obstructive pulmonary disease (COPD).[14] Although a depressed respiratory drive seems to play a role in CO_2 retention, other factors include an increase in dead space ventilation and ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch caused by the loss of hypoxic pulmonary vasoconstriction and the Haldane effect (decreased hemoglobin affinity for CO_2 in the presence of increased O_2 saturation), which mandates an increase in ventilation to eliminate the excess CO_2.[7]

TABLE 14.1 Causes of Acute Respiratory Acidosis

Increased Load	Depressed Pump
Enhanced Ventilatory Demand Hyperthermia Agitation Seizures High-carbohydrate diet High-carbohydrate dialysate (peritoneal dialysis) Sorbent-regenerative hemodialysis	**Depressed Central Drive** General anesthesia Sedative overdose (opiates, benzodiazepines, tricyclic antidepressants, barbiturates) Head trauma Cerebrovascular accident Obesity-hypoventilation syndrome Cerebral edema Brain tumor Encephalitis Brainstem lesion
Increased Dead Space Ventilation Acute lung injury Multilobar pneumonia Cardiogenic pulmonary edema Pulmonary embolism Positive-pressure ventilation Supplemental oxygen	**Abnormal Neuromuscular Transmission** High spinal cord injury Guillain–Barré syndrome Status epilepticus Botulism, tetanus Crisis in myasthenia gravis Familial periodic paralysis Drugs or toxic agents (e.g., curare, succinylcholine, aminoglycosides, organophosphate poisoning)
Augmented Airway Flow Resistance ***Upper Airway Obstruction*** Coma-induced hypopharyngeal obstruction Aspiration of foreign body or vomitus Laryngospasm Angioedema Inadequate laryngeal intubation Laryngeal obstruction after intubation ***Lower Airway Obstruction*** Status asthmaticus Exacerbation in chronic obstructive pulmonary disease **Lung Stiffness** **Atelectasis** **Pleural and Chest Wall Stiffness** Pneumothorax Hemothorax Flail chest Abdominal distention Peritoneal dialysis	**Muscle Dysfunction** Fatigue Hyperkalemia Hypokalemia

TABLE 14.2 Causes of Chronic Respiratory Acidosis

Increased Load	Depressed Pump
Increased Dead Space Ventilation Emphysema Pulmonary fibrosis Pulmonary vascular disease	**Depressed Central Drive** Central sleep apnea Obesity-hypoventilation syndrome Methadone/heroin addiction Brain tumor Bulbar poliomyelitis Hypothyroidism
Augmented Airway Flow Resistance ***Upper Airway Obstruction*** Tonsillar and peritonsillar hypertrophy Paralysis of vocal cords Tumor of vocal cords or larynx Airways stenosis after prolonged intubation Thymoma, aortic aneurysm ***Lower Airway Obstruction*** Chronic obstructive pulmonary disease	**Abnormal Neuromuscular Transmission** High spinal cord injury Poliomyelitis Multiple sclerosis Muscular dystrophy Amyotrophic lateral sclerosis Diaphragmatic paralysis
Lung Stiffness Severe chronic interstitial lung disease **Pleural and Chest Wall Stiffness** Kyphoscoliosis Thoracic cage disease Thoracoplasty Obesity	**Muscle Dysfunction** Myopathic disease (e.g., polymyositis)

TABLE 14.3 Secondary Response to Alterations in Acid-Base Status

Condition	Initiating Mechanism	Expected Response: Change (Δ) in $[HCO_3^-]$ or PaCO_2	Maximal Level of Response
Respiratory acidosis	Increase in PaCO_2		
Acute		Increase in $[HCO_3^-] \approx 0.1\ \Delta$Pa$CO_2$	30 mmol/l
Chronic		Increase in $[HCO_3^-] \approx 0.35\ \Delta$Pa$CO_2$	45 mmol/l
Respiratory alkalosis	Decrease in PaCO_2		
Acute		Decrease in $[HCO_3^-] \approx 0.2\ \Delta$Pa$CO_2$	16-18 mmol/l
Chronic		Decrease in $[HCO_3^-] \approx 0.4\ \Delta$Pa$CO_2$	12-15 mmol/l
Metabolic acidosis	Decrease in $[HCO_3^-]$	Decrease in Pa$CO_2 \approx 1.2\ \Delta[HCO_3^-]$	10 mm Hg (1.3 kP)
Metabolic alkalosis	Increase in $[HCO_3^-]$	Increase in Pa$CO_2 \approx 0.7\ \Delta[HCO_3^-]$	65 mm Hg (8.7 kP)

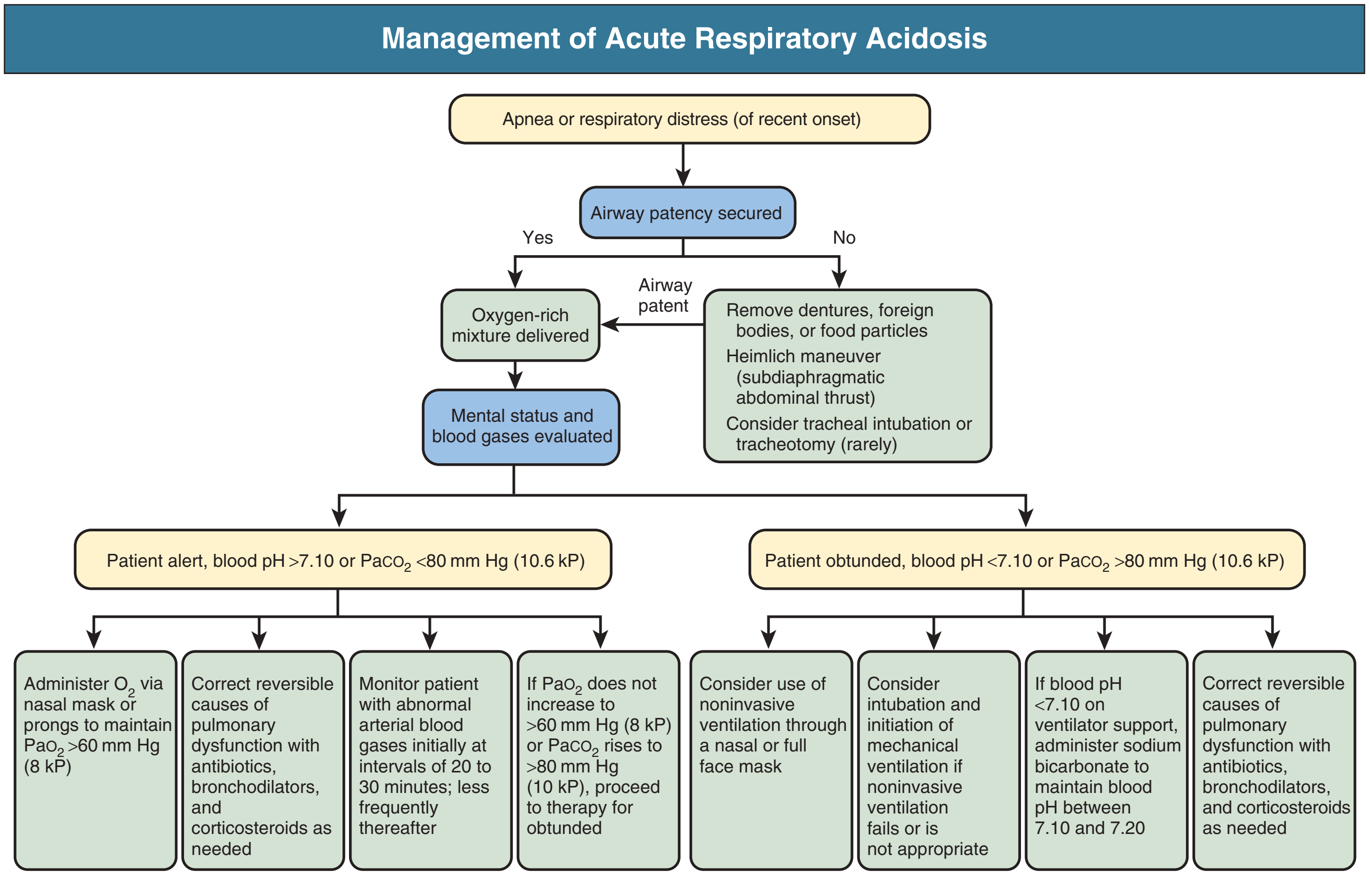
Management of Acute Respiratory Acidosis
Apnea or respiratory distress (of recent onset)
Airway patency secured
Yes
No
Oxygen-rich mixture delivered
Airway patent
Remove dentures, foreign bodies, or food particles
Heimlich maneuver (subdiaphragmatic abdominal thrust)
Consider tracheal intubation or tracheotomy (rarely)
Mental status and blood gases evaluated
Patient alert, blood pH >7.10 or Paco_2 <80 mm Hg (10.6 kP)
Patient obtunded, blood pH <7.10 or Paco_2 >80 mm Hg (10.6 kP)
Administer O_2 via nasal mask or prongs to maintain Pao_2 >60 mm Hg (8 kP)
Correct reversible causes of pulmonary dysfunction with antibiotics, bronchodilators, and corticosteroids as needed
Monitor patient with abnormal arterial blood gases initially at intervals of 20 to 30 minutes; less frequently thereafter
If Pao_2 does not increase to >60 mm Hg (8 kP) or Paco_2 rises to >80 mm Hg (10 kP), proceed to therapy for obtunded
Consider use of noninvasive ventilation through a nasal or full face mask
Consider intubation and initiation of mechanical ventilation if noninvasive ventilation fails or is not appropriate
If blood pH <7.10 on ventilator support, administer sodium bicarbonate to maintain blood pH between 7.10 and 7.20
Correct reversible causes of pulmonary dysfunction with antibiotics, bronchodilators, and corticosteroids as needed

Fig. 14.2 Management of Acute Respiratory Acidosis.

Figs. 14.2 and 14.3 outline the management of acute respiratory acidosis and chronic respiratory acidosis. When possible, treatment must be directed at removal or amelioration of the underlying cause. Immediate efforts should focus on securing a patent airway and delivering supplemental oxygen to maintain a Pao_2 of at least 60 mm Hg but not higher than 100 mm Hg and peripheral oxygen saturation greater than 90%.[15] Supplemental O_2 can be administered to the spontaneously breathing patient with nasal cannulas, Venturi masks (calibrated to deliver Fio_2 between 24% and 50%), or nonrebreathing masks. Oxygen flow rates up to 5 l/min can be used with nasal cannulas; each increment of 1 l/min increases the fraction of inspired O_2 concentration (Fio_2) by approximately 4%. Venturi masks are most useful in patients with COPD because the Po_2 can be titrated, thus minimizing the risk for CO_2 retention. Patients expected to require low levels of supplemental O_2 may be started at 1 to 2 l/min via nasal cannula or 24% to 28% FiO_2 via Venturi mask, with gradual increases of 1 l/min or 4% to 7% FiO_2.

If the target Po_2 is not achieved with these measures and the patient is conscious, cooperative, hemodynamically stable, and able to protect the lower airway, a method of noninvasive ventilation through a mask can be used, such as bilevel positive airway pressure (BiPAP). With BiPAP, the inspiratory-pressure support decreases the work of breathing and the expiratory-pressure support improves gas exchange by preventing alveolar collapse.

Endotracheal intubation and mechanical ventilation should be initiated if adequate oxygenation cannot be secured by noninvasive measures, if progressive hypercapnia or obtundation develops, or if the patient is unable to cough and clear secretions.[16] Minute ventilation should be raised so Paco_2 gradually returns to near its long-term baseline and excretion of excess HCO_3^- by the kidneys is accomplished (assuming that Cl^- is provided). By contrast, overly rapid reduction in the Paco_2 risks the development of posthypercapnic alkalosis, with potentially serious consequences. If it develops, posthypercapnic alkalosis can be ameliorated by providing Cl^- (usually as KCl), and administering acetazolamide at doses of 250 to 500 mg once or twice daily. Vigorous treatment of pulmonary infections, bronchodilator therapy, and removal of secretions can be beneficial. Avoidance of tranquilizers and sedatives, use of naloxone when indicated, gradual reduction of supplemental oxygen, aiming at a Pao_2 of about 60 mm Hg (8 kP), and treatment of a superimposed metabolic alkalosis will optimize the ventilatory drive.

Mechanical ventilation with tidal volumes of 10 to 15 ml/kg body weight often leads to alveolar overdistention and volutrauma. Therefore an alternative approach called *permissive hypercapnia* (or controlled mechanical hypoventilation) has been successfully applied to prevent barotrauma.[4,17] In this form of treatment, lower tidal volumes of less than 6 ml/kg and lower peak inspiratory pressures are used. Further, Paco_2 is allowed to increase as high as 80 mm Hg, and blood pH can decrease to as low as 7.00 to 7.10, while adequate oxygenation is maintained. Because the patient usually requires neuromuscular blockade, accidental disconnection from the ventilator can cause sudden death. Contraindications to permissive hypercapnia include cerebrovascular disease, brain edema, increased ICP, seizures, depressed cardiac function, arrhythmias, and severe pulmonary hypertension. Correction of acidemia attenuates the adverse hemodynamic effects of permissive hypercapnia.[18] It appears prudent, although still controversial, to keep the blood pH at approximately 7.30 by the administration of intravenous alkali when controlled hypoventilation is prescribed.[1,19]

Cardiopulmonary bypass represents a form of mechanical cardiopulmonary support often applied intraoperatively to facilitate cardiac

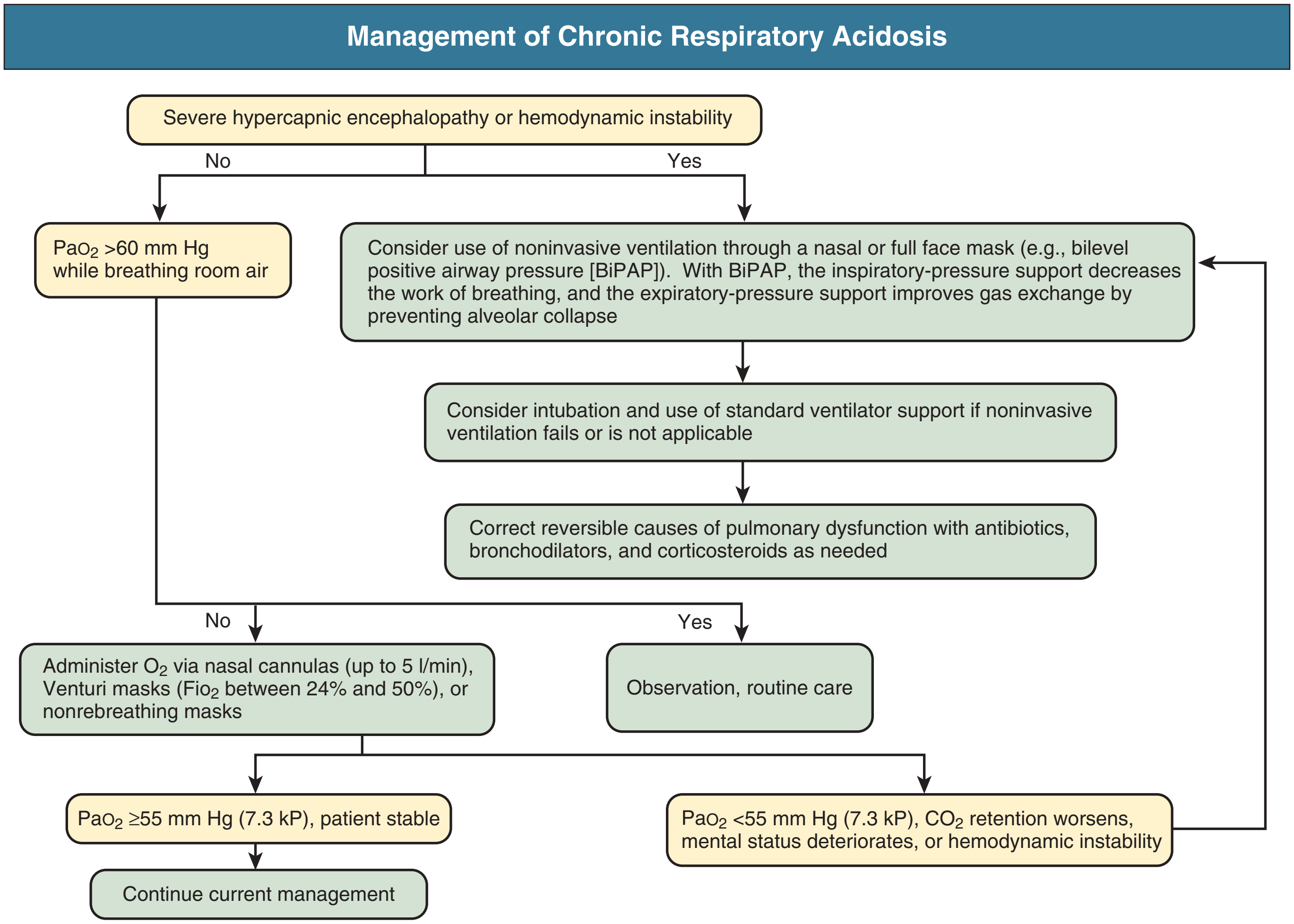
Management of Chronic Respiratory Acidosis
Severe hypercapnic encephalopathy or hemodynamic instability
No
Yes
PaO2 >60 mm Hg while breathing room air
Consider use of noninvasive ventilation through a nasal or full face mask (e.g., bilevel positive airway pressure [BiPAP]). With BiPAP, the inspiratory-pressure support decreases the work of breathing, and the expiratory-pressure support improves gas exchange by preventing alveolar collapse
Consider intubation and use of standard ventilator support if noninvasive ventilation fails or is not applicable
Correct reversible causes of pulmonary dysfunction with antibiotics, bronchodilators, and corticosteroids as needed
No
Yes
Administer O2 via nasal cannulas (up to 5 l/min), Venturi masks (Fio2 between 24% and 50%), or nonrebreathing masks
Observation, routine care
PaO2 ≥55 mm Hg (7.3 kP), patient stable
PaO2 <55 mm Hg (7.3 kP), CO2 retention worsens, mental status deteriorates, or hemodynamic instability
Continue current management

Fig. 14.3 Management of Chronic Respiratory Acidosis.

surgery. A more prolonged type of extracorporeal life support, known as extracorporeal membrane oxygenation (ECMO), can be used in the intensive care unit in neonates, children, and adults to secure tissue oxygenation and CO_2 removal. Application of ECMO involves either a venoarterial (VA) or venovenous (VV) vascular access. Both types provide respiratory support but only VA ECMO provides hemodynamic support.

RESPIRATORY ALKALOSIS (PRIMARY HYPOCAPNIA)

Definition

Respiratory alkalosis is initiated by a reduction in CO_2 tension of body fluids and in whole body CO_2 stores. The secondary decrease in serum [HCO_3^-] observed in acute and chronic hypocapnia is an integral part of the respiratory alkalosis. Whole-body CO_2 stores are decreased and $Paco_2$ is less than 35 mm Hg (4.7 kP) in patients with simple respiratory alkalosis (at rest and at sea level). An element of respiratory alkalosis still may occur with higher levels of $Paco_2$ in patients with metabolic alkalosis, in whom a normal $Paco_2$ is inappropriately low.

Etiology and Pathogenesis

Respiratory alkalosis is the most frequent acid-base disorder encountered because it occurs in normal pregnancy and with high-altitude residence.[2,20,21] It is also the most common acid-base abnormality in critically ill patients, occurring either as the simple disorder or as a component of mixed disturbances, and is an adverse prognostic sign, especially if $Paco_2$ is below 20 to 25 mm Hg (2.7 to 3.3 kP). The hyperventilation syndrome is characterized by episodes of acute hyperventilation associated with fear, anxiety, and sense of impending doom in the absence of significant cardiopulmonary disease.[22] The presence of hypocapnia signifies transient or persistent alveolar hyperventilation relative to the prevailing CO_2 production, thus leading to negative CO_2 balance. Primary hypocapnia might also originate from the extrapulmonary elimination of CO_2 by dialysis or other extracorporeal circulation (e.g., heart-lung machine).

Table 14.4 provides the major causes of respiratory alkalosis.[12] In most patients, primary hypocapnia reflects alveolar hyperventilation caused by increased ventilatory drive arising from the lung, the peripheral chemoreceptors (carotid and aortic), the brainstem chemoreceptors, or signals originating in other brain centers.

The response of the brainstem chemoreceptors to CO_2 can be augmented by systemic diseases (e.g., liver disease, sepsis), pharmacologic agents, and volition. Hypoxemia is a major stimulus of alveolar ventilation, but Pao_2 values below 60 mm Hg (8 kP) are required to elicit this effect consistently. Alveolar hyperventilation can be the result of maladjusted mechanical ventilators, psychogenic hyperventilation, and central nervous system lesions.

In severe circulatory failure, arterial hypocapnia may coexist with venous and therefore tissue hypercapnia; under these conditions, the body CO_2 stores have been enriched, so there is respiratory acidosis rather than respiratory alkalosis. This entity, which we have termed *pseudorespiratory alkalosis,* develops in patients with profound

TABLE 14.4 Causes of Respiratory Alkalosis

Hypoxemia or Tissue Hypoxia	Drugs and Hormones
Decreased inspired O_2 tension High altitude Bacterial or viral pneumonia Aspiration of food, foreign body, or vomitus Laryngospasm Drowning Cyanotic heart disease Severe anemia Left shift deviation of oxyhemoglobin (HbO_2) dissociation curve Hypotension Severe circulatory failure Pulmonary edema Pseudorespiratory alkalosis	Respiratory stimulants (doxapram, nikethamide, ethamivan, progesterone, medroxyprogesterone) Salicylates Nicotine Xanthines Dinitrophenol Pressor hormones (epinephrine, norepinephrine, angiotensin II)
Central Nervous System Stimulation	**Miscellaneous**
Voluntary Pain Anxiety-hyperventilation syndrome Psychosis Fever Subarachnoid hemorrhage Cerebrovascular accident Meningoencephalitis Tumor Trauma	Exercise Pregnancy Gram-positive septicemia Gram-negative septicemia Hepatic failure Mechanical hyperventilation Heat exposure Recovery from metabolic acidosis
Pulmonary Diseases With Stimulation of Chest Receptors	
Pneumonia Asthma Pneumothorax Hemothorax Flail chest Acute respiratory distress syndrome Cardiogenic and noncardiogenic pulmonary edema Pulmonary embolism Pulmonary fibrosis	

depression of cardiac function and pulmonary perfusion but relative preservation of alveolar ventilation, including patients with advanced circulatory failure and those undergoing cardiopulmonary resuscitation (CPR). The severely reduced pulmonary blood flow limits the CO_2 delivered to the lungs for excretion, thereby increasing the venous P_{CO_2}. However, the increased $\dot{V}/\dot{Q}$ ratio causes a larger than normal removal of CO_2 per unit of blood traversing the pulmonary circulation, thereby giving rise to arterial eucapnia or frank hypocapnia. A progressive widening of the arteriovenous difference in pH and P_{CO_2} develops in circulatory failure and during cardiac arrest (Fig. 14.4). In both situations, there is severe tissue O_2 deprivation and it can be completely disguised by the reasonably preserved arterial O_2 values. Appropriate monitoring of acid-base composition and oxygenation in patients with advanced cardiac dysfunction requires mixed (or central) venous blood sampling in addition to the sampling of arterial blood.

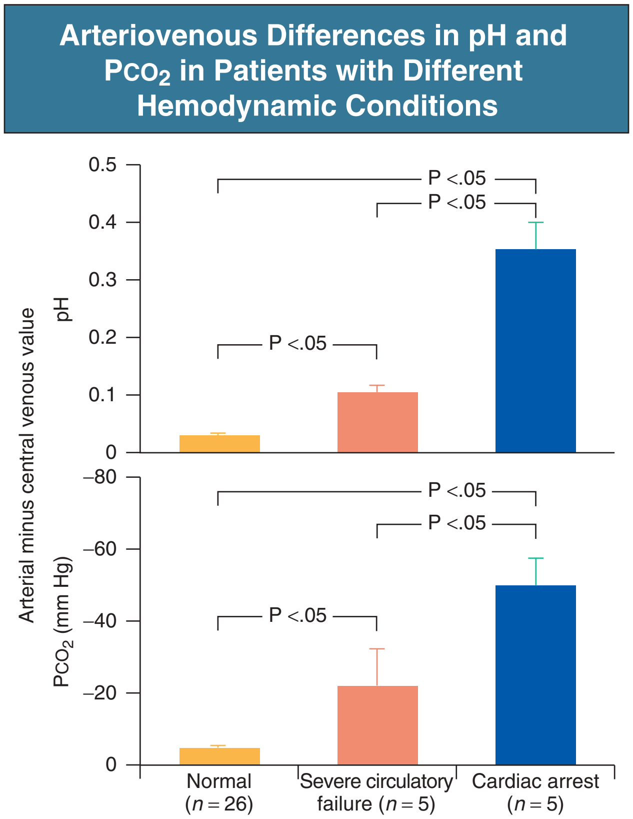

Fig. 14.4 Arteriovenous Differences in pH and P_{CO_2} in Patients With Different Hemodynamic Conditions.

Secondary Physiologic Response

Adaptation to acute hypocapnia is characterized by an immediate decrement in serum $[HCO_3^-]$ that results from nonrenal mechanisms, principally alkaline titration of the non-HCO_3^- body buffers (see second equation under Respiratory Acidosis). This adaptation is completed within 5 to 10 minutes of the onset of hypocapnia, and if there is no further change in Pa_{CO_2}, no additional changes in acid-base equilibrium occur for several hours.[7]

Adaptation to chronic hypocapnia entails an additional, larger decrease in serum $[HCO_3^-]$ as a consequence of renal adjustments that reflect a damping of renal H^+ secretion over approximately 2 to 3 days.[10] Quantitative aspects of the secondary physiologic responses to acute and chronic hypocapnia are shown in Table 14.3.

Clinical Manifestations

A rapid decrease in Pa_{CO_2} to half-normal values or lower is typically accompanied by numbness and paresthesias of the extremities, chest discomfort (especially in patients manifesting increased airway resistance), circumoral numbness, lightheadedness, dyspnea, frequent sighing, and confusion. These manifestations are regularly expressed in patients with hyperventilation syndrome. These patients also report dyspnea at rest; they need to sigh frequently, and minimal exertion may result in significant dyspnea. Muscle cramps, increased deep tendon reflexes, carpopedal spasm, and generalized seizures occur infrequently. Cerebral vasoconstriction occurs during acute hypocapnia; in severe cases, cerebral blood flow might decrease below 50% of normal values. Hypocapnia can have deleterious effects on the brain of premature infants; in patients with traumatic brain injury, acute stroke, or general anesthesia; and after sudden exposure to very high altitude.[23] Long-term neurologic sequelae can develop when immature brains are exposed to PaCO_2 levels below 15 mm Hg (2 kP) for even short periods. Furthermore, abrupt correction of hypocapnia in these patients leads to cerebral vasodilation, which might cause reperfusion injury or intraventricular hemorrhage.

Brain injury caused by hypocapnia probably results from cerebral ischemia. Other factors include hypocapnia itself, alkalemia, pH-induced shift of the oxyhemoglobin (HbO_2) dissociation curve, decreased serum levels of ionized calcium and potassium, depletion of the antioxidant glutathione by cytotoxic excitatory amino acids, increases in anaerobic metabolism, cerebral oxygen demand, neuronal dopamine, and seizure activity.

The cardiovascular manifestations of respiratory alkalosis differ in passive and active hyperventilation. The induction of acute hypocapnia in anesthetized patients (i.e., passive hyperventilation) results in a decrease in cardiac output, an increase in peripheral resistance, and a decrease in the systemic blood pressure. By contrast, active hyperventilation does not change or might even increase cardiac output and leaves systemic blood pressure virtually unchanged. This discrepant response probably reflects the decrease in venous return caused by mechanical ventilation in passive hyperventilation and the reflex tachycardia consistently observed in active hyperventilation. Sustained hypocapnia induced by exposure to high altitude for several weeks results in a cardiac output within control values or higher. Although it does not lead to cardiac arrhythmias in normal individuals, acute hypocapnia appears to contribute to the generation of atrial and ventricular tachyarrhythmias in patients with ischemic heart disease; such arrhythmias are frequently resistant to standard forms of therapy. Chest pain and ischemic ST-T wave changes have been observed in acutely hyperventilating subjects with no evidence of fixed lesions on coronary angiography.

The view that hypocapnia poses minimal risk to health under most conditions is not accurate. Substantial hypocapnia (<25 mm Hg) in hospitalized patients, whether spontaneous or deliberately induced, may result in transient or permanent damage in the brain as well as the respiratory and cardiovascular systems.[23]

Diagnosis

Evaluation of the patient history, physical examination, and ancillary laboratory data are required to establish the diagnosis of respiratory alkalosis.[12,20] Careful observation can detect abnormal patterns of breathing in some patients, although marked hypocapnia can occur without a clinically evident increase in respiratory effort. ABG determinations are required to confirm the presence of hyperventilation.

The diagnosis of respiratory alkalosis, especially the chronic form, is frequently missed; physicians often misinterpret the electrolyte pattern of hyperchloremic hypobicarbonatemia as indicative of normal anion gap metabolic acidosis. If the acid-base profile reveals hypocapnia in association with alkalemia, at least an element of respiratory alkalosis must be present. However, hypocapnia might be associated with a normal or an acidic pH because of the concomitant presence of additional acid-base disorders. Mild degrees of chronic hypocapnia may leave blood pH within the high-normal range. The diagnosis of respiratory alkalosis can have important clinical implications; it often suggests an unrecognized, serious disorder or signals the gravity of a known underlying disease.

Treatment

Fig. 14.5 summarizes the management of patients with respiratory alkalosis. Severe hypocapnia in hospitalized patients must be prevented whenever possible, and if it is present, abrupt correction should be avoided because rapid correction of severe hypocapnia leads to vasodilation of ischemic areas, resulting in reperfusion injury in the brain and lung. Severe alkalemia caused by acute primary hypocapnia requires corrective measures that depend on whether serious clinical manifestations are present. Such measures can be directed at reducing serum $[\text{HCO}_3^-]$, increasing PaCO_2, or both. Even if baseline serum $[\text{HCO}_3^-]$ is moderately decreased, reducing it further is effective with relatively little risk. Rebreathing into a closed system (e.g., a paper bag) is not recommended for the acute management of the hyperventilation syndrome because of the potential of hypoxemia in patients with underlying respiratory or cardiovascular disease. The long-term management of the hyperventilation syndrome centers on education regarding the nature of the underlying condition and cognitive-behavioral therapy. Other measures may include breathing retraining, β-blockers, benzodiazepines, and serotonin reuptake inhibitors.

Respiratory alkalosis resulting from severe hypoxemia requires O_2 therapy. The oral administration of 250 to 500 mg acetazolamide twice daily can be beneficial in the management of signs and symptoms of high-altitude sickness, a syndrome characterized by hypoxemia and respiratory alkalosis.[20] Hypocapnia in patients receiving mechanical ventilation often can be corrected by resetting the ventilator. Patients maintained on chronic hemodialysis who develop an acute illness resulting in marked hyperventilation may require dialysis using low-bicarbonate dialysate. Management of pseudorespiratory alkalosis must be directed at optimizing systemic hemodynamics.

MIXED ACID-BASE DISTURBANCES

Definition

Mixed acid-base disturbances are defined as the simultaneous presence of two or more acid-base disorders. Such association might include two or more simple acid-base disorders (e.g., metabolic acidosis and respiratory alkalosis), two or more forms of a simple disturbance having different time course or pathogenesis (e.g., acute and chronic respiratory acidosis or high anion gap and hyperchloremic metabolic acidosis, respectively), or a combination of these two forms.[24] The secondary or adaptive response to a simple acid-base disorder cannot be taken as one of the components of a mixed disorder.

Etiology and Pathogenesis

Mixed acid-base disturbances are seen in hospitalized patients, especially in the critically ill.[25] Careful characterization of these is required to ensure appropriate therapy. Clinical settings are commonly associated with mixed acid-base disorders, including cardiorespiratory arrest, sepsis, drug intoxications, diabetes mellitus, and organ failure (especially renal, hepatic, and pulmonary failure). Patients with severe renal impairment or end-stage renal disease (ESRD) are prone to mixed acid-base disturbances of great complexity and severity.[26] In these conditions, metabolic acidosis of the high anion gap type is frequently accompanied by a component of hyperchloremic acidosis, inability to mount an appropriate secondary response to chronic respiratory acidosis or alkalosis, inability to respond to a load of fixed acids (e.g., lactic acid) or a primary loss of alkali (e.g., diarrhea) with the expected increase in net acid excretion, and inability to respond to an alkali load with bicarbonaturia despite an increased serum $[\text{HCO}_3^-]$. Thus these patients are particularly vulnerable to the development of both extreme acidemia and extreme alkalemia.

A practical classification of mixed acid-base disorders recognizes three main groups of disturbances (Fig. 14.6). Representative examples are depicted in Table 14.5.

Metabolic Acidosis and Respiratory Acidosis

The expected hypocapnia secondary to metabolic acidosis is estimated by $\Delta\text{Pa}\text{CO}_2/\Delta[\text{HCO}_3^-] = 1.2$ mm Hg/mmol/l (Δ indicates change). If

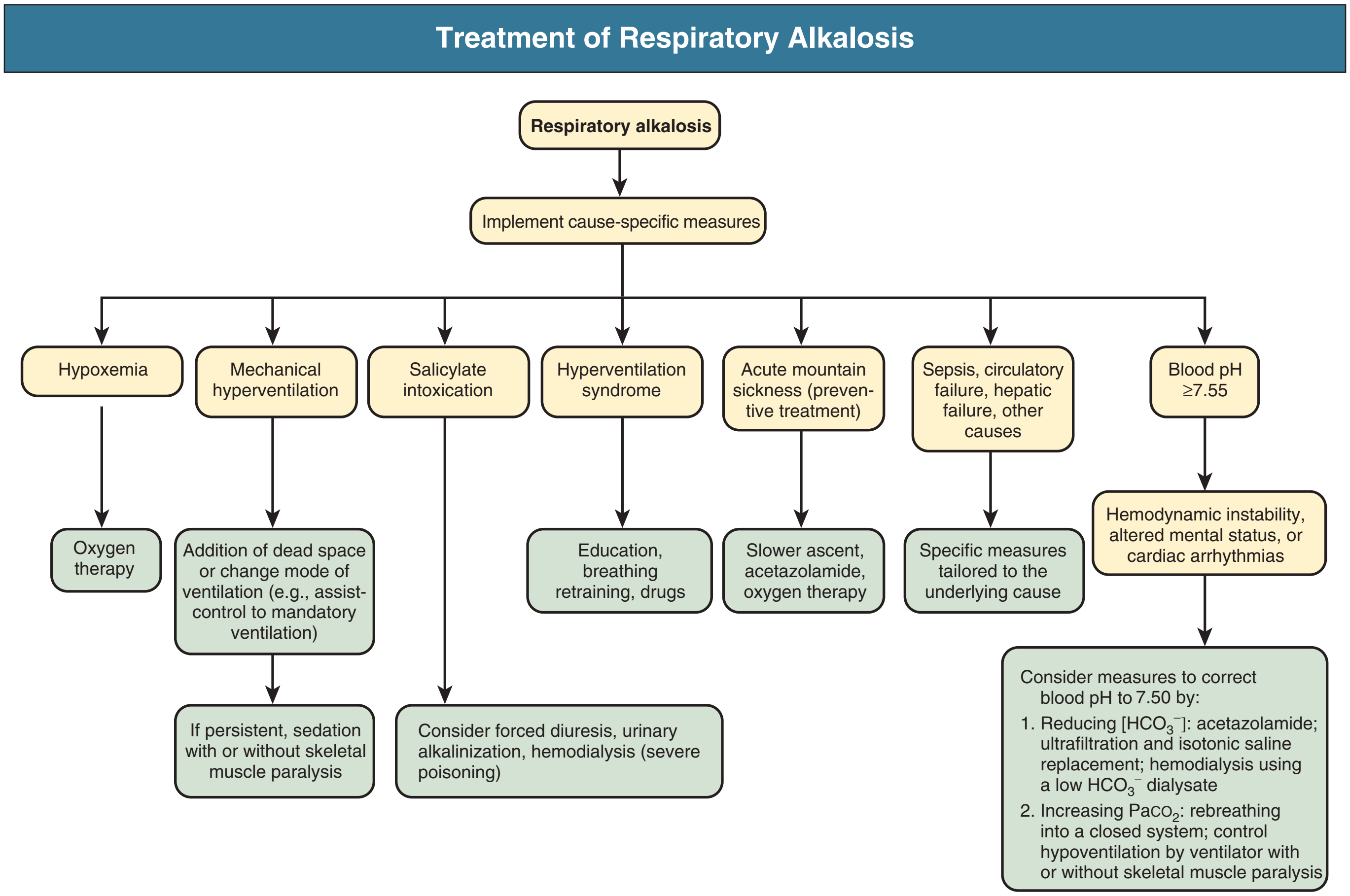
Treatment of Respiratory Alkalosis
Respiratory alkalosis
Implement cause-specific measures
Hypoxemia
Mechanical hyperventilation
Salicylate intoxication
Hyperventilation syndrome
Acute mountain sickness (preventive treatment)
Sepsis, circulatory failure, hepatic failure, other causes
Blood pH ≥7.55
Oxygen therapy
Addition of dead space or change mode of ventilation (e.g., assist-control to mandatory ventilation)
Education, breathing retraining, drugs
Slower ascent, acetazolamide, oxygen therapy
Specific measures tailored to the underlying cause
Hemodynamic instability, altered mental status, or cardiac arrhythmias
If persistent, sedation with or without skeletal muscle paralysis
Consider forced diuresis, urinary alkalinization, hemodialysis (severe poisoning)
Consider measures to correct blood pH to 7.50 by:
1. Reducing [HCO3−]: acetazolamide; ultrafiltration and isotonic saline replacement; hemodialysis using a low HCO3− dialysate
2. Increasing PaCO2: rebreathing into a closed system; control hypoventilation by ventilator with or without skeletal muscle paralysis

Fig. 14.5 Treatment of Respiratory Alkalosis.

measured PaCO_2 exceeds 5 mm Hg of the estimated value, respiratory acidosis is also present. The expected ventilatory response to metabolic acidosis also can be estimated by applying the Winters formula, $\text{Pa}\text{CO}_2 = 1.5 \times [\text{HCO}_3^-] + 8 \pm 2$. Clinical examples of metabolic acidosis combined with respiratory acidosis include untreated cardiopulmonary arrest, circulatory failure in patients with COPD, severe renal failure associated with hypercapnic respiratory failure, various intoxications, and hypokalemic (or less frequently hyperkalemic) paralysis of respiratory muscles in patients with diarrhea or renal tubular acidosis (RTA) (Fig. 14.7; see Table 14.5, Example 4).

Metabolic Alkalosis and Respiratory Alkalosis

Metabolic alkalosis combined with respiratory alkalosis may be encountered in patients with primary hypocapnia associated with chronic liver disease who develop metabolic alkalosis from a variety of causes, including vomiting, nasogastric drainage, diuretics, profound hypokalemia, and alkali administration (e.g., absorption of antacids; infusion of lactated Ringer solution, alimentation solutions, citrated blood products), especially in the patient with renal impairment. Mixed metabolic/respiratory alkalosis also occurs in critically ill patients, particularly those undergoing mechanical ventilation, and in patients with respiratory alkalosis, caused by either pregnancy or heart failure, who experience metabolic alkalosis attributable to diuretics or vomiting (Fig. 14.8; see Table 14.5, Example 6).

Metabolic Alkalosis and Respiratory Acidosis

Metabolic alkalosis and respiratory acidosis is one of the most frequently encountered mixed acid-base disorders. The usual clinical setting is COPD in conjunction with diuretic therapy, but it can occur with other causes of metabolic alkalosis (e.g., vomiting, administration of corticosteroids) (Fig. 14.9; see Table 14.5, Example 5). Critically ill patients with respiratory failure caused by acute respiratory distress syndrome and occasionally those with profound hypokalemia with diaphragmatic muscle weakness also might develop mixed metabolic alkalosis and respiratory acidosis.

Metabolic Acidosis and Respiratory Alkalosis

As with respiratory acidosis and metabolic alkalosis, the combination of metabolic acidosis and respiratory alkalosis is characterized by normal or near-normal blood pH; its two components exert offsetting effects on systemic acidity (Fig. 14.10). This disorder is common in the intensive care unit and is generally associated with high mortality. Causes of the primary hypocapnia include fever, hypotension, gram-negative septicemia, pulmonary edema, hypoxemia, and mechanical hyperventilation. The component of metabolic acidosis in turn might be lactic acidosis (e.g., complicating shock, hepatic failure) or renal acidosis. Respiratory alkalosis and lactic acidosis may occur in acute severe asthma. In some patients, the lactic acidosis appears to be caused by excessive use of β_2-adrenergic agonists and corticosteroids. The resulting increased ventilatory demands might worsen abnormal lung mechanics and precipitate ventilatory failure.[27,28] Salicylate intoxication is another cause of mixed metabolic acidosis and respiratory alkalosis. Stimulation of the ventilatory center in the brainstem accounts for the respiratory alkalosis, whereas the accelerated production of organic acids including pyruvic, lactic, and ketoacids, and, to a lesser extent the accumulation of salicylic acid itself are responsible for the metabolic acidosis.

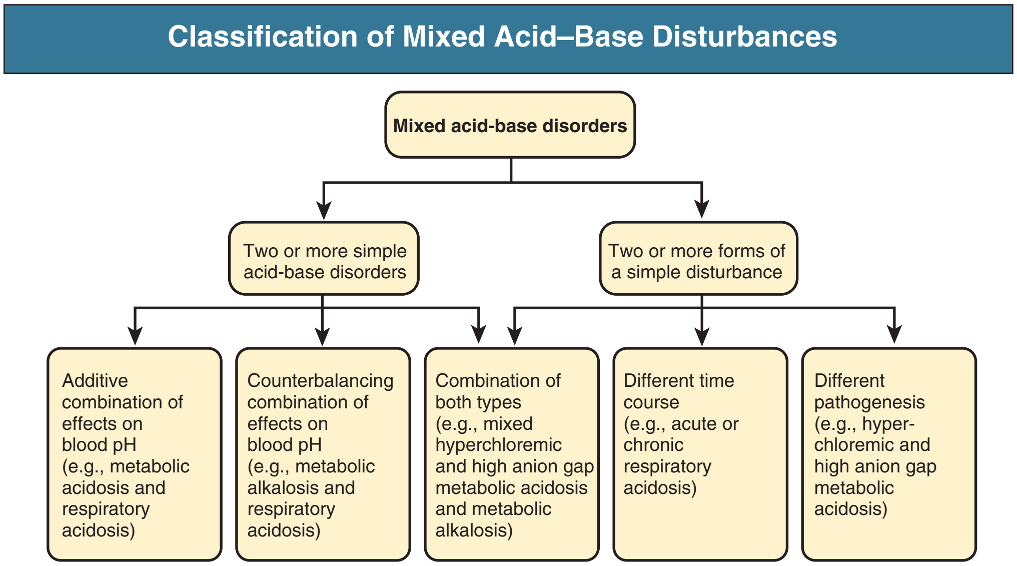
Classification of Mixed Acid–Base Disturbances
Mixed acid-base disorders
Two or more simple acid-base disorders
Two or more forms of a simple disturbance
Additive combination of effects on blood pH (e.g., metabolic acidosis and respiratory acidosis)
Counterbalancing combination of effects on blood pH (e.g., metabolic alkalosis and respiratory acidosis)
Combination of both types (e.g., mixed hyperchloremic and high anion gap metabolic acidosis and metabolic alkalosis)
Different time course (e.g., acute or chronic respiratory acidosis)
Different pathogenesis (e.g., hyper-chloremic and high anion gap metabolic acidosis)

Fig. 14.6 Classification of Mixed Acid-Base Disturbances.

TABLE 14.5 Representative Examples of Mixed Acid-Base Disorders

Type of Mixed Disorder	No.*	pH	$Paco_2$† (mm Hg)	HCO_3^- (mmol/l)	Na^+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)	Anion gap (mmol/l)	Clinical Circumstances
Hyperchloremic and high anion gap metabolic acidosis	1	7.12	16	5	137	3.6	114	18	Diabetic ketoacidosis with adequate salt and water balance
Mixed high anion gap metabolic acidosis and metabolic alkalosis	2	7.36	31	17	132	4.0	89	26	Alcoholic liver disease, vomiting, and lactic acidosis
	3	7.40	40	24	143	5.5	95	24	Diabetic ketoacidosis and lactic acidosis after bicarbonate therapy
Mixed high anion gap metabolic acidosis and respiratory acidosis	4	7.18	44	16	133	5.7	100	17	Hepatic, renal, and pulmonary failure
Metabolic alkalosis and respiratory acidosis	5	7.44	55	36	135	3.8	84	15	COPD and diuretics
Metabolic alkalosis and respiratory alkalosis	6	7.60	40	38	131	3.6	77	16	Congestive heart failure and diuretics
Acute on chronic respiratory acidosis	7	7.22	80	32	141	4.3	99	10	COPD and therapy with oxygen-rich mixtures

*Number for representative example as cited in text.

†To convert to kP, multiply by 0.1333.

COPD, Chronic obstructive pulmonary disease.

Anion gap is calculated as $[Na^+] - ([Cl^-] + [HCO_3^-])$

Metabolic Acidosis and Metabolic Alkalosis

Metabolic acidosis and metabolic alkalosis are typically observed in patients with alcoholic liver disease who develop fasting ketoacidosis or lactic acidosis in conjunction with metabolic alkalosis caused by vomiting, diuretics, or other causes (see Table 14.5, Examples 2 and 3). Protracted vomiting or nasogastric suction superimposed on uremic acidosis, diabetic ketoacidosis, or metabolic acidosis caused by diarrhea also might generate this offsetting metabolic combination. A similar picture might develop after administration of alkali during CPR or as therapy for diabetic ketoacidosis.

Mixed Metabolic Acidosis

Mixed high anion gap metabolic acidosis in patients with diabetic or alcoholic ketoacidosis may be combined with lactic acidosis resulting from circulatory failure. Uremic patients with associated lactic acidosis or ketoacidosis provide another example of mixed high anion gap acidosis. Mixed hyperchloremic metabolic acidosis is seen in patients with RTA or those receiving carbonic anhydrase inhibitors who also have substantial fecal losses of HCO_3^- caused by severe diarrhea. Mixed hyperchloremic and high anion gap metabolic acidosis occurs in patients with profuse diarrhea whose circulation becomes sufficiently

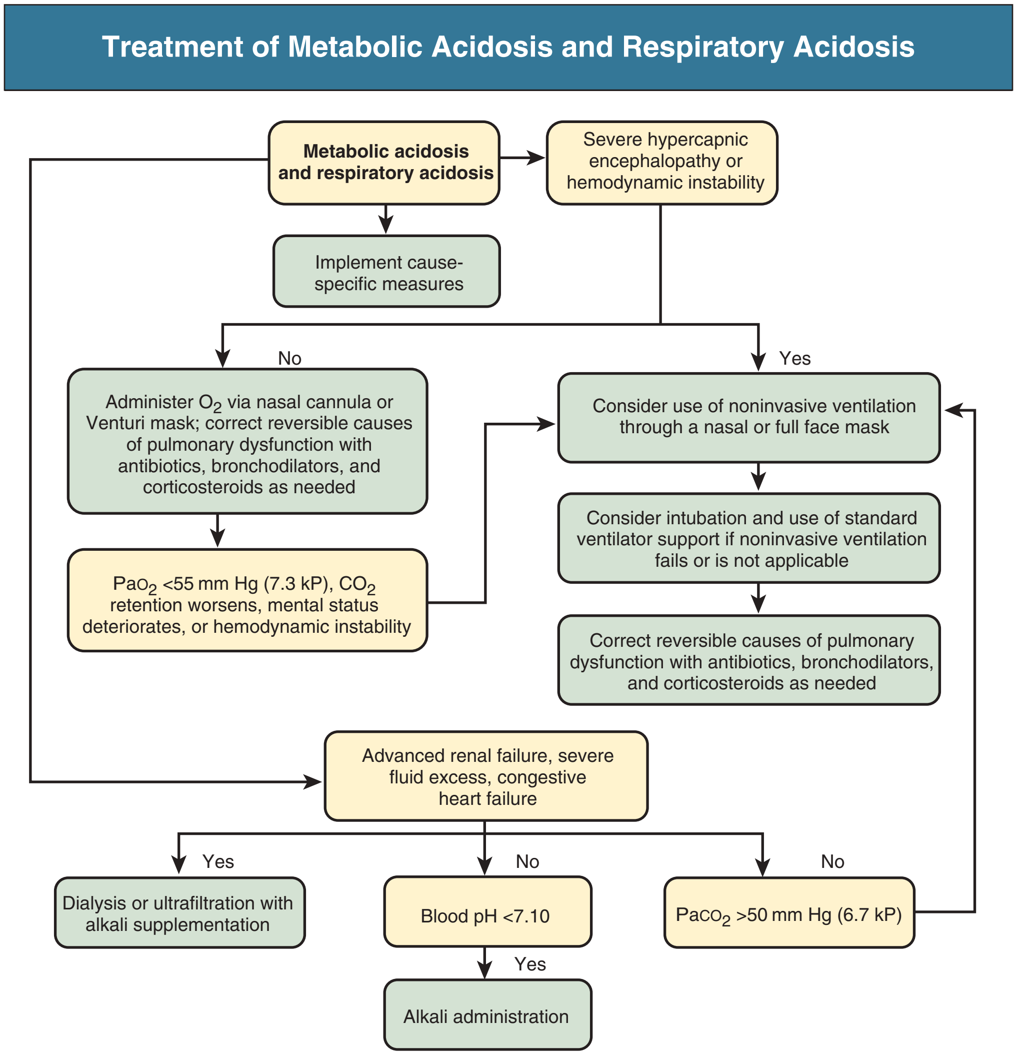
Treatment of Metabolic Acidosis and Respiratory Acidosis
Metabolic acidosis and respiratory acidosis
Severe hypercapnic encephalopathy or hemodynamic instability
Implement cause-specific measures
No
Yes
Administer O2 via nasal cannula or Venturi mask; correct reversible causes of pulmonary dysfunction with antibiotics, bronchodilators, and corticosteroids as needed
Consider use of noninvasive ventilation through a nasal or full face mask
Consider intubation and use of standard ventilator support if noninvasive ventilation fails or is not applicable
PaO2 <55 mm Hg (7.3 kP), CO2 retention worsens, mental status deteriorates, or hemodynamic instability
Correct reversible causes of pulmonary dysfunction with antibiotics, bronchodilators, and corticosteroids as needed
Advanced renal failure, severe fluid excess, congestive heart failure
Yes
No
No
Dialysis or ultrafiltration with alkali supplementation
Blood pH <7.10
PaCO2 >50 mm Hg (6.7 kP)
Yes
Alkali administration

Fig. 14.7 Treatment of Metabolic Acidosis and Respiratory Acidosis.

compromised to generate in turn a high anion gap metabolic acidosis from renal failure or lactic acidosis. Patients with diabetic ketoacidosis whose renal function is maintained at reasonable levels by adequate salt and water intake might develop an element of hyperchloremic metabolic acidosis because of preferential excretion of ketone anions and conservation of Cl^- (see Table 14.5, Example 1).[29]

Mixed Metabolic Alkalosis

The coexistence of several processes with each contributing to a primary increase in serum $[HCO_3^-]$, including diuretic therapy, vomiting, mineralocorticoid excess, and severe potassium depletion, will give rise to mixed metabolic alkalosis.

Triple Disorders

The most frequent triple disorders comprise two cardinal metabolic disturbances in conjunction with either respiratory acidosis or respiratory alkalosis, such as in severely ill patients with COPD and CO_2 retention who simultaneously develop metabolic alkalosis (usually caused by diuretics and a Cl^--restricted diet) and metabolic acidosis (usually lactic acidosis caused by hypoxemia, hypotension, or sepsis). This type of triple disorder also might be encountered during CPR when an element of metabolic alkalosis caused by alkali administration is superimposed on preexisting respiratory acidosis and metabolic (lactic) acidosis. Patients with respiratory alkalosis caused by advanced congestive heart failure also might have diuretic-induced metabolic alkalosis and lactic acidosis from tissue hypoperfusion. Such triple acid-base disorders also can be seen in patients with chronic alcoholism who develop metabolic alkalosis from vomiting, lactic acidosis from volume depletion or ethanol intoxication, and respiratory alkalosis from hepatic encephalopathy or sepsis.

Less common triple disorders encompass two cardinal respiratory disturbances in combination with either metabolic acidosis or metabolic alkalosis. Typically, this is seen in critically ill patients with chronic respiratory acidosis who experience an abrupt reduction in Pa_{CO_2} because of mechanical ventilation and superimposed metabolic acidosis (usually lactic acidosis, reflecting circulatory failure) or metabolic alkalosis (e.g., from gastric fluid loss or diuretics). With superimposed metabolic alkalosis, extreme alkalemia might ensue because of the concomitant presence of hypocapnia and hyperbicarbonatemia. Even more infrequently, this same clinical setting might lead to a quadruple acid-base disorder in which all four cardinal acid-base disturbances coexist.

Clinical Manifestations

The symptoms and signs of the underlying disease that give rise to the observed mixed acid-base disorder dominate the clinical picture, but the development of severe abnormalities in either Pa_{CO_2} (severe

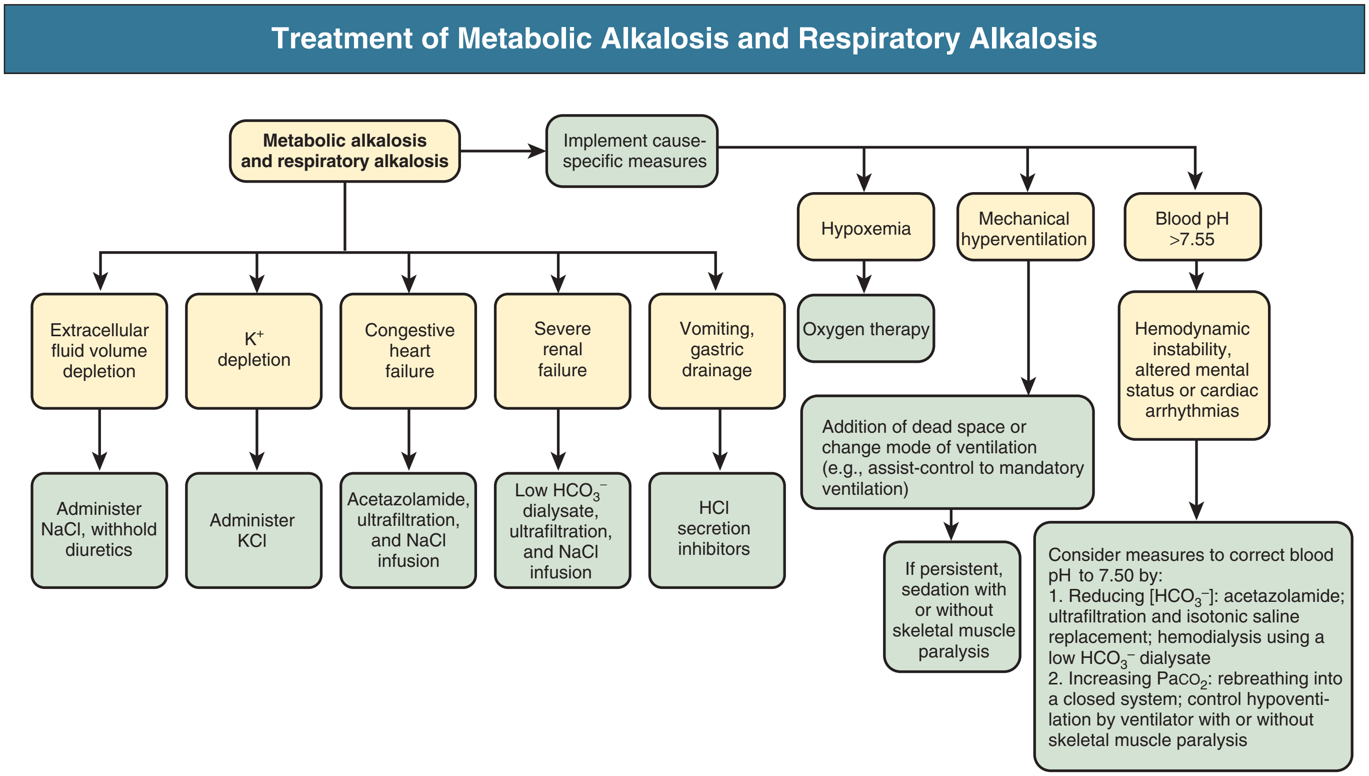
Treatment of Metabolic Alkalosis and Respiratory Alkalosis
Metabolic alkalosis and respiratory alkalosis
Implement cause-specific measures
Hypoxemia
Mechanical hyperventilation
Blood pH >7.55
Extracellular fluid volume depletion
K+ depletion
Congestive heart failure
Severe renal failure
Vomiting, gastric drainage
Oxygen therapy
Hemodynamic instability, altered mental status or cardiac arrhythmias
Addition of dead space or change mode of ventilation (e.g., assist-control to mandatory ventilation)
Administer NaCl, withhold diuretics
Administer KCl
Acetazolamide, ultrafiltration, and NaCl infusion
Low HCO3− dialysate, ultrafiltration, and NaCl infusion
HCl secretion inhibitors
If persistent, sedation with or without skeletal muscle paralysis
Consider measures to correct blood pH to 7.50 by:
1. Reducing [HCO3−]: acetazolamide; ultrafiltration and isotonic saline replacement; hemodialysis using a low HCO3− dialysate
2. Increasing PaCO2: rebreathing into a closed system; control hypoventilation by ventilator with or without skeletal muscle paralysis

Fig. 14.8 Treatment of Metabolic Alkalosis and Respiratory Alkalosis.

hypocapnia or hypercapnia) or systemic acidity (profound acidemia or alkalemia) might be responsible for the superimposition of additional clinical manifestations. On the one hand, profound hypocapnia might induce obtundation, generalized seizures, and occasionally even coma or death due to a critical reduction in cerebral blood flow. Rarely, angina pectoris also might occur. On the other hand, severe hypercapnia might generate a profound encephalopathy with the classic features of pseudotumor cerebri, including headaches, obtundation, vomiting, and bilateral papilledema, caused by increased ICP. Extreme acidemia results in depression of the central nervous system as well as the cardiovascular system.[7] Reduction in myocardial contractility and peripheral vascular resistance triggered by acidemia might result in severe hypotension. Profound alkalemia might elicit paresthesias, tetany, cardiac dysrhythmias, or generalized seizures.

Diagnosis

The basic principles underlying the diagnosis of mixed acid-base disorders are identical to those required for the identification of simple acid-base disturbances. These include a careful history and physical examination (which will provide important insights into the prevailing acid-base status, as well as useful clues to the differential diagnosis), assessment of the accuracy of the acid-base data by ensuring the available values for pH, Pa_{CO_2}, and serum [HCO$_3^-$] satisfy the mathematical constraints of the Henderson-Hasselbach equation; analysis of the serum anion gap and other ancillary laboratory data; and knowledge of the quantitative aspects of the adaptive response to each of the four simple acid-base disturbances. Even experienced clinicians risk misdiagnosis of the prevailing acid-base status by bypassing this systematic approach.[3]

Normal acid-base values do not prove normal acid-base status, because they might be the fortuitous result of mixed acid-base disorders (e.g., high anion gap acidosis treated with alkali infusion, diarrhea-induced metabolic acidosis in conjunction with vomiting-induced metabolic alkalosis). A given set of acid-base parameters is never diagnostic of a particular acid-base disorder, but it is consistent with a range of acid-base abnormalities. An apparently clear-cut simple acid-base disorder might actually reflect the interplay of a number of coexisting acid-base disturbances.

A critical component of the diagnostic process is the examination of the serum anion gap (Table 14.6), which provides important insights into the nature of the prevailing changes in serum [HCO$_3^-$]. An elevated serum anion gap might offer the first clue to the presence of disordered acid-base status despite normal acid-base parameters. With a serum [HCO$_3^-$] deficit (Δ[HCO$_3^-$]$_p$), a normal or subnormal value for the serum anion gap denotes that the entire decrease in [HCO$_3^-$] can be attributed to acidifying processes resulting in the loss of alkali (e.g., diarrhea, RTA) or to respiratory alkalosis.

By comparison, with a high anion gap metabolic acidosis, there is usually a close reciprocal stoichiometry between the decrease in serum [HCO$_3^-$] and the increase in the anion gap, termed the Δ(anion gap). A reduction in serum [HCO$_3^-$] of 10 mmol/l is therefore associated with a Δ(anion gap) of 10 mmol/l. Addition of the value for the Δ(anion gap) to the prevailing level of serum [HCO$_3^-$] allows the derivation of the basal value of [HCO$_3^-$] existing before the development of the high anion gap metabolic acidosis. This helps distinguish between a pure high anion gap metabolic acidosis and a mixed high and normal anion gap metabolic acidosis, and to detect a mixed high anion gap metabolic acidosis and metabolic alkalosis. Additional diagnostic insights may come from other laboratory data, including the serum potassium, glucose, urea nitrogen, and creatinine concentrations; semiquantitative measures for ketonemia or ketonuria; screening of blood or urine for toxins; and estimation of the serum osmolar gap.

Mild acid-base disorders pose particular diagnostic difficulty because of the overlap of values for the simple disturbances near the normal range. In such patients, any of several simple disorders or a variety of

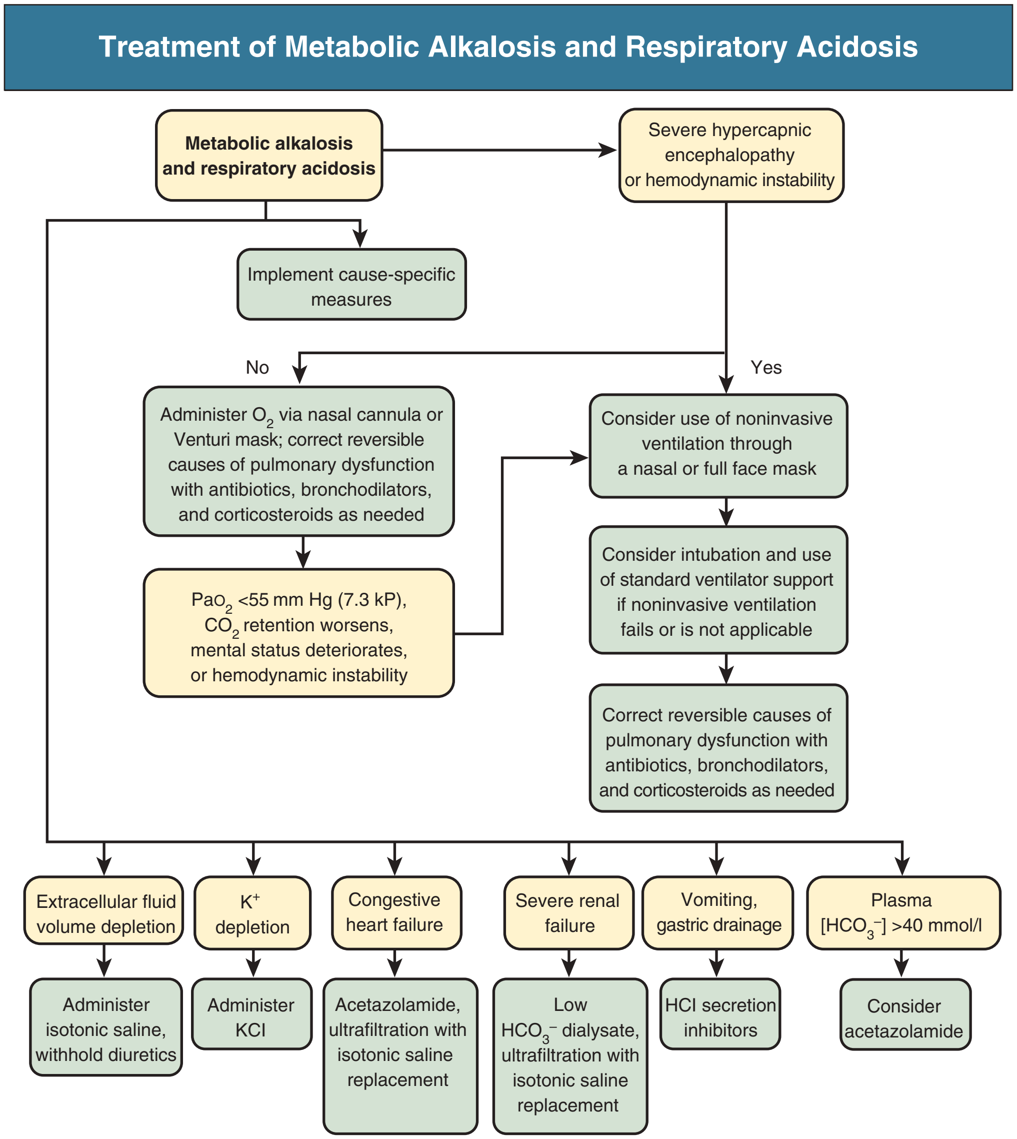
Treatment of Metabolic Alkalosis and Respiratory Acidosis
Metabolic alkalosis and respiratory acidosis
Severe hypercapnic encephalopathy or hemodynamic instability
Implement cause-specific measures
No
Yes
Administer O_2 via nasal cannula or Venturi mask; correct reversible causes of pulmonary dysfunction with antibiotics, bronchodilators, and corticosteroids as needed
Consider use of noninvasive ventilation through a nasal or full face mask
Pao_2 <55 mm Hg (7.3 kP), CO_2 retention worsens, mental status deteriorates, or hemodynamic instability
Consider intubation and use of standard ventilator support if noninvasive ventilation fails or is not applicable
Correct reversible causes of pulmonary dysfunction with antibiotics, bronchodilators, and corticosteroids as needed
Extracellular fluid volume depletion
K^+ depletion
Congestive heart failure
Severe renal failure
Vomiting, gastric drainage
Plasma $[HCO_3^-]$ >40 mmol/l
Administer isotonic saline, withhold diuretics
Administer KCl
Acetazolamide, ultrafiltration with isotonic saline replacement
Low HCO_3^- dialysate, ultrafiltration with isotonic saline replacement
HCl secretion inhibitors
Consider acetazolamide

Fig. 14.9 Treatment of Metabolic Alkalosis and Respiratory Acidosis.

TABLE 14.6 Blood Parameters in Diagnosis of Mixed Metabolic Acid-Base Disorders

Blood Composition	Normal	High Anion Gap Acidosis	High Anion Gap and Normal Anion Gap Acidosis	Metabolic Alkalosis	High Anion Gap Acidosis and Metabolic Alkalosis
pH	7.40	7.29	7.10	7.50	7.38
$Paco_2$ (mm Hg)	40	30	20	45	35
Bicarbonate (mmol/l)	24	14	6	34	20
Anion gap (mmol/l)	10	20	20	12	26
ΔBicarbonate	0	–10	–18	+10	–4
ΔAnion gap	0	+10	+10	+2	+16

mixed disturbances might fully account for the acid-base data under evaluation.

Treatment

The management of mixed acid-base disturbances is aimed at restoration of the altered acid-base status by treatment of each simple acid-base disorder involved.[1,2,24,30] Figs. 14.7 to 14.10 provide recommendations for treatment of patients with some common mixed acid-base disturbances.

Given the variable response time to therapy of the individual components, it is crucial to be aware of the effect that graded correction might have on systemic acidity. The asynchronous reversal of the individual components might give therapeutic advantage, but on other occasions might prove catastrophic. For example, extreme acidemia caused by metabolic acidosis and respiratory acidosis or extreme alkalemia caused by metabolic alkalosis and respiratory alkalosis might be safely corrected by a rapid return of $Paco_2$ toward normal. By

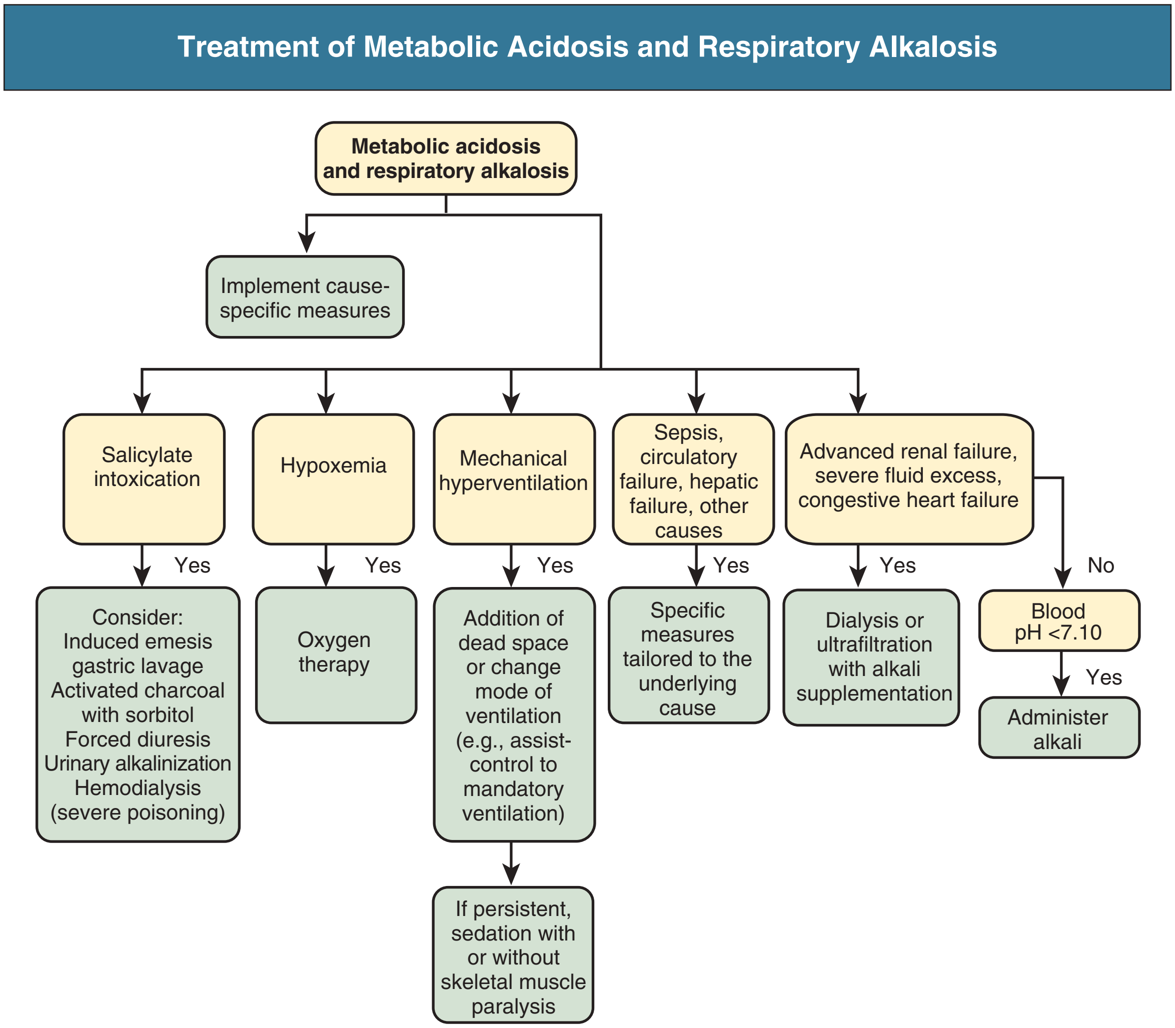
Treatment of Metabolic Acidosis and Respiratory Alkalosis
Metabolic acidosis and respiratory alkalosis
Implement cause-specific measures
Salicylate intoxication
Hypoxemia
Mechanical hyperventilation
Sepsis, circulatory failure, hepatic failure, other causes
Advanced renal failure, severe fluid excess, congestive heart failure
Yes
Yes
Yes
Yes
Yes
No
Consider: Induced emesis gastric lavage Activated charcoal with sorbitol Forced diuresis Urinary alkalinization Hemodialysis (severe poisoning)
Oxygen therapy
Addition of dead space or change mode of ventilation (e.g., assist-control to mandatory ventilation)
Specific measures tailored to the underlying cause
Dialysis or ultrafiltration with alkali supplementation
Blood pH <7.10
Yes
Administer alkali
If persistent, sedation with or without skeletal muscle paralysis

Fig. 14.10 Treatment of Metabolic Acidosis and Respiratory Alkalosis.

comparison, an asynchronous return of $Paco_2$ to normal in a patient with profound metabolic acidosis and superimposed respiratory alkalosis might prove disastrous. Similarly, extreme caution should be exercised in treating patients with respiratory acidosis and metabolic alkalosis, one of the most common mixed acid-base disorders. Although therapeutic measures to improve alveolar ventilation should be instituted, an abrupt decrease in $Paco_2$ risks development of severe alkalemia. Therefore aggressive measures should be taken to treat metabolic alkalosis, making certain that reversal of the metabolic component does not lag behind treatment of the respiratory element. In fact, because the ventilatory drive in patients with chronic respiratory acidosis depends in part on the prevailing acidemia, reversal of a complicating element of metabolic alkalosis regularly results in improved alveolar ventilation, thus achieving a decrease in $Paco_2$ and an increase in Pao_2.

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SELF-ASSESSMENTS QUESTIONS

1. Which of the following statements is correct regarding acute and chronic adaptation to respiratory acid-base disorders in patients with end-stage renal disease (essentially without any renal function)?
   A. Both acute and chronic adaptation are normal.
   B. Acute adaptation is normal but chronic adaptation is increased.
   C. Acute adaptation is absent but chronic adaptation is normal.
   D. Both acute and chronic adaptation are absent.
   E. Acute adaptation is normal but chronic adaptation is absent.
2. A 60-year-old man with a history of chronic obstructive pulmonary disease was admitted to the hospital with increasing shortness of breath on exertion and a cough productive of sputum. He was receiving a bronchodilator as an outpatient. On physical examination, he was afebrile, blood pressure was 130/85 mm Hg without orthostatic changes, heart rate was 92 beats/min, and respiratory rate was 24/min. Chest examination revealed scattered expiratory wheezes and diminished breath sounds. Cardiac examination showed no murmurs or gallops. There was 1+ lower extremity edema. Blood work on admission revealed the following:

Sodium	136 mmol/l	pH	7.32
Potassium	3.6 mmol/l	$PaCO_2$	62 mm Hg
Chloride	96 mmol/l	PaO_2	64 mm Hg (O_2 2 l/min)
Bicarbonate	31 mmol/l		

   Which acid-base disorder are these data consistent with?
   A. Acute respiratory acidosis
   B. Chronic respiratory acidosis
   C. Metabolic acidosis
   D. Chronic respiratory acidosis and metabolic acidosis
3. The patient described in question 2 was treated with steroids, antibiotics, and bronchodilators. Because of peripheral edema and a chest radiograph that showed pulmonary congestion, he was given diuretics and maintained on a low-sodium diet. Over the next several days, the patient's breathing symptoms improved. Repeat blood work obtained 72 hours from admission revealed the following:

Sodium	135 mmol/l	pH	7.40
Potassium	3.3 mmol/l	$PaCO_2$	64 mm Hg
Chloride	88 mmol/l	PaO_2	59 mm Hg (O_2 2 l/min)
Bicarbonate	38 mmol/l		

   These data consistent with which acid-base disorder?
   A. Metabolic alkalosis
   B. Acute respiratory acidosis
   C. Chronic respiratory acidosis
   D. Chronic respiratory acidosis and metabolic acidosis
   E. Chronic respiratory acidosis and metabolic alkalosis

15

Introduction to Glomerular Disease

Clinical Presentations

Jürgen Floege, John Feehally

DEFINITION

Glomerular disease has clinical presentations that vary from the asymptomatic individual who is found to have hypertension, edema, hematuria, or proteinuria at a routine medical assessment to a patient who has fulminant illness with acute kidney injury (AKI) possibly associated with life-threatening extrarenal disease (Fig. 15.1). The most dramatic symptomatic presentations are uncommon. Asymptomatic urine abnormalities are much more common, but less specific, and may also indicate a wide range of nonglomerular urinary tract disease.

CLINICAL EVALUATION OF GLOMERULAR DISEASE

The history, physical examination, and investigations are aimed at excluding nonglomerular disease, finding evidence of associated multisystem disease, and establishing renal function.

History

The majority of glomerular diseases do not lead to symptoms that patients will report. However, specific questioning may reveal edema, hypertension, foamy urine, or urinary abnormalities during prior routine testing (e.g., during scheduled medical examinations). Multisystem diseases associated with glomerular disease include diabetes, hypertension, amyloid, lupus, and vasculitis. Apart from the individual history suggestive of these diseases, a positive family history also may be obtained in some cases and may suggest a genetic cause. Classic genetic causes of renal disease may include Alport syndrome, especially if associated with hearing loss (see Chapter 46); uncommon familial forms of immunoglobulin A (IgA) nephropathy (see Chapter 23); focal segmental glomerulosclerosis (FSGS) secondary to mutations in podocin or other molecules involved in glomerular permeability (see Chapters 18 and 19); some forms of complement-mediated glomerulonephritis (GN) (see Chapter 22); hemolytic uremic syndrome (HUS; see Chapter 29); and other rare conditions (see Chapter 28). Morbid obesity can be associated with FSGS. Certain drugs and toxins may cause glomerular disease, including nonsteroidal antiinflammatory drugs (NSAIDs) and interferon in minimal change disease (MCD); penicillamine, NSAIDs, and mercury (e.g., in skin-lightening creams) in membranous nephropathy; pamidronate and heroin in FSGS; smoking with nodular glomerulosclerosis; and cyclosporine, tacrolimus, mitomycin C, and oral contraceptives in HUS. Recent or persistent infection, especially streptococcal infection, infective endocarditis, and certain viral infections (see Chapters 21, 55, and 56), also may be associated with a variety of glomerular diseases.

Malignant neoplasms associated with glomerular disease include lung, breast, and gastrointestinal (GI) adenocarcinoma in membranous nephropathy; Hodgkin disease in MCD; non-Hodgkin lymphoma in membranoproliferative glomerulonephritis (GN); and renal cell carcinoma in amyloid disease (see Chapter 27). Patients will occasionally present with the renal disease as the first manifestation of a tumor.

Physical Examination

The presence of dependent pitting edema suggests nephrotic syndrome, heart failure, or cirrhosis. In the nephrotic patient, edema is often periorbital in the morning (Fig. 15.2), whereas the face is not affected overnight in edema associated with heart failure (edema distributes by gravity, and patients often cannot lie flat in the setting of heart failure because of orthopnea resulting from pulmonary congestion) or cirrhosis (because of pressure on the diaphragm from ascites). As severity of nephrosis progresses, edema of genitals and the abdominal wall becomes apparent, and accumulation of fluid in body spaces leads to ascites and pleural effusions. Edema is unpleasant, leading to feelings of tightness in the limbs and a bloated abdomen, with practical problems of clothes and shoes no longer fitting. Surprisingly, however, edema may become massive in nephrotic syndrome before patients seek medical help; fluid gains of 20 kg (44 lb) or more are not unusual (Fig. 15.3). The edema becomes firm and stops pitting only when it is long-standing. In children, fluid retention may be striking with nephritic syndrome. Chronic hypoalbuminemia is also associated with loss of normal pink color under the nails, resulting in white nails or white bands if nephrotic syndrome is transient (Muehrcke lines, Fig. 15.4). Xanthelasmas may be present as a result of the hyperlipidemia associated with long-standing nephrotic syndrome (Fig. 15.5).

The presence of pulmonary signs should suggest one of the so-called pulmonary-renal syndromes (see Boxes 24.3 and 24.4). Palpable purpura may be seen in vasculitis, systemic lupus, cryoglobulinemia, or endocarditis.

Clinical Presentations of Glomerular Disease

Asymptomatic
Proteinuria 150 mg to 3 g per day
Hematuria >2 red blood cells per high-power field in spun urine or $>10 \times 10^6$ cells/liter (red blood cells usually dysmorphic)

Macroscopic hematuria
Brown/red painless hematuria (no clots); typically coincides with intercurrent infection
Asymptomatic hematuria ± proteinuria between attacks

Nephrotic syndrome
Proteinuria: adult >3.5 g/day; child >40 mg/h per m^2
Hypoalbuminemia <3.5 g/dl
Edema
Hypercholesterolemia
Lipiduria

Nephritic syndrome
Oliguria
Hematuria: red cell casts
Proteinuria: usually <3 g/day
Edema
Hypertension
Abrupt onset, usually self-limiting

Rapidly progressive glomerulonephritis
Renal failure over days/weeks
Proteinuria: usually <3 g/day
Hematuria: red cell casts
Blood pressure often normal
May have other features of vasculitis

Chronic glomerulonephritis
Hypertension
Renal impairment
Proteinuria often >3 g/day
Shrunken smooth kidneys

Fig. 15.1 Clinical presentation of various glomerular diseases.

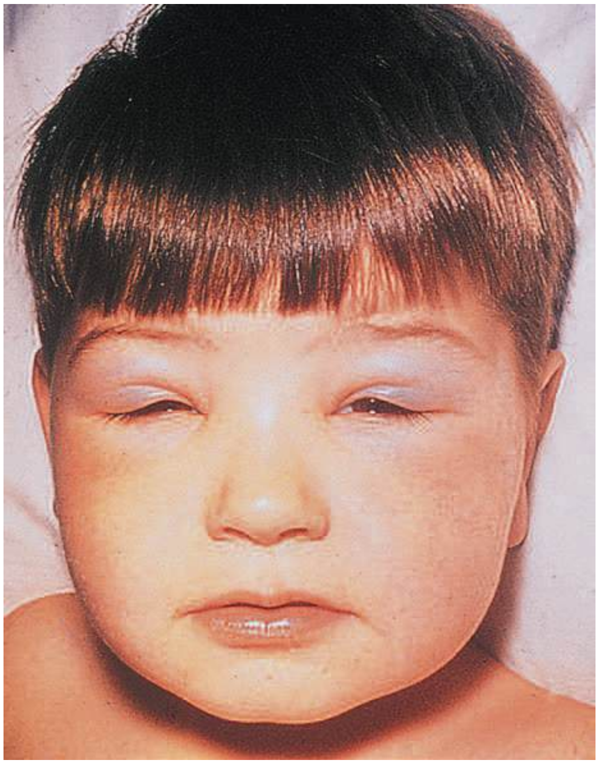


Fig. 15.2 Nephrotic edema. Periorbital edema in the early morning in a nephrotic child. The edema resolves during the day under the influence of gravity.

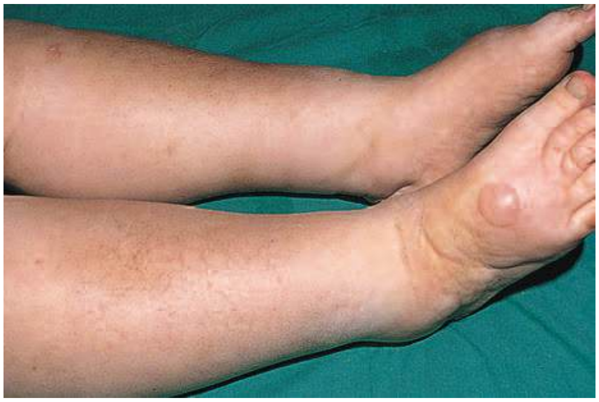


Fig. 15.3 Nephrotic Edema. Severe peripheral edema in nephrotic syndrome; note the blisters caused by intradermal fluid.

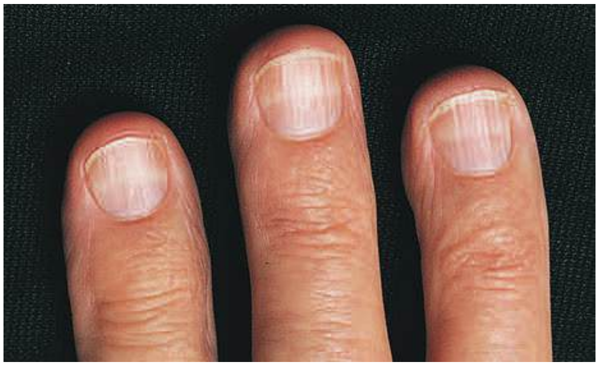


Fig. 15.4 Muehrcke lines (bands) in nephrotic syndrome. The *white line* grew during a transient period of hypoalbuminemia caused by the nephrotic syndrome.

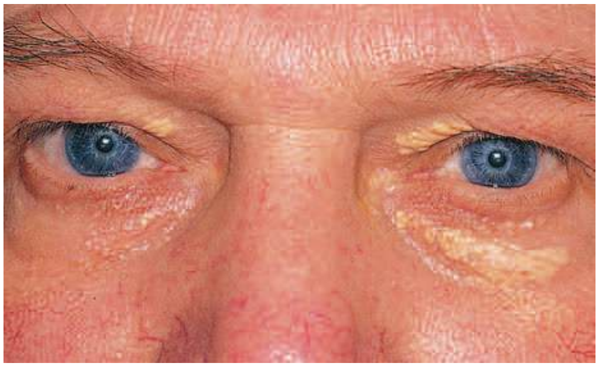


Fig. 15.5 Xanthelasmas in nephrotic syndrome. These prominent xanthelasmas developed within 2 months in a patient with recent onset of severe nephrotic syndrome and serum cholesterol level of 550 mg/dl (14.2 mmol/l).

Laboratory Studies

Assessment of renal function and careful examination of the urine are critical (see Chapters 3 and 4). The quantity of urine protein and the presence or absence of dysmorphic red cells and casts will help classify the clinical presentation (see Fig. 15.1).

Certain serologic tests are helpful. These include antinuclear and anti-DNA antibodies for lupus, cryoglobulins and rheumatoid factor suggesting cryoglobulinemia, anti–glomerular basement membrane (anti-GBM) antibodies for Goodpasture disease, antineutrophil cytoplasmic autoantibody (ANCA) for vasculitis, and antistreptolysin O

TABLE 15.1 **Hypocomplementemia in Glomerular Disease**

Pathways Affected	Complement Changes	Glomerular Disease	Nonglomerular Disease
Classical pathway activation	C3 ↓, C4 ↓, CH50 ↓	Lupus nephritis (especially Class IV) Cryoglobulinemia Membranoproliferative GN type 1	
Alternative pathway activation	C3 ↓, C4 normal, CH50 ↓	Poststreptococcal GN GN associated with other infection* (e.g., endocarditis, shunt nephritis) HUS	Atheroembolic renal disease
	plus C3 nephritic factor	Dense deposit disease	
Reduced complement synthesis	Acquired		Hepatic disease Malnutrition
	Hereditary C2 or C4 deficiency Factor H deficiency	Lupus nephritis Familial HUS Dense deposit disease	

*Glomerulonephritis *(GN)* with visceral abscesses is generally associated with normal or increased complement (elevations occur because complement components are acute-phase reactants). *CH50,* 50% hemolyzing dose of complement; *HUS,* hemolytic uremic syndrome.

titer or streptozyme test for poststreptococcal GN. Serum and urine electrophoresis will detect monoclonal light chains or heavy chains, and assays for free light chains in serum or urine may aid in their quantification, as in myeloma-associated amyloid or light-chain deposition disease.

Testing for the presence of ongoing bacterial or viral infections is also useful. This includes blood cultures and testing for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection.

Measurement of systemic complement pathway activation by testing for serum C3, C4, and CH50 (50% hemolyzing dose of complement) is often helpful in limiting the differential diagnosis (Table 15.1).

The importance of genetic evaluation in patients with GN is discussed in Chapters 19 and 22.

Imaging

Ultrasound scanning is recommended in the workup to ensure the presence of two kidneys, to rule out obstruction or anatomic abnormalities, and to assess kidney size. Renal size is often normal in GN, although large kidneys (>14 cm) are sometimes seen in nephrotic syndrome associated with diabetes, amyloid disease, or HIV infection. Large kidneys also can occasionally be seen with any acute severe GN and acute interstitial nephritis. The occurrence of small kidneys (<9 cm) and/or severe cortical thinning suggests advanced chronic kidney disease (CKD) and should limit enthusiasm for renal biopsy or aggressive immunosuppressive therapies.

Renal Biopsy

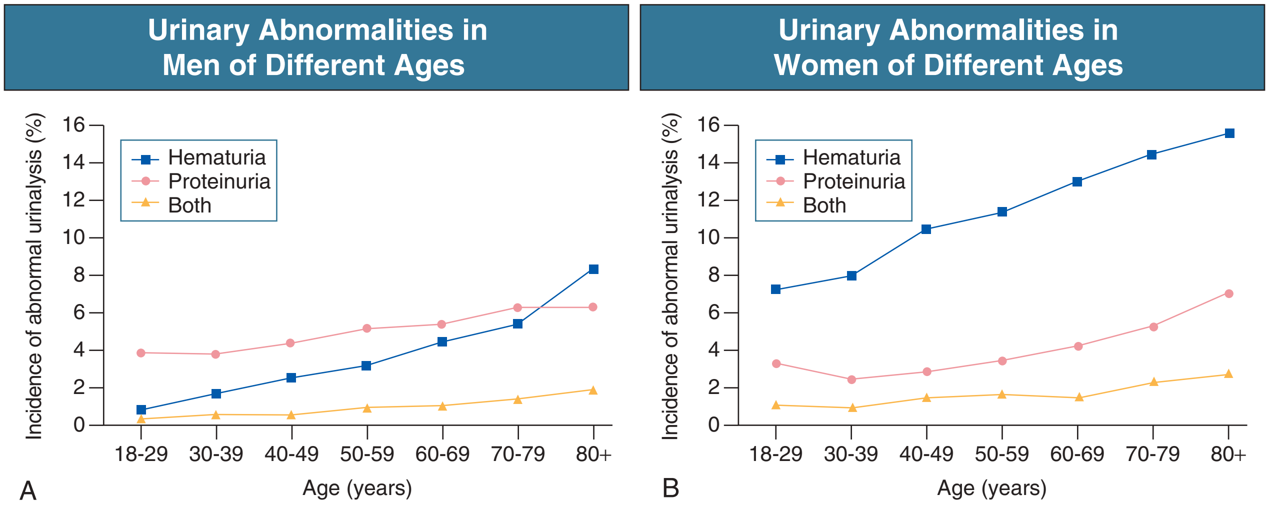
Renal biopsy is generally required to establish the type of glomerular disease and to guide treatment decisions (see Chapter 6). In some patients, however, renal biopsy is not performed. If nephrotic children (age 2 to 12) have no unusual clinical features, the probability of MCD is so high that corticosteroids can be initiated without biopsy (see Chapter 17). In patients with acute nephritic syndrome, if all features point to poststreptococcal GN, especially in an epidemic, biopsy can be reserved for the minority who do not show early spontaneous improvement (see Chapter 55). In Goodpasture disease (see Chapter 24), the presence of lung hemorrhage and rapidly progressive renal failure with urinary red cell casts and high levels of circulating anti-GBM antibody establishes the diagnosis without the need for a biopsy, although a biopsy may still provide valuable prognostic information. In patients with systemic features of vasculitis, a positive ANCA titer, negative blood cultures, and a tissue biopsy specimen from another site showing vasculitis are sufficient to secure a diagnosis of renal vasculitis. Again, however, renal biopsy may provide important clues to disease activity and chronicity. Biopsy is also not generally performed in patients with long-standing diabetes with characteristic findings suggestive of diabetic nephropathy and other evidence of microvascular complications of diabetes (see Chapter 30). Biopsy may not be indicated in many patients with glomerular disease presenting with minor, asymptomatic urine abnormalities and well-preserved renal function because the prognosis is excellent and histologic findings will not alter management.

ASYMPTOMATIC URINE ABNORMALITIES

Urine testing that detects proteinuria or microhematuria is often the first evidence of glomerular disease. The random nature of urine testing in most communities inevitably means that much mild glomerular disease remains undetected. In some countries, symptomless individuals may have a urine test only if they require medical approval for some key life event, such as obtaining life insurance, joining the armed forces, or sometimes for employment purposes. In other countries, for example, Japan, urinalysis is performed routinely in school or for employment. These different practices may partly account for the apparently variable incidence of certain diseases, such as IgA nephropathy, which often manifests as asymptomatic proteinuria and microhematuria. Asymptomatic low-grade proteinuria and microhematuria and the combination of the two, also increase in prevalence with age[1] (Fig. 15.6). Nevertheless, there is no evidence to justify routine population-wide screening for asymptomatic urine abnormalities as renal biopsy and therapeutic intervention are rarely required when renal function is preserved. For certain high-risk populations, such as patients with diabetes or hypertension, evaluation of albuminuria may be useful as it carries increased risk for cardiovascular disease.

Asymptomatic Microhematuria

Microhematuria is defined as the presence of more than two red blood cells (RBCs) per high-power field in a spun urine sediment (3000 rpm for 5 minutes) or more than 10×10^6 RBCs/l. Microhematuria is common in many glomerular diseases, especially IgA nephropathy and thin basement membrane nephropathy, although there are many other causes


Urinary Abnormalities in Men of Different Ages

Urinary Abnormalities in Women of Different Ages

Fig. 15.6 Prevalence of asymptomatic proteinuria and hematuria with age. Mass screening of a population of 107,192 adult men (A) and women (B) in Okinawa, Japan. Hematuria is more common in women. (Modified from reference 1.)

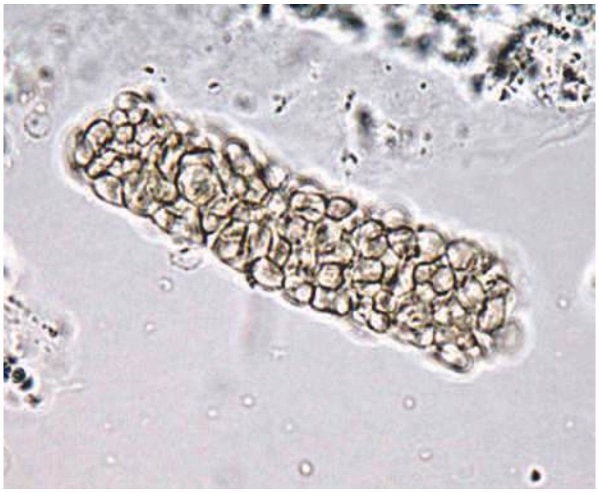


Fig. 15.7 Red blood cell cast. An RBC cast typical of glomerular hematuria.

of hematuria (see Chapters 46 and 59). A glomerular origin especially should be considered if more than 5% of RBCs are acanthocytes or dysmorphic (see Chapter 4) or if the hematuria is accompanied by RBC casts or proteinuria (Fig. 15.7).

Pathogenesis

Glomerular hematuria is thought to result from small breaks in the GBM that allow extravasation of RBCs into the urinary space. This may occur in the peripheral capillary wall but more often occurs in the paramesangial basement membrane, particularly in diseases involving injury to the mesangium (mesangiolysis). As long as the renal tubules are intact, low amounts of serum proteins lost together with RBCs in damaged glomeruli can be fully reabsorbed, resulting in "isolated" microhematuria.

Evaluation

The evaluation of microhematuria, discussed further in Chapters 46 and 59, begins with a thorough history. Urine culture should exclude urinary or prostatic infection. Phase contrast microscopy should follow in cases of persistent microhematuria to search for dysmorphic RBCs and RBC casts. In the absence of urine infection or a bladder catheter, any detectable proteinuria (>0.3 g/24 h) in the patient with asymptomatic microhematuria virtually excludes "urologic" bleeding and strongly suggests a glomerular origin. If this evaluation is nondiagnostic, renal imaging is performed to exclude anatomic lesions such as stones, tumors, polycystic kidneys, or arteriovenous malformations.

In those older than 40 years who have persistent isolated microhematuria without evidence of a glomerular origin (see previous discussion), cystoscopy is mandatory to exclude uroepithelial malignant disease. In people younger than 40 years, such malignant disease is so rare that cystoscopy is not recommended. If all the prior study results are normal, a glomerular cause is likely.[2] The glomerular cause can be determined only by renal biopsy, but this is rarely done because the prognosis is excellent in patients with normal renal function, normal blood pressure, and low-grade proteinuria (<0.5 g/day). However, repeated evaluation and prolonged follow-up are mandatory for as long as the urinary abnormality persists.

Asymptomatic Non-Nephrotic Proteinuria

The hallmark of glomerular disease is the excretion of protein in the urine. Normal urine protein excretion is less than 150 mg/24 h, consisting of 20 to 30 mg of albumin, 10 to 20 mg of low-molecular-weight proteins that undergo glomerular filtration, and 40 to 60 mg of secreted proteins (e.g., Tamm-Horsfall, IgA). Proteinuria is identified and quantified by dipstick testing or by assay in timed urine collections; Chapter 4 discusses test interpretation.

An albumin excretion rate of 30 to 300 mg of albumin per day (previously termed *microalbuminuria*), equivalent to a urine albumin-to-creatinine (gram/gram) ratio of 0.03 to 0.3, is detected by quantitative immunoassay or by special urine dipsticks because this is below the sensitivity of the normal dipstick (see Chapter 30). This measurement is primarily used to identify diabetic individuals at risk for development of nephropathy and to assess cardiovascular risk, for example, in patients with hypertension.

Non-nephrotic proteinuria is usually defined as a urine protein excretion of less than 3.5 g/24 h or a urine protein-to-creatinine ratio of less than 3 g/g. Whereas nephrotic-range proteinuria is absolutely characteristic of glomerular disease, lower levels of proteinuria (<3.5 g/24 h) is much less specific and may occur with a wide range of nonglomerular parenchymal diseases as well as with nonparenchymal renal and urinary tract conditions that must be excluded by clinical evaluation and investigation.

Increased urine protein excretion may result from alterations in glomerular permeability or tubulointerstitial disease, although only in glomerular disease will it be in the nephrotic range. Protein excretion also can increase if there is greater filtration through normal glomeruli (overflow proteinuria).

Overflow Proteinuria

Overflow proteinuria is typical of urinary light-chain excretion. It is seen in myeloma but can occur in other settings (e.g., release of lysozyme by leukemic cells) and should be suspected when the urine dipstick is negative for albumin despite detection of large amounts of proteinuria by other tests.

Tubular Proteinuria

Tubulointerstitial disease can be associated with low-grade proteinuria (usually <2 g/day). In addition to the loss of tubular proteins such as α_1- or β_2-microglobulin, there will also be some albuminuria secondary to impaired tubular reabsorption of filtered albumin. Tubular proteinuria accompanying glomerular proteinuria is an adverse prognostic sign in various glomerular diseases because it usually indicates advanced tubulointerstitial damage.

Glomerular Proteinuria

Glomerular proteinuria is further classified into transient or hemodynamic (functional) proteinuria, proteinuria that is present only during the day (orthostatic), and persistent or fixed proteinuria.

Functional proteinuria. Functional proteinuria refers to the transient non-nephrotic proteinuria that can occur with fever, exercise, heart failure, and hyperadrenergic or hyperreninemic states. Functional proteinuria is benign, usually assumed to be hemodynamic in origin, and the result of increases in single-nephron flow or pressure.

Orthostatic proteinuria. In children and young adults, low-grade glomerular proteinuria may be orthostatic, meaning that proteinuria is absent when urine is generated in the recumbent position. If there is no proteinuria in early-morning urine, the diagnosis of orthostatic proteinuria can be made. In patients with fixed orthostatic proteinuria, renal plasma flow and glomerular filtration rate (GFR) decrease in the upright position because of a lower systemic blood pressure. As recently proposed, the decreased GFR translates into a lower *streaming potential* across the filtration barrier, which under physiologic conditions, retains albumin within the blood. When GFR and filtration pressure are reduced beyond a certain threshold, albumin is no longer excluded efficiently from the filter by electrophoresis and consequently leaks through the filter, explaining reversible low-grade proteinuria in the upright position in these patients.[3]

Total urine protein in the patient with orthostatic proteinuria is usually less than 1 g/24 h; hematuria and hypertension are absent. Renal biopsy usually shows normal morphology or occasionally mild glomerular change. The prognosis is uniformly good, and renal biopsy is not indicated.[4]

Fixed non-nephrotic proteinuria. Fixed non-nephrotic proteinuria is usually caused by glomerular disease. If GFR is preserved and proteinuria is less than 0.5 to 1 g/day, biopsy is not indicated but prolonged follow-up is necessary if significant proteinuria persists, to rule out the possibility of disease progression. Previous studies indicate that the biopsy findings in these patients can be similar to those seen in nephrotic syndrome (most commonly FSGS or membranous nephropathy), although milder lesions are more common, particularly mesangial proliferative GN or IgA nephropathy. In general, other than regular monitoring and blood pressure control as needed, no treatment is necessary.

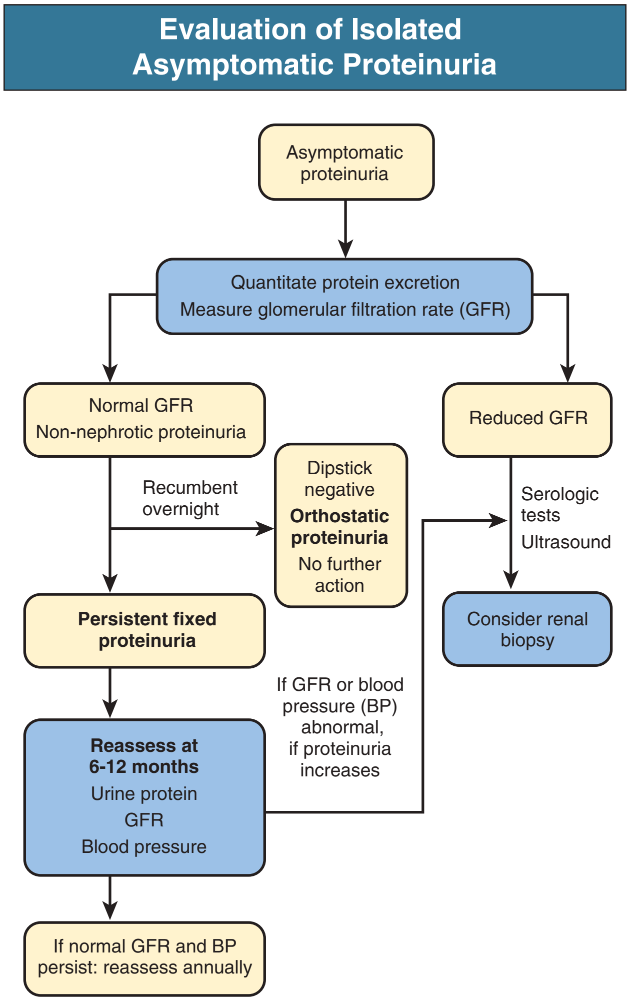

Evaluation of Isolated Asymptomatic Proteinuria
Asymptomatic proteinuria
Quantitate protein excretion
Measure glomerular filtration rate (GFR)
Normal GFR
Non-nephrotic proteinuria
Reduced GFR
Recumbent overnight
Dipstick negative
Orthostatic proteinuria
No further action
Serologic tests
Ultrasound
Persistent fixed proteinuria
Consider renal biopsy
If GFR or blood pressure (BP) abnormal, if proteinuria increases
Reassess at 6-12 months
Urine protein
GFR
Blood pressure
If normal GFR and BP persist: reassess annually

Fig. 15.8 Evaluation of patients with isolated asymptomatic proteinuria.

Although it is controversial, many nephrologists will perform a renal biopsy in patients with normal GFR if non-nephrotic proteinuria exceeds 1 g/day, in particular if it persists after initiation of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy.

Fig. 15.8 summarizes the evaluation of isolated asymptomatic proteinuria.

Asymptomatic Proteinuria With Hematuria

Patients with coincident asymptomatic hematuria and proteinuria have a much greater risk for significant glomerular injury, hypertension, and progressive renal dysfunction. Minor histologic changes are less common. Renal biopsy is often performed even if urine protein is only 0.5 to 1 g/24 h if there is also persistent microhematuria with casts and/or declining renal function.

MACROHEMATURIA

Episodic painless macrohematuria associated with glomerular disease is often brown or "smoky" rather than red, and clots are unusual. Macrohematuria must be distinguished from other causes of red or brown urine, including hemoglobinuria, myoglobinuria, porphyrias, consumption of food dyes (particularly beetroot), and intake of drugs (especially rifampin/rifampicin).

Macrohematuria caused by glomerular disease is seen mainly in children and young adults and is rare after age 40. Most cases are caused by IgA nephropathy, but hematuria may occur with other glomerular and nonglomerular renal diseases, including acute interstitial nephritis. Although macrohematuria is typically painless, the patient may have an accompanying dull loin ache that suggests other diagnoses, such as stone disease or loin-pain hematuria syndrome (see Chapter 57). In IgA nephropathy, the frank hematuria is usually episodic, occurring within a day of an upper respiratory tract infection. There is a clear distinction between this history and the 2- to 3-week latency between an upper respiratory tract infection and hematuria that is highly suggestive of postinfectious (usually poststreptococcal) GN; furthermore, patients with poststreptococcal disease usually will have other features of nephritic syndrome.

Macrohematuria requires urologic evaluation, including cystoscopy, at any age unless the history (as described previously) is characteristic of glomerular hematuria.

NEPHROTIC SYNDROME

Definition

Nephrotic syndrome is pathognomonic of glomerular disease. It is a clinical syndrome with a characteristic pentad[5] (see Fig. 15.1). Patients may be nephrotic with preserved renal function, but in many, progressive renal failure will become superimposed when nephrotic syndrome is prolonged.

Independent of the risk for progressive renal failure, the nephrotic syndrome has far-reaching metabolic effects that can influence the general health of the patient. Fortunately, some episodes of nephrotic syndrome are self-limited, and a few patients respond completely to specific treatment (e.g., corticosteroids in MCD). For most patients, however, it is a relapsing or chronic condition. Not all patients with proteinuria above 3.5 g/24 h will have full nephrotic syndrome; some have a normal serum albumin concentration and no edema. This difference presumably reflects the varied response of protein metabolism; some patients sustain an increase in albumin synthesis in response to heavy proteinuria that may even normalize serum albumin.

Etiology

Table 15.2 shows the major causes of nephrotic syndrome. Proteinuria in the nephrotic range in the absence of edema and hypoalbuminemia has similar causes. The relative frequency of the different glomerular diseases varies with age (Table 15.3). Although it is predominant in childhood, MCD remains common at all ages.[6] The prevalence of FSGS in African Americans is increased, which may explain why FSGS is becoming more common in U.S. adults but not in European adults.[7,8]

TABLE 15.2 Common Glomerular Diseases Presenting as Nephrotic Syndrome in Adults

Disease	Associations	Serologic Tests
Minimal change disease (MCD)	Allergy, atopy, NSAIDs, Hodgkin disease	None
Focal segmental glomerulosclerosis (FSGS)	African Americans HIV infection Heroin, pamidronate	— HIV antibody —
Membranous nephropathy (MN)	Idiopathic drugs: Gold, penicillamine, NSAIDs Infections: Hepatitis B and C; malaria Lupus nephritis Malignancy: Breast, lung, gastrointestinal tract	Anti-PLA_2R antibody Hepatitis B surface antigen, anti–hepatitis C virus antibody Anti-DNA antibody —
Membranoproliferative glomerulonephritis (MPGN) type I	C4 nephritic factor	C3 ↓, C4 ↓
Dense deposit disease	C3 nephritic factor	C3 ↓, C4 normal
Cryoglobulinemic MPGN	Hepatitis C	Anti–hepatitis C virus antibody, rheumatoid factor, C3 ↓, C4 ↓, CH50 ↓
Amyloid disease	Myeloma Rheumatoid arthritis, bronchiectasis, Crohn disease (and other chronic inflammatory conditions), familial Mediterranean fever	Plasma free light chains Serum protein electrophoresis, urine immunoelectrophoresis C-reactive protein
Diabetic nephropathy	Other diabetic microangiopathy	None

HIV, Human immunodeficiency virus; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PLA_2R,* phospholipase A_2 receptor.

TABLE 15.3 Age-Related Variations in the Prevalence of Nephrotic Syndrome

	PREVALENCE (%)				
	Child (<15 yr)	Young Adult Whites	Blacks	Middle and Old Age Whites	Blacks
Minimal change disease (MCD)	78	23	15	21	16
Focal segmental glomerulosclerosis (FSGS)	8	19	55	13	35
Membranous nephropathy (MN)	2	24	26	37	24
Membranoproliferative glomerulonephritis (MPGN)	6	13	0	4	2
Other glomerulonephritides	6	14	2	12	12
Amyloid	0	5	2	13	11

Data modified from references 6 and 7.

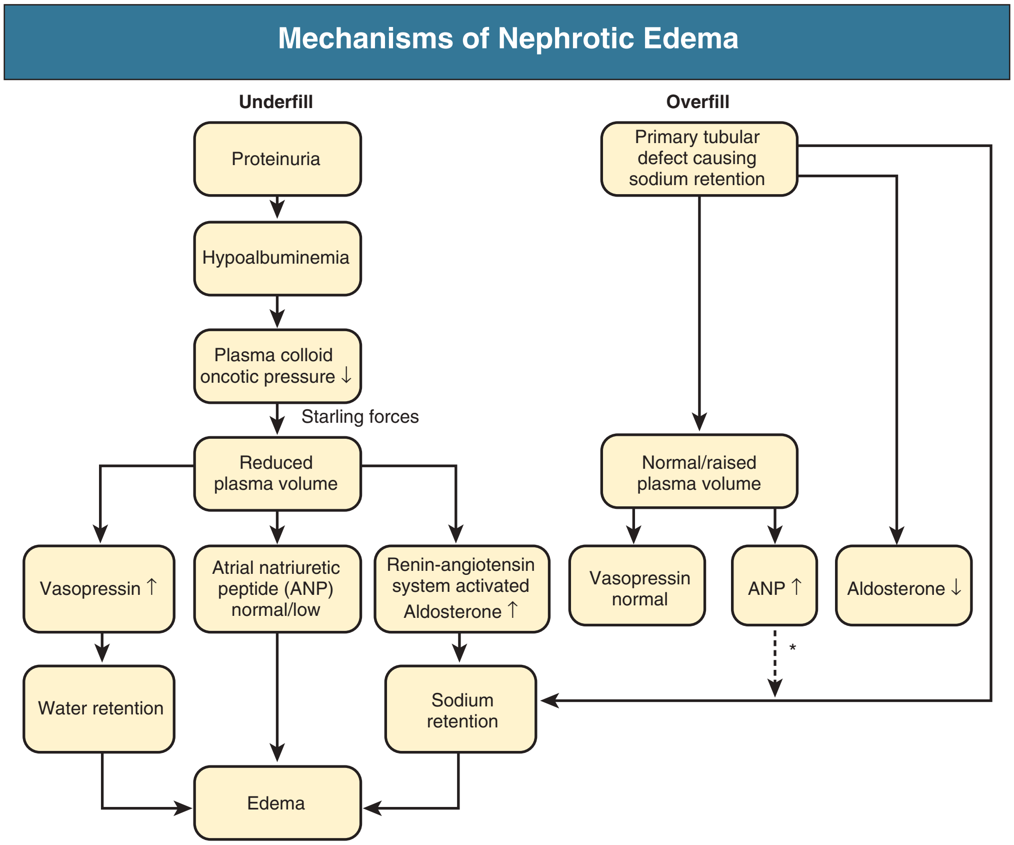

Mechanisms of Nephrotic Edema
Underfill
Overfill
Proteinuria
Hypoalbuminemia
Plasma colloid oncotic pressure ↓
Starling forces
Reduced plasma volume
Vasopressin ↑
Atrial natriuretic peptide (ANP) normal/low
Renin-angiotensin system activated Aldosterone ↑
Water retention
Sodium retention
Edema
Primary tubular defect causing sodium retention
Normal/raised plasma volume
Vasopressin normal
ANP ↑
Aldosterone ↓
*

Fig. 15.9 **Mechanisms of nephrotic edema.*** The kidney is relatively resistant to atrial natriuretic peptide (ANP) in this setting, so ANP has little effect in countering sodium retention.

Hypoalbuminemia

Hypoalbuminemia is mainly a consequence of urinary losses. The liver responds by increasing albumin synthesis, but this compensatory mechanism appears to be blunted in nephrotic syndrome.[9] The end result is that serum albumin falls further. White bands in the nails (Muehrcke lines) are a characteristic clinical sign of hypoalbuminemia (see Fig. 15.4). The increase in protein synthesis in response to proteinuria is not discriminating; as a result, proteins not being lost in the urine may actually increase in concentration in plasma. This is chiefly determined by molecular weight; large molecules will not spill into the urine and will increase in the plasma, whereas smaller proteins, although synthesized to excess, will enter the urine and will decrease in the plasma. These variations in plasma proteins are clinically important in two areas: hypercoagulability and hyperlipidemia (see later discussion).

Edema

At least two major mechanisms are involved in the formation of nephrotic edema: underfill and overfill[10] (Fig. 15.9; see Chapter 7). In the first mechanism, which is more common in children with MCD, the edema appears to result from the low serum albumin, producing a decrease in plasma oncotic pressure, which allows increased transudation of fluid from capillary beds into the extracellular space according to the laws of Starling. The consequent decrease in circulating blood volume *(underfill)* results in a secondary stimulation of the renin-angiotensin system (RAS), resulting in aldosterone-induced sodium retention in the distal tubule. This attempt to compensate for hypovolemia merely aggravates edema because the low oncotic pressure alters the balance of forces across the capillary wall in favor of hydrostatic pressure, forcing more fluid into the interstitial space rather than retaining it within the vascular compartment.

However, a much more common mechanism for edema, occurring in most nephrotic patients, is a primary defect in the ability of the distal nephron to excrete sodium, possibly related to activation of the epithelial sodium channel (ENaC) by proteolytic enzymes that enter the tubular lumen in heavy proteinuria.[11] As a result, there is an increased blood volume; suppression of renin, angiotensin, and vasopressin; and a tendency to hypertension rather than to hypotension. The kidney is also relatively resistant to the actions of atrial natriuretic peptide. An elevated blood volume results *(overfill),* which, in association with the low plasma oncotic pressure, provokes transudation of fluid into the extracellular space and edema. In addition to activation of the ENaC (see earlier discussion), it has been hypothesized that inflammatory leukocytes in the interstitium, which are found in many glomerular diseases, may impair sodium excretion by producing angiotensin II and oxidants (oxidants inactivate local nitric oxide, which is natriuretic).[12]

Metabolic Consequences of Nephrotic Syndrome

Negative Nitrogen Balance

The heavy proteinuria leads to marked negative nitrogen balance, usually measured in clinical practice by serum albumin. Nephrotic syndrome is a wasting illness, but the degree of muscle loss is masked by edema and not fully apparent until the patient is rendered edema free. Loss of 10% to 20% of lean body mass can occur. Albumin turnover is increased in response to the tubular catabolism of filtered protein rather than merely to urinary protein loss. Increasing protein intake does not improve albumin metabolism because the hemodynamic response to an increased intake is a rise in glomerular pressure, increasing urine protein losses. A low-protein diet in turn will reduce proteinuria, but also reduces the albumin synthesis rate and in the longer term may increase the risk for a worsening negative nitrogen balance.

Hypercoagulability

Multiple proteins of the coagulation cascade have altered levels in nephrotic syndrome; in addition, platelet aggregation is enhanced.[13] The net effect is a hypercoagulable state that is enhanced further by immobility, coincidental infection, and hemoconcentration if the patient has a contracted plasma volume (Fig. 15.10). Not only is venous thromboembolism common at any site, but spontaneous arterial thrombosis may rarely occur. Arterial thrombosis may occur in adults in the context of atheroma, promoting coronary and cerebrovascular events in particular, but it also occurs in nephrotic children, in whom spontaneous thrombosis of major limb arteries is an uncommon but feared complication. Up to 10% of nephrotic adults and 2% of children will have a clinical episode of thromboembolism. For unexplained reasons, the risk appears particularly high in those with membranous nephropathy.[14] Individual levels of coagulation proteins are not helpful in assessing the risk for thromboembolism, and serum albumin is mostly used as a surrogate marker. Thromboembolic events increase greatly if the serum albumin concentration decreases to less than 2 g/dl.

The hypoproteinemia and dysproteinemia produce a marked increase in erythrocyte sedimentation rate (ESR), which no longer serves as a marker of an acute phase response in nephrotic patients.

Renal vein thrombosis is an important complication of nephrotic syndrome (see Chapter 41). Although once considered possible, renal vein thrombosis is no longer thought to cause nephrotic syndrome. Renal vein thrombosis is reported clinically in up to 8% of nephrotic patients, but when sought systematically by ultrasound or contrast venography, the frequency increases to 10% to 50%. Symptoms when the thrombosis is acute may include flank pain and hematuria; rarely, AKI can occur if the thrombosis is bilateral. However, the thrombosis often develops insidiously with minimal symptoms or signs because of the development of collateral blood supply. Pulmonary embolism is an important complication.

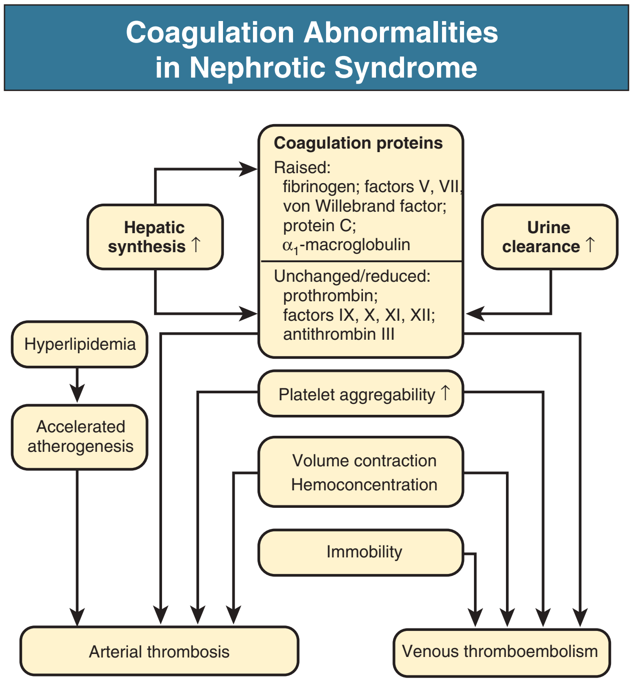

Coagulation Abnormalities in Nephrotic Syndrome
Coagulation proteins
Raised:
fibrinogen; factors V, VII, von Willebrand factor; protein C; α_1-macroglobulin
Unchanged/reduced:
prothrombin; factors IX, X, XI, XII; antithrombin III
Hepatic synthesis ↑
Urine clearance ↑
Hyperlipidemia
Accelerated atherogenesis
Platelet aggregability ↑
Volume contraction
Hemoconcentration
Immobility
Arterial thrombosis
Venous thromboembolism

Fig. 15.10 Coagulation abnormalities in nephrotic syndrome.

Hyperlipidemia and Lipiduria

Hyperlipidemia is such a frequent finding in patients with heavy proteinuria that it is regarded as an integral feature of nephrotic syndrome.[15] Clinical stigmata of hyperlipidemia, such as xanthelasmas, may have a rapid onset (see Fig. 15.5). Serum cholesterol concentration can be above 500 mg/dl (13 mmol/l), although serum triglyceride levels are highly variable. The lipid profile in nephrotic syndrome is known to be highly atherogenic in other populations (Fig. 15.11). The presumption that coronary heart disease is increased in nephrotic syndrome because of the combination of hypercoagulation and hyperlipidemia has been difficult to prove. Many patients who are nephrotic for more than 5 to 10 years will develop additional cardiovascular risk factors, including hypertension and uremia, so it is difficult to separate these influences. However, it is now generally accepted that nephrotic patients do have about a fivefold increased risk for coronary death, except for those with MCD, presumably because the nephrotic state is transient before remission with corticosteroid treatment and does not subject the patient with MCD to prolonged hyperlipidemia.

Experimental evidence shows that hyperlipidemia contributes to progressive renal disease by various mechanisms, with protection afforded by lipid-lowering agents. However, clinical evidence to support a role of statins in slowing CKD progression is inconclusive.[16] Adequate prospective clinical studies on this issue remain to be done, and lipid-lowering drugs are indicated in nephrotic syndrome primarily for cardiovascular reasons.

Several mechanisms account for the lipid abnormalities in nephrotic syndrome. These include increased hepatic synthesis of low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and lipoprotein(a) secondary to the hypoalbuminemia; defective peripheral lipoprotein

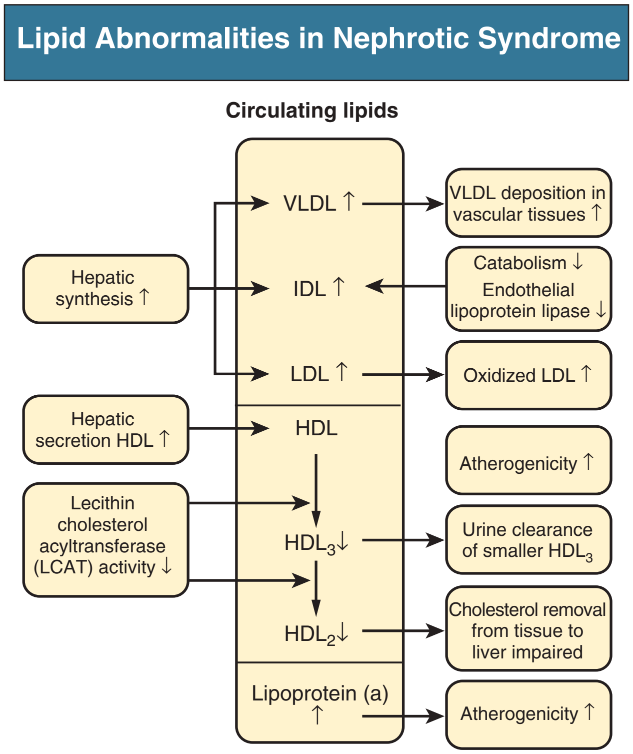

Lipid Abnormalities in Nephrotic Syndrome
Circulating lipids
Hepatic synthesis ↑
VLDL ↑
IDL ↑
LDL ↑
VLDL deposition in vascular tissues ↑
Catabolism ↓
Endothelial lipoprotein lipase ↓
Oxidized LDL ↑
Hepatic secretion HDL ↑
HDL
Atherogenicity ↑
Lecithin cholesterol acyltransferase (LCAT) activity ↓
HDL_3↓
Urine clearance of smaller HDL_3
HDL_2↓
Cholesterol removal from tissue to liver impaired
Lipoprotein (a) ↑
Atherogenicity ↑

Fig. 15.11 Lipid abnormalities in nephrotic syndrome. Changes in high-density lipoprotein *(HDL)* are more controversial than those in very-low-density lipoprotein *(VLDL)*. *IDL*, Intermediate-density lipoprotein; *LDL*, low-density lipoprotein.

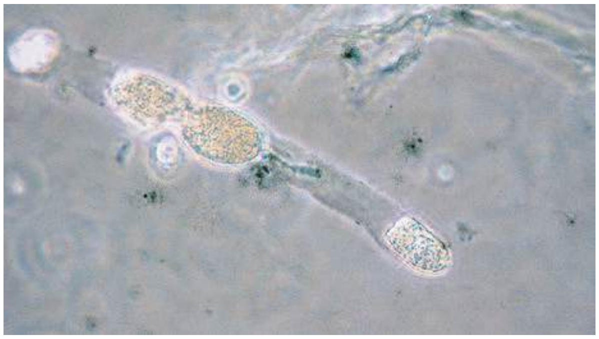


Fig. 15.12 Fat in the urine. This hyaline cast contains oval fat bodies, which are tubular epithelial cells full of fat. Oval fat bodies often appear brown.

lipase activity resulting in increased VLDL; and urinary losses of high-density lipoprotein (HDL; see Fig. 15.11).

Lipiduria, the fifth component of the nephrotic syndrome pentad, is manifested by the presence of refractile accumulations of lipid in cellular debris and casts (oval fat bodies and fatty casts; Fig. 15.12). However, the lipiduria appears to be a result of the proteinuria and not the plasma lipid abnormalities.

Other Metabolic Effects of Nephrotic Syndrome

Vitamin D–binding protein is lost in the urine, resulting in low plasma 25-hydroxyvitamin D levels, but plasma free vitamin D is usually normal, and overt osteomalacia or uncontrolled hyperparathyroidism is very unusual in nephrotic syndrome in the absence of renal impairment. Thyroid-binding globulin is lost in the urine and total circulating thyroxine reduced, but again free thyroxine and thyroid-stimulating hormone are normal, and there are no clinical alterations in thyroid status. Occasional patients have been described with copper, iron, or zinc deficiency caused by the loss of binding proteins in the urine.

Drug binding may be altered by the decrease in serum albumin. Although most drugs do not require dose modifications, one important exception is clofibrate, which produces severe myopathy in nephrotic patients when administered at normal doses. Reduced protein binding also may reduce the dose of warfarin (Coumadin) required to achieve adequate anticoagulation or the dose of furosemide required to achieve adequate fluid loss (see later discussion).

Infection

Nephrotic patients are prone to bacterial infection. Before corticosteroids were shown to be effective in childhood nephrotic syndrome, sepsis was the most common cause of death and remains a major problem in the developing world. Primary peritonitis, especially that caused by pneumococci, is particularly characteristic of nephrotic children. It is less common with increasing age; by 20 years most adults have antibodies against pneumococcal capsular antigens. Peritonitis caused by both β-hemolytic streptococci and gram-negative organisms occurs, but staphylococcal peritonitis is not reported. Cellulitis, especially in areas of severe edema, is also common, most frequently caused by β-hemolytic streptococci.

The increased risk for infection has several explanations. Large fluid collections are sites for bacteria to grow easily; nephrotic skin is fragile, creating sites of entry; and edema may dilute local humoral immune factors. Loss of IgG and complement factor B (of the alternative pathway) in the urine impairs host ability to eliminate encapsulated organisms such as pneumococci. Zinc and transferrin are lost in the urine, and both are required for normal lymphocyte function. Neutrophil phagocytic function is impaired in patients with nephrotic syndrome, and several forms of in vitro T cell dysfunction are described, although their clinical significance is unclear.

BOX 15.1 Causes of Acute Kidney Injury in Nephrotic Syndrome

- Pre-renal failure caused by volume depletion
- Acute tubular necrosis caused by volume depletion and/or sepsis
- Intrarenal edema
- Renal vein thrombosis
- Transformation of underlying glomerular disease (e.g., crescentic nephritis superimposed on membranous nephropathy)
- Adverse effects of drug therapy
- Acute allergic interstitial nephritis secondary to various drugs, including diuretics
- Hemodynamic response to nonsteroidal antiinflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)

Acute and Chronic Changes in Renal Function

Acute Kidney Injury

Patients with nephrotic syndrome are at risk for the development of AKI,[17] through a variety of mechanisms (Box 15.1). These include volume depletion or sepsis, resulting in either pre-renal AKI or acute tubular necrosis[18]; transformation of the underlying disease, such as development of crescentic nephritis in a patient with membranous nephropathy; development of bilateral renal vein thrombosis; increased disposition to pre-renal AKI from NSAIDs and ACE inhibitors or ARBs; and increased risk for allergic interstitial nephritis secondary to drugs, including diuretics. In addition, in very rare cases, AKI may result from intrarenal edema with compression of tubules and, as with nephrotic patients with pre-renal azotemia, may respond with diuresis to albumin infusions combined with a loop diuretic.

Chronic Kidney Disease

With the exception of MCD, most causes of nephrotic syndrome are associated with some risk for the development of progressive renal failure. In this regard, one of the greatest risk factors for progression is the degree of proteinuria (see Chapter 79). Progression is uncommon if there is sustained proteinuria of less than 2 g/day. The risk increases in proportion to the severity of the proteinuria, with marked risk for progression when protein excretion is more than 5 g/day (Fig. 15.13). Proteinuria identifies patients with severe glomerular injury; however, experimental and clinical evidence also suggests that proteinuria itself may be toxic, especially to the tubulointerstitium.[19] In experimental models, measures that reduce proteinuria (e.g., ACE inhibitors) also prevent tubulointerstitial disease and progressive renal failure.

NEPHRITIC SYNDROME

In *nephrotic* syndrome, the glomerular injury is manifested primarily as an increase in permeability of the capillary wall to protein. By contrast, in *nephritic* syndrome, there is evidence of glomerular inflammation resulting in a reduction in GFR, non-nephrotic proteinuria, edema and hypertension (secondary to sodium retention), and hematuria with RBC casts.

The classic nephritic syndrome presentation is seen with acute post-streptococcal GN in children, but this complication has become rare.

TABLE 15.4 Differentiation Between Nephrotic Syndrome and Nephritic Syndrome

Typical Features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red blood cell casts	Absent	Present
Serum albumin	Low	Normal/slightly reduced

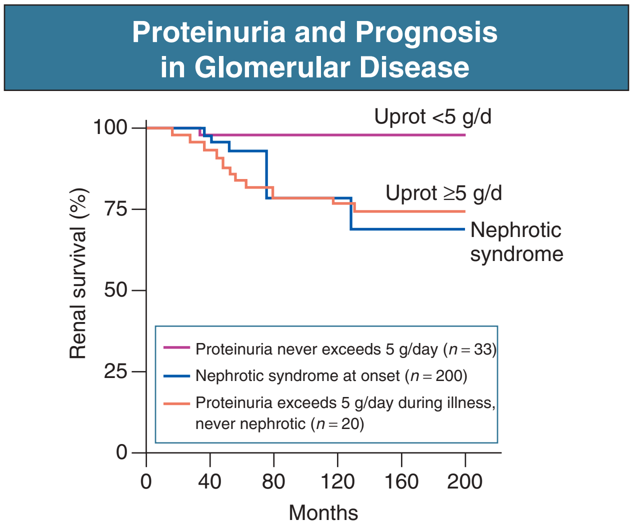


Fig. 15.13 Proteinuria and prognosis in glomerular disease. The influence of heavy proteinuria on long-term renal function in 253 patients with primary glomerular disease at Manchester Royal Infirmary, United Kingdom. Heavy proteinuria at any time during long-term follow-up substantially worsens the prognosis even without frank nephrotic syndrome. (Courtesy Dr. C. D. Short.)

These children usually present with rapid onset of oliguria, weight gain, and generalized edema over a few days. The hematuria results in brown rather than red urine, and clots are not seen. The urine contains protein, RBCs, and RBC casts. Because proteinuria is rarely in the nephrotic range, serum albumin concentration is usually normal. Circulating volume increases with hypertension, and pulmonary edema follows without evidence of primary cardiac disease.

The distinction between typical nephrotic syndrome and nephritic syndrome is usually straightforward on clinical and laboratory grounds (Table 15.4). The use of these clinical descriptions for patients with suspected GN at first presentation helps narrow the differential diagnosis. However, the classification systems are imperfect, and patients with certain glomerular disease patterns, such as membranoproliferative GN, may present with nephrotic syndrome, nephritic syndrome, or a combination of both syndromes.

Etiology

Table 15.5 lists the primary glomerular diseases associated with nephritic syndrome and the serologic tests helpful in diagnosis. The classification is even more challenging than for nephrotic syndrome, because some diseases are identified by histology (IgA nephropathy), others by serology and histology (ANCA-associated vasculitis and lupus nephritis), and others by etiology (postinfectious GN).

TABLE 15.5 Common Glomerular Diseases Presenting As Nephritic Syndrome

Disease	Associations	Serologic Tests
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	Antistreptolysin titer, streptozyme antibody
Other postinfectious disease		
Endocarditis	Cardiac murmur	Blood cultures, C3 ↓
Abscess	—	Blood cultures, C3, C4 normal or increased
Shunt	Treated hydrocephalus	Blood cultures, C3 ↓
IgA nephropathy	Upper respiratory or gastrointestinal infection	Serum IgA ↑
Lupus nephritis	Other multisystem features of lupus	Antinuclear antibody, anti–double-stranded DNA antibody, C3 ↓, C4 ↓

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Rapidly progressive glomerulonephritis (RPGN) describes the clinical situation in which glomerular injury is so acute and severe that renal function deteriorates markedly over days or weeks. The patient may present as a uremic emergency, with nephritic syndrome that is not self-limited but moves on rapidly to renal failure, or with rapidly deteriorating renal function when being investigated for extrarenal disease (many of the patterns of GN associated with RPGN occur as part of a systemic immune illness).

The histologic counterpart of RPGN is crescentic GN. The proliferative cellular response seen outside the glomerular tuft but within Bowman space is known as a "crescent" because of its shape on histologic cross section (see Fig. 16.8). Typically, the glomerular tuft also shows segmental necrosis or focal segmental necrotizing GN; this is particularly characteristic of the vasculitis syndromes.

The term *rapidly progressive* GN is therefore often used to describe acute deterioration in renal function in association with a crescentic nephritis. Unfortunately, not all patients with a nephritic urine sediment and AKI will fit this syndrome. For example, AKI may also occur in milder glomerular disease if it is complicated by accelerated hypertension, renal vein thrombosis, or acute tubular necrosis. This emphasizes the need to obtain histologic confirmation of the clinical diagnosis.

ETIOLOGY

Table 15.6 shows the primary glomerular diseases associated with RPGN and helpful serologic tests. As with nephritic syndrome, different assessment methods are useful for different diseases causing RPGN.

PROGRESSIVE CHRONIC KIDNEY DISEASE

In most types of chronic GN, a proportion of patients (often between 25% and 50%) will have slowly progressive renal impairment. If no

TABLE 15.6 Glomerular Diseases Presenting as Rapidly Progressive Glomerulonephritis

Disease	Associations	Serologic Tests
Goodpasture Syndrome		
	Lung hemorrhage	Anti–glomerular basement membrane antibody (occasionally antineutrophil cytoplasmic antibody [ANCA] present)
Vasculitis		
Granulomatosis with polyangiitis (Wegener granulomatosis)	Upper and lower respiratory tract involvement	Cytoplasmic ANCA
Microscopic polyangiitis	Multisystem involvement	Perinuclear ANCA
Pauci-immune crescentic glomerulonephritis	Renal involvement only	Perinuclear ANCA
Immune Complex Disease		
Systemic lupus erythematosus	Other multisystem features of lupus	Antinuclear antibody, anti–double-stranded DNA antibody, C3 ↓, C4 ↓
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	Antistreptolysin titer, streptozyme antibody C3 ↓, C4 normal
IgA nephropathy; IgA vasculitis (Henoch-Schönlein purpura [HSP])	Characteristic rash ± abdominal pain in HSP	Serum IgA ↑ (30%) C3 and C4 normal
Endocarditis		
	Cardiac murmur; other systemic features of bacteremia	Blood cultures ANCA (occasionally) C3 ↓, C4 normal

Note the overlap between these diseases and those in Table 15.5. A number of glomerular diseases may present with either nephritic syndrome or RPGN.

clinical event early in the course of the disease brings them to medical attention, patients may present late with established hypertension, proteinuria, and renal impairment. In long-standing GN, the kidneys shrink but remain smooth and symmetric. Renal biopsy at this stage is more hazardous and less likely to provide diagnostic material. Light microscopy often shows nonspecific features of end-stage renal disease (ESRD), consisting of focal or global glomerulosclerosis and dense tubulointerstitial fibrosis, and it may not be possible to define with confidence that a glomerular disease was the initiating renal injury, let alone define the glomerular pattern more precisely. Immunofluorescence may be more helpful; in particular, mesangial IgA may be present in adequate amounts to allow a diagnosis of IgA nephropathy to be made. However, when renal imaging shows small kidneys, only rarely will biopsy be appropriate. For this reason, chronic GN often has been a presumptive diagnosis in patients presenting late with shrunken kidneys, proteinuria, and renal impairment. This is imprecise and has led to an overestimate of the frequency of GN as a cause of ESRD in registry data. GN should be diagnosed only if there is confirmatory histologic evidence.

TREATMENT OF GLOMERULAR DISEASE

General Principles

Before any therapeutic decisions, it should always be ascertained that glomerular disease is *primary* and that no specific therapy is available. For example, treatment of an underlying infection or tumor may result in remission of GN. In the remaining cases, both general supportive treatment (see Chapter 79) and disease-specific therapy should be considered. Supportive treatment includes measures to treat blood pressure, reduce proteinuria, control edema, and address other metabolic consequences of nephrotic syndrome. If successful, these relatively nontoxic therapies can prevent the need for immunosuppressive drugs, which have multiple potential side effects. Supportive therapy is usually not necessary in corticosteroid-sensitive MCD with rapid remission or in patients with IgA nephropathy, Alport syndrome, or thin basement membrane nephropathy, provided the patient exhibits no proteinuria above 0.5 g/day, loss of GFR, or hypertension.

Hypertension

Hypertension is very common in GN; it is virtually universal as chronic GN progresses toward ESRD and is the key modifiable factor in preserving renal function. Sodium and water overload is an important part of the pathogenetic process, and high-dose diuretics with moderate dietary sodium restriction are usually an essential part of the treatment. As in other chronic renal diseases, the aim of blood pressure control is not only to protect against the cardiovascular risks of hypertension, but also to delay progression of the renal disease. In the Modification of Diet in Renal Disease (MDRD) study, patients with proteinuria (>1 g/day) had a better outcome if their blood pressure was reduced to 125/75 mm Hg rather than to the previous standard of 140/90 mm Hg.[20,21] The recent Kidney Disease: Improving Global Outcomes (KDIGO) CKD guideline recommends a blood pressure target below 130/80 mm Hg in proteinuric patients,[22] but the recent SPRINT trial and some other studies suggest that a systolic blood pressure target in the 120s may be more effective in some populations (see Chapters 36 and 79). There are strong theoretical and experimental reasons for ACE inhibitors and ARBs to be first-choice therapy, and this is now well documented in clinical studies.[23-25] Nondihydropyridine calcium channel blockers may also have a beneficial effect on proteinuria as well as on blood pressure. In contrast, dihydropyridine calcium channel blockers may exacerbate proteinuria because of their ability to dilate the afferent arteriole, but these agents are considered relatively safe to use if the patient is receiving either an ACE inhibitor or an ARB. As in primary hypertension, lifestyle modification (salt restriction, weight normalization, regular exercise, and smoking cessation) should be an integral part of the therapy.[22] If target blood pressure cannot be achieved with these measures, antihypertensive therapy should be stepped up according to current guidelines (see Chapter 36).

Treatment of Proteinuria

Besides hypertension, proteinuria represents the second key modifiable factor to preserve GFR in patients with glomerular disease (see Chapters 79 and 80). Most studies suggest that the progressive loss of renal function observed in many glomerular diseases can largely be prevented if proteinuria can be reduced to levels below 0.5 g/d. This may be because many of the measures to reduce protein excretion (e.g., ACE inhibitors, ARBs) also reduce glomerular hypertension, which contributes to progressive renal failure. However, there is also increasing evidence that proteinuria or factors present in proteinuric urine may be toxic to the tubulointerstitium.[19] In nephrotic patients, a reduction of proteinuria to a non-nephrotic range can induce serum proteins to rise, with alleviation of many of the metabolic complications of nephrotic syndrome.

Most of the agents used to reduce urinary protein excretion do so hemodynamically, by either blocking efferent arteriolar constriction (ACE inhibitors or ARBs) or reducing preglomerular pressure (most other classes of antihypertensive drugs). As mentioned, dihydropyridine calcium antagonists are the exception because they preferentially dilate the afferent arteriole and thereby can increase intraglomerular pressure and thus exacerbate proteinuria. Some of the agents, such as ACE inhibitors and ARBs, also may directly reduce the increased glomerular capillary wall permeability. A consequence of this type of therapy is a reduction in GFR; in general, however, the decrease in GFR is of a lower magnitude than the decrease in protein excretion. The antiproteinuric agents of choice are ACE inhibitors and ARBs, which reduce proteinuria by an average of 40% to 50%, particularly if the patient is on dietary salt restriction. There is little clinical evidence to suggest that ACE inhibitors differ from ARBs in this respect. The combination of ACE inhibitors and ARBs increases the risk for AKI when used in older people with vascular disease and diabetes.[26] Similar concerns relate to the combination of ACE inhibitor or ARB with a direct renin inhibitor.[27] However, the combination of ACE inhibitors and ARBs has additive antiproteinuric effect with low risk in younger patients with glomerular proteinuria.[28]

In addition, whereas other classes of antihypertensive agents will reduce proteinuria coincident with a decrease in systemic blood pressure, particularly the nondihydropyridine calcium channel blockers such as diltiazem, both ACE inhibitors and ARBs usually reduce proteinuria independent of blood pressure. If doses are increased slowly to minimize symptomatic hypotension, treatment with ACE inhibitors and ARBs is usually possible in the normotensive proteinuric patient. Common side effects include hyperkalemia in patients with advanced CKD, which may necessitate a loop diuretic but rarely should lead to cessation of ACE inhibitors and ARBs, and cough with ACE inhibitors, in which case ARBs should be used instead. Because both agents lower GFR, a 10% to 30% increase in serum creatinine concentration may be observed. Unless serum creatinine continues to increase, this moderate increase reflects the therapeutic effect of ACE inhibitors and ARBs and should not prompt their withdrawal. Finally, if proteinuria persists despite maximum allowed or tolerated doses of ACE inhibitors or ARBs, a low dose of an aldosterone antagonist may overcome so-called aldosterone breakthrough and further reduce proteinuria (see Chapter 79). Hyperkalemia is an important safety aspect, similar to the ACE inhibitor and ARB combination mentioned earlier.

The NSAIDs lessen proteinuria by reducing intrarenal prostaglandin production and dipyridamole through adenosine-mediated afferent arteriolar vasoconstriction. Given the safety of the therapies discussed previously, as well as the risk for profound decreases in GFR, salt retention, and diuretic resistance with NSAIDs, these are generally contraindicated despite their potential benefit on proteinuria.

A low-protein diet will lessen proteinuria but must be advised with great care because of the risk for malnutrition.[22] Adequate compensation must be made for urine protein losses,[29] and the patient must be carefully monitored for evidence of malnutrition (see Chapter 86). Whether a low-protein diet is still antiproteinuric in patients treated with a full dose of ACE inhibitor or ARB is not established.

Treatment of Hyperlipidemia

Treatment of hyperlipidemia (or hypercholesterolemia) in patients with glomerular disease should usually follow the guidelines that apply to the general population to prevent cardiovascular disease. A statin or statin/ezetimibe combination is recommended in adults older than 50 with CKD stage 3 to 5. Statins alone are also recommended in adults over 50 with earlier-stage CKD. In younger adults, statins should be considered if the patient has significant comorbidity (coronary disease, diabetes mellitus, stroke) (see Chapter 81). Statin therapy may protect from a decrease in GFR, although this is not firmly established. Dietary restriction alone has only modest effects on hyperlipidemia in glomerular disease, particularly nephrotic syndrome. Side effects of some medications, such as rhabdomyolysis provoked by fibrates, occur more frequently in patients with renal failure. The addition of a bile acid sequestrant such as cholestyramine may lower LDL further and increase high-density lipoprotein, but it is usually not tolerated because of GI effects.

Avoidance of Nephrotoxic Substances

Apart from NSAIDs, which may induce AKI, particularly in patients with preexisting renal impairment and dehydration, other nephrotoxic substances, such as radiocontrast agents, some cytotoxic drugs, and antibiotics (e.g., aminoglycosides), also should be used with caution in patients with glomerular disease and renal impairment or nephrotic syndrome. There is also increasing concern that proton pump inhibitors may be associated with increased risk for both acute interstitial nephritis and CKD, and thus their use should be restricted to documented indications when histamine-2 blockers are not effective.

Special Therapeutic Issues in Patients With Nephrotic Syndrome

Treatment of Nephrotic Edema

In contrast to the lack of therapies in the past (Fig. 15.14), the mainstay of current treatment of nephrotic edema is diuretic therapy accompanied by moderate dietary sodium restriction (60 to 80 mmol/24 h). Nephrotic patients are diuretic resistant even if GFR is normal. Loop diuretics must reach the renal tubule to be effective, and transport from the peritubular capillary requires protein binding, which is reduced in hypoalbuminemia. When the drug reaches the renal tubule, it will become 70% bound to protein present in the urine and therefore be less effective. Oral diuretics with twice-daily administration are usually preferred, given the longer therapeutic effect compared with intravenous diuretics.

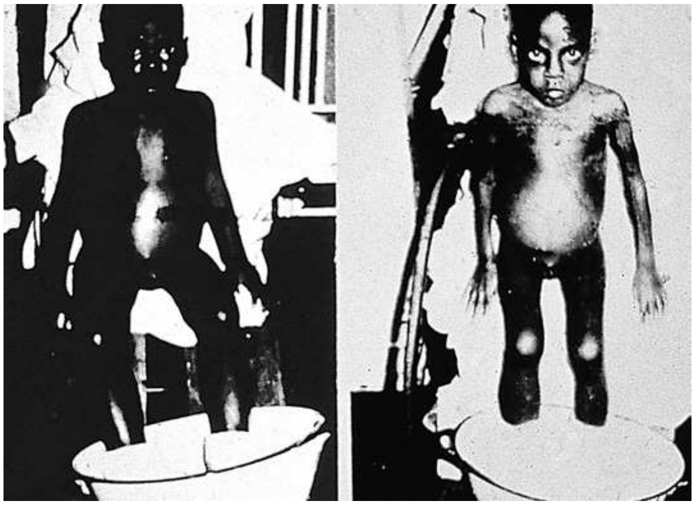


Fig. 15.14 Treatment of nephrotic edema before the availability of diuretics. Edema in nephrotic syndrome was very difficult to treat. In 1953, this child with anasarca stands in a bowl while edema fluid drips out through small tubes placed through needles in the skin of the feet. Nevertheless, this was effective treatment. The two pictures of the same child were taken 4 days apart, during which time the child lost 4.5 kg (10 lb), or 18% of body weight. (Courtesy Dr. Robert Vernier.)

However, in severe nephrosis, GI absorption of the diuretic may be uncertain because of intestinal wall edema, and intravenous diuretic by bolus injection or infusion may be necessary to provoke an effective diuresis. Alternatively, combining a loop diuretic with a thiazide diuretic or with metolazone may overcome diuretic resistance (see Chapter 7). A third alternative is adding amiloride to loop diuretics because nephrotic syndrome is associated with activation of the ENAC channel. Significant hypovolemia is not often a clinical problem, provided fluid removal is controlled and gradual. Daily weight is the best measurement of progress; ideally it should decrease by no more than 1 to 2 kg/day. Nephrotic children are much more prone to hypovolemic shock than adults. A stepwise approach to diuretic use is required, aiming at fluid removal in adults of no more than 2 kg daily, moving on to the next drug level if this is not achieved (Fig. 15.15).

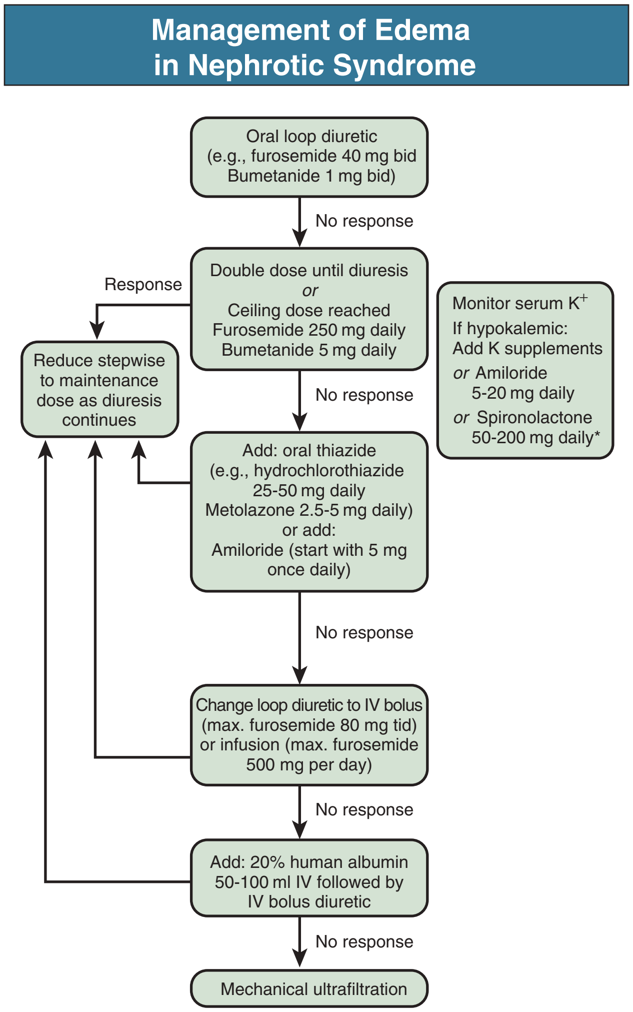

Management of Edema
in Nephrotic Syndrome
Oral loop diuretic (e.g., furosemide 40 mg bid Bumetanide 1 mg bid)
No response
Double dose until diuresis or Ceiling dose reached Furosemide 250 mg daily Bumetanide 5 mg daily
Response
Reduce stepwise to maintenance dose as diuresis continues
Monitor serum K$^+$
If hypokalemic: Add K supplements
or Amiloride 5-20 mg daily
or Spironolactone 50-200 mg daily*
No response
Add: oral thiazide (e.g., hydrochlorothiazide 25-50 mg daily Metolazone 2.5-5 mg daily) or add: Amiloride (start with 5 mg once daily)
No response
Change loop diuretic to IV bolus (max. furosemide 80 mg tid) or infusion (max. furosemide 500 mg per day)
No response
Add: 20% human albumin 50-100 ml IV followed by IV bolus diuretic
No response
Mechanical ultrafiltration

Fig. 15.15 **Management of edema in the patient with nephrotic syndrome.** Edema is often diuretic resistant, but the response is not predictable. Therefore stepwise escalation of therapy is appropriate until diuresis occurs. Even when there is anasarca, diuresis should not proceed faster than 2 kg/day in adults to minimize the risk for clinically significant hypovolemia. Mechanical ultrafiltration is rarely required for nephrotic edema unless there is associated renal impairment. *Spironolactone is less effective in nephrotic syndrome than in cirrhosis and is often poorly tolerated because of gastrointestinal side effects. Spironolactone should be used with great caution if the glomerular filtration rate is very low. *bid,* Twice daily.

Correction of Hypoproteinemia

In view of the problems associated with either increased protein administration or dietary protein restriction in nephrotic patients, adequate dietary protein should be ensured (0.8 to 1 g/kg/day) with a high carbohydrate intake to maximize use of that protein. In patients with heavy proteinuria, the amount of urinary protein loss should be added to dietary protein intake.

In the rare setting of proteinuria so severe that the patient is dying of the complications of nephrotic syndrome, the physician may need to resort to nephrectomy to prevent continued protein losses. This may be done as a *medical* nephrectomy: the deliberate use of NSAIDs combined with ACE inhibitors and diuretic to lessen proteinuria by provoking AKI. If medical nephrectomy alone does not adequately reduce proteinuria, bilateral renal artery embolization can be considered. It is a painful procedure and is not always as successful as might be expected (perhaps because of collateral arterial supply to the kidneys, which is not blocked by embolization). A final alternative is bilateral nephrectomy, which is increasingly being performed by laparoscopic surgery with reduced morbidity compared to classical surgical removal. Bilateral nephrectomy is commonly used in the management of infants with congenital nephrotic syndrome.

Treatment of Hypercoagulability

The risk for thrombotic events becomes progressively more important as serum albumin values decrease to less than 2.5 g/dl. Immobility as a consequence of edema or intercurrent illness further aggravates the risk. Prophylactic low-dose anticoagulation (e.g., heparin 5000 U subcutaneously twice daily) is indicated at times of high risk, such as relative immobilization in the hospital and albumin levels between 2 and 2.5 g/dl. Full-dose anticoagulation with low-molecular-weight heparin or warfarin should be considered if serum albumin decreases to less than 2 g/dl,[13,30] and this is mandatory if a thrombosis or pulmonary embolism is documented. Heparin is used for initial anticoagulation, but an increased dose may be needed because part of the action of heparin depends on circulating antithrombin III, which is often reduced in nephrotic patients. Warfarin (target international normalized ratio [INR] 2 to 3) is the long-term treatment of choice but should be adjusted with special care because of altered protein binding, which may require dose reductions. Newer oral anticoagulants have not been systematically tested so far in this situation.

Management of Infection

A high degree of clinical suspicion for infection is vital in nephrotic patients. Especially in nephrotic children, ascitic fluid should be examined microscopically and cultured if there is any suspicion of systemic infection. Bacteremia is common even if clinical signs are localized. ESR is unhelpful, but an elevated C-reactive protein level may be informative. Parenteral antibiotics should be started once culture specimens are taken, and the regimen should include coverage for pneumococci. If repeated infections occur, serum immunoglobulins should be measured. If serum IgG is less than 600 mg/dl, evidence in an uncontrolled study showed that infection risk is reduced by monthly administration of intravenous immune globulin (10 to 15 g) to keep the IgG levels above 600 mg/dl.[31]

Disease-Specific Therapies

Specific treatments for glomerular diseases are discussed in the subsequent chapters; the general principles are discussed here. Because most glomerular disease is thought to have an immune pathogenesis, treatment has generally consisted of immunosuppressive therapy aimed at blocking both the systemic and local effects. In the patient with glomerular disease resulting from ineffectual elimination of a foreign antigen, treatment involves measures to eliminate this antigen whenever possible, such as antibiotics in endocarditis-associated GN or antiviral therapy for cryoglobulinemia resulting from hepatitis C infection.

In general, the more severe and acute the presentation of GN, the more successful is immunosuppressive treatment. Immunosuppression in several patterns of chronic GN has had minimal success. When renal function is declining rapidly, as in RPGN, the toxicity of intensive regimens becomes acceptable for a short period, although it would be unacceptable if prolonged. Furthermore, the nonspecific nature of most immunosuppressive treatments results in widespread interruption of immune and inflammatory events at multiple levels. In the acute situation, this broad-based attack is a virtue; in more indolent disease, more specific treatment is needed but is largely unavailable. Despite great increases in the understanding of immune mechanisms in glomerular disease since the 1970s, most immunosuppressive therapies are not yet much more specific or precise. The mainstays of treatment remain agents that were available in the 1960s—corticosteroids, azathioprine, and cyclophosphamide. Other, newer immunosuppressive agents developed for use in transplantation, including cyclosporine, tacrolimus, and mycophenolate mofetil, or those developed in oncology, including rituximab, have emerging indications in glomerular disease. Novel agents, including some that modify inflammation (e.g., spleen tyrosine kinase inhibitors) or B cell immunity (e.g., inhibitors of B cell activation factor), are now being studied in clinical trials in glomerular disease, but as yet have no proven indications.

The use of immunosuppressive therapies to treat patients with GN has certain drawbacks. In many diseases, treatment is based on small series, and good prospective controlled trials are often lacking. Because of both the rarity and the variable natural history of GN, proof of efficacy for a particular therapy often requires a multicenter approach with prolonged follow-up, which is logistically difficult. If sufficient glomerular damage is present, proteinuria and progressive deterioration of renal function may occur by nonimmune pathways that may not be responsive to immunosuppressive therapies. This is particularly relevant in patients in whom the GN has already resulted in advanced CKD. Unfortunately, good noninvasive markers to assess disease activity are missing in most clinical circumstances. Given the frequent uncertainty of the response to immunosuppressive therapy, it becomes mandatory to weigh the potential benefits against the risks of therapy.

Immunosuppression may be associated with reactivation of tuberculosis and hepatitis B infection and also can lead to a hyperinfection syndrome in patients with *Strongyloides* infection. Therefore high-risk patients should be tested for these diseases before embarking on therapy.

Alkylating agents such as cyclophosphamide and chlorambucil have considerable toxicity. In the short term, leukopenia is common, as is alopecia, although hair will regrow within a few months with discontinuation of therapy. These agents can cause infertility (observed in adults with cumulative doses of cyclophosphamide >200 mg/kg and chlorambucil 10 mg/kg). There is also an increased incidence of leukemias (observed with total doses of cyclophosphamide >80 g and chlorambucil 7 g). Cyclophosphamide is also a bladder irritant, and treatment can result in hemorrhagic cystitis and bladder carcinoma, particularly after therapy lasting more than 6 months.[32] Irritation of the bladder is caused by a metabolite, acrolein. The effect can be minimized in patients receiving intravenous cyclophosphamide by enforcing a good diuresis and administering mesna. The dose of mesna (milligrams) should equal the dose of cyclophosphamide (milligrams); 20% is given intravenously with the intravenous cyclophosphamide, and the remaining 80% should be given in two equal oral doses at 2 and 6 hours. Chlorambucil and cyclophosphamide also require dose reduction in the setting of renal impairment. Given all these concerns, oral treatment with these agents should ideally be limited to 12 weeks.

The modes of action and potential adverse effects of corticosteroids, azathioprine, and other immunosuppressive agents occasionally used in glomerular disease are discussed further in Chapter 101.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements regarding proteinuria is correct?
   - **A.** Tubular proteinuria is characterized by equal amounts of α_1-microglobulin and immunoglobulins.
   - **B.** Proteinuria exceeding 3.5 g/day (i.e., "nephrotic" proteinuria) inevitably results in hypoalbuminemia.
   - **C.** In orthostatic proteinuria, urinary protein is typically increased with the patient lying down.
   - **D.** Overflow proteinuria is typical of urinary light chain excretion.
   - **E.** Functional proteinuria typically occurs after heavy meals with high protein intake.
2. Which of the following statements regarding general treatment of glomerular disease is *incorrect*?
   - **A.** The KDIGO chronic kidney disease (CKD) guideline recommends a blood pressure target below 130/80 mm Hg in proteinuric patients.
   - **B.** Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may directly reduce the increased glomerular capillary wall permeability.
   - **C.** Common side effects of ACE inhibitors and ARBs in patients with advanced CKD include hyperkalemia, which may necessitate a loop diuretic.
   - **D.** Statin or a statin-ezetimibe combination is recommended in all adults younger than 50 years with CKD.
   - **E.** A low-protein diet will lessen proteinuria but must be advised with great care because of the risk of malnutrition.
3. Which statement regarding the treatment of nephrotic syndrome is correct?
   - **A.** Nephrotic patients are diuretic resistant only if GFR is greatly impaired.
   - **B.** Patients with heavy proteinuria should be advised to consume a high-protein diet of about 2 to 3 g/kg/d.
   - **C.** Full-dose anticoagulation with low-molecular-weight heparin or warfarin should be considered if serum albumin decreases to less than 2 g/dl.
   - **D.** Ascitic fluid should be examined regularly by microscopy and culture independently of a suspicion of systemic infection.
   - **E.** Nephrotic children are no more prone to hypovolemic shock than adults.

16

Introduction to Glomerular Disease: Histologic Classification and Pathogenesis

John Feehally, Jürgen Floege

HISTOLOGIC CLASSIFICATION

Glomerular disease may have a wide variety of etiologies and clinical presentations (see Chapter 15). Some glomerular diseases are given the generic title of glomerulonephritis (GN), which implies an immune or inflammatory pathogenesis. Although a specific diagnosis can be made in some patients based on clinical presentation and laboratory tests, in most patients a renal biopsy is useful for both classification and prognosis. Ideally, the renal biopsy should be examined by light microscopy, immunohistology, and electron microscopy (EM). Using this approach, a histologic pattern can be diagnosed. Some histologic patterns can be coupled with other laboratory tests to identify a specific etiology, but in many cases the condition is idiopathic. However, because treatments are often developed for specific histologic patterns, this approach is currently favored in the management of most patients with glomerular disorders.

HISTOPATHOLOGY

The full assessment of a renal biopsy requires light microscopy, EM, and examination for deposits of complement and immunoglobulin by immunofluorescence (IF) or immunoperoxidase (IP) techniques.

Light Microscopy

In GN the dominant, but not the only, histologic lesions are in glomeruli (Fig. 16.1). GN is described as *focal* (only some glomeruli are involved) or *diffuse.* In any individual glomerulus, injury may be *segmental* (affecting only part of any glomerulus) or *global.* Sampling error is possible in a renal biopsy; the extent of a focal lesion may be misjudged in a small biopsy specimen, and sections through glomeruli may miss segmental lesions. Lesions also may be hypercellular because of an increase in endogenous endothelial or mesangial cells (termed *proliferative*) and an infiltration of inflammatory leukocytes (termed *exudative*). Severe acute inflammation may produce glomerular necrosis, which is often segmental. Multiple processes can cause thickening of the walls of the glomerular capillaries, including an increase in glomerular basement membrane (GBM) material and immune deposits. Segmental sclerosis and scarring may occur and are characterized by segmental capillary collapse with the accumulation of hyaline material and mesangial matrix and often with attachment of the capillary wall to the Bowman capsule (synechiae or adhesion formation).

The classic stains used in light microscopy include hematoxylin-eosin (HE) and the periodic acid–Schiff (PAS) reaction, which is particularly effective for evaluating cellularity and matrix expansion. More specific stains include methenamine silver, which stains GBM and other matrix black and may reveal a double contour to the GBM because of the interposition of cellular material or may show increased mesangial matrix not easily seen with other techniques. Trichrome staining is also useful to show areas of scarring (blue) and immune deposits (red).

Crescents are inflammatory collections of cells in Bowman space. Crescents develop when severe glomerular injury results in local rupture of the capillary wall or Bowman capsule, allowing plasma proteins and inflammatory material to enter into the Bowman space. Crescents consist of proliferating parietal and some visceral epithelial cells, infiltrating fibroblasts, and lymphocytes and monocytes/macrophages, often with local fibrin deposition. They are called “crescents” because of their appearance when the glomerulus is cut in one plane for histology. These cell collections are destructive, rapidly increase in size, and may lead to glomerular tuft occlusion (see Fig. 16.1). If the acute injury is stopped, the crescents may either resolve with restitution of normal morphology or heal by fibrosis, causing irreversible loss of renal function. Crescents are most frequently observed with vasculitis, in Goodpasture disease, and in severe acute GN of any cause.

Tubulointerstitial injury and fibrosis can accompany GN and usually are strongly correlated with prognosis (see Chapter 78).

Immunofluorescence and Immunoperoxidase Microscopy

Indirect immunofluorescence (IF) and immunoperoxidase (IP) staining are both used to identify immune reactants (Fig. 16.2). Examination consists of staining for immunoglobulins (IgG, IgA, and IgM), for components of the complement system (usually C3, C4, and C1q), and for the presence of fibrin, which is typically observed in crescents and in capillaries in thrombotic disorders such as hemolytic uremic syndrome (HUS) and the antiphospholipid syndrome. Immune deposits may occur along the capillary loops or in the mesangium. They may be continuous (linear) or discontinuous (granular) along the capillary wall or in the mesangium.

Electron Microscopy

Electron microscopy (EM) is valuable for defining the morphology of the basement membranes, which is abnormal in some forms of hereditary nephropathy (e.g., Alport syndrome and thin basement membrane nephropathy; see Chapter 46), and for identifying fibrils (e.g., in amyloidosis) or tubuloreticular intracellular structures (e.g., in lupus nephritis). EM is also useful for localizing the site of immune deposits, which are usually homogeneous and electron dense (Fig. 16.3). Electron-dense deposits are seen in the mesangium or along the capillary wall on the subepithelial or subendothelial side of the GBM. Infrequently, the electron-dense material follows a linear pattern within the GBM.

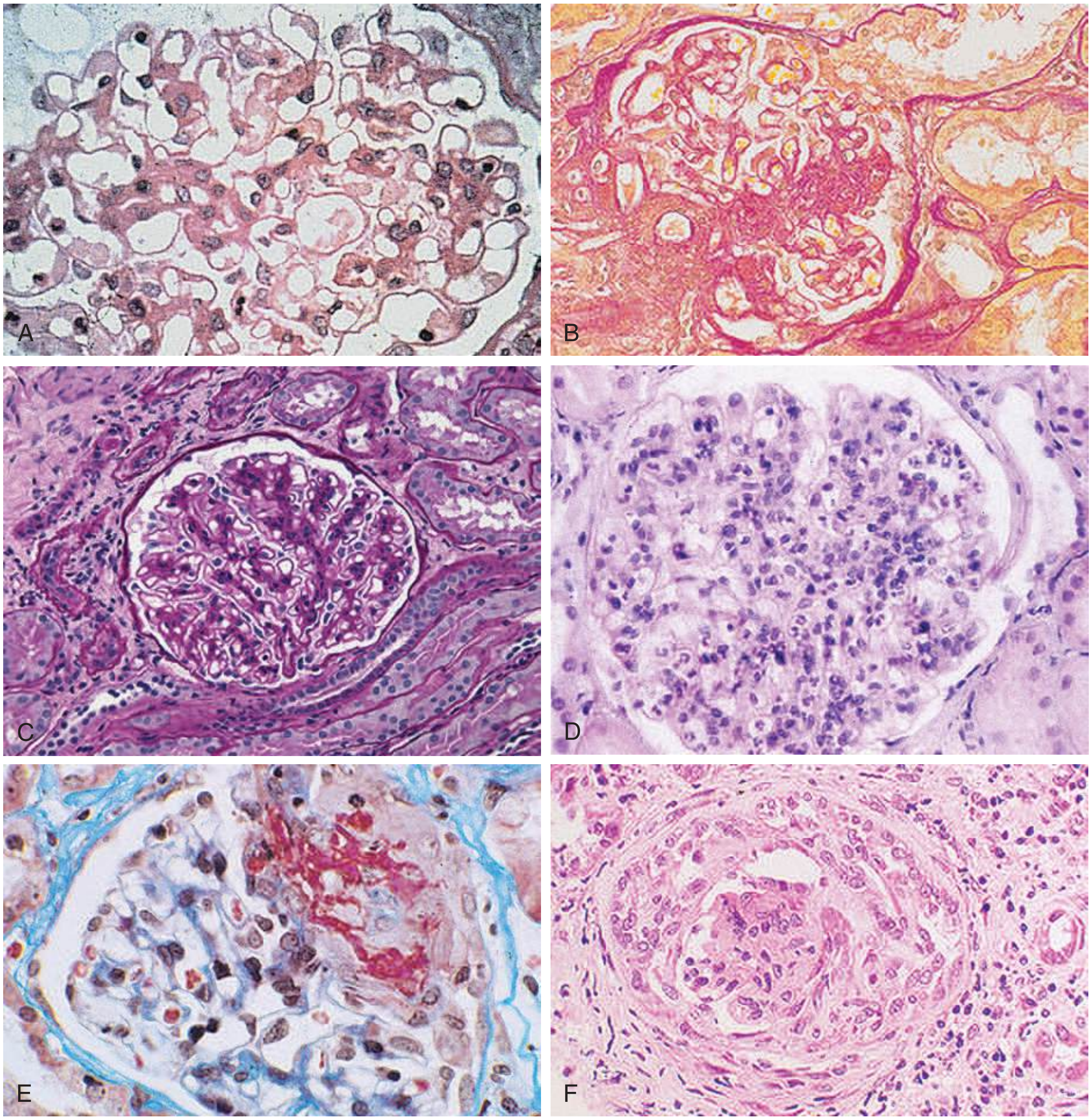

Fig. 16.1 Pathology of glomerular disease: light microscopy. Characteristic patterns of glomerular disease illustrating the range of histologic appearances and the descriptive terms used. (A) Normal glomerulus: Minimal change disease. (B) Segmental sclerosis: Focal segmental glomerulosclerosis. (C) Diffuse mesangial hypercellularity: IgA nephropathy. (D) Diffuse endocapillary hypercellularity: Poststreptococcal glomerulonephritis. (E) Segmental necrosis: Renal vasculitis. (F) Crescent formation: Anti–glomerular basement membrane disease. (A and B, Hematoxylin-eosin; C, D, and F, periodic acid–Schiff; E, trichrome.)

The sites of immune deposits are helpful in the classification of the types of GN.

GENERAL MECHANISMS OF GLOMERULAR INJURY

Proteinuria

Proteinuria, accompanied by variable degrees of hematuria, is the hallmark of glomerular disease. The endothelial glycocalyx and the GBM may repel proteins in part through their highly negative charge (proteins are mostly negatively charged as well) and prevent them from entering Bowman space. The key barrier for protein is the slit diaphragm between the podocyte foot processes[1,2] (Fig. 16.4). The slit diaphragm consists of several transmembrane proteins that extend from adjacent interdigitating foot processes to form a zipper-like scaffold on the outer side of the GBM (Fig. 19.2 and Chapter 1).

The importance of the slit diaphragm in proteinuric states has been documented in numerous hereditary types of nephrotic syndrome in which the mutations involve various slit diaphragm proteins (see Chapter 19). These diseases usually manifest as a type of steroid-resistant minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS). Whereas most recessive mutations of slit diaphragm or podocyte proteins manifest in childhood or even prenatally, dominant mutations tend to manifest in early adult life.[2] An exception is steroid-resistant autosomal recessive nephrotic syndrome, in which the homozygous mutation in

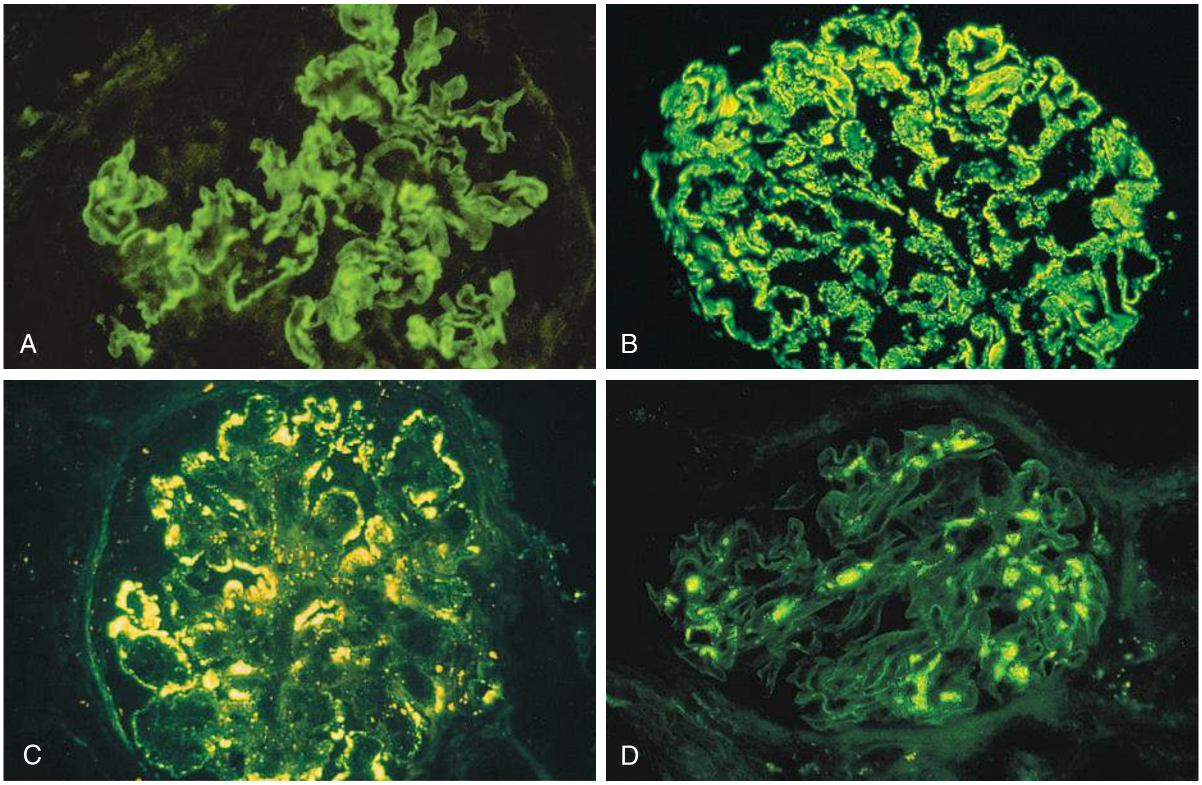

Fig. 16.2 Pathology of glomerular disease: immunofluorescence microscopy. Common patterns of glomerular staining found by immunofluorescence. (A) Linear capillary wall IgG: Anti–glomerular basement membrane disease. (B) Fine granular capillary wall IgG: Membranous nephropathy. (C) Coarse granular capillary wall IgG: Membranoproliferative glomerulonephritis type I. (D) Granular mesangial IgA: IgA nephropathy.

podocin *(NPHS2)* presents in childhood, but the heterozygous mutation, when it coexists with the p.R229Q variant polymorphism, may manifest clinically in young adulthood (age 20 to 35 years of age).[3]

Although it may result from injury or mutation of slit diaphragm proteins, proteinuria may be caused by nonspecific injury to the podocyte in many cases. When the podocyte is injured, it may undergo shape changes with swelling and loss or fusion of the foot processes. Filtration is reduced at sites where the foot processes fuse (possibly accounting for reduction of filtration coefficient K_f seen in nephrotic syndrome), but there are gaps where the podocytes are detached from the GBM. Massive protein filtration may occur at these sites; structurally, the capillary wall defects are likely to correspond to the large pores noted in functional studies[4] (Fig. 16.5). Podocyte immaturity also can result in nephrotic syndrome, perhaps from incomplete differentiation and slit diaphragm development. Congenital nephrotic syndrome with mesangial sclerosis has been linked with mutations in phospholipase C epsilon gene *(PLCE1),* which is important in podocyte development.[5]

In addition to podocyte damage, and in particular slit diaphragm defects, proteinuria also can result from changes in the glomerular endothelium, especially its glycocalyx, as well as from changes in the GBM and altered electrical forces across the GBM.

Severe albuminuria reflects a glomerular defect, but some albumin is normally filtered but then endocytosed and metabolized in the proximal tubule or is transcytosed intact through the tubular cell. Proximal tubular dysfunction can therefore result in albuminuria if endocytosis is impaired, although this is generally in the non-nephrotic range.

Antibody and Antigen

Many glomerular diseases are associated with deposition or glomerular trapping of immunoglobulins, often with components of the complement system, and with the presence of electron-dense deposits by EM. These findings likely represent immune complexes. Experimentally, immune complexes can localize in glomeruli by two major mechanisms. In some conditions, such as mesangial proliferative GN, membranoproliferative GN (MPGN), or lupus nephritis, the immune complexes are thought to originate in the circulation and to be passively trapped in the mesangium or subendothelial areas. However, circulating immune complexes cannot readily pass across the GBM. Therefore the presence of immunoglobulin G (IgG) on the subepithelial aspect of the basement membrane, such as occurs in membranous nephropathy, either results from the direct binding of podocyte antigens by antibody or represents binding of an antibody to an antigen that was temporarily "trapped" or bound at this site (in situ complex formation).[6] GN also may occur only with complement activation in the glomeruli in the absence of IgG, as occurs in dense deposit disease (DDD), in which ribbon-like deposits replace the basement membrane (see Chapter 22). Some antigens may deposit in glomeruli and directly activate the alternative pathway of complement in the absence of IgG, as may occur in poststreptococcal GN (PSGN). Immunoglobulin with aberrant characteristics may also aggregate in glomeruli and activate complement in the absence of antigen, as occurs in IgA nephropathy with aberrantly glycosylated IgA (see Chapter 23).[7]

Normally, immune complexes are removed from the circulation by binding of the complex to the C3b receptors on erythrocytes. The immune complexes are then removed and degraded during transit of the erythrocytes in the liver and spleen. If antigenemia persists or clearance of complexes is impaired (e.g., chronic liver disease), immune complexes may deposit in the glomerulus by binding to Fc receptors on mesangial cells or by passive deposition in the mesangium or subendothelial space. Physical characteristics of the complexes also may favor deposition, including avidity, charge, and size. However, quantification of circulating

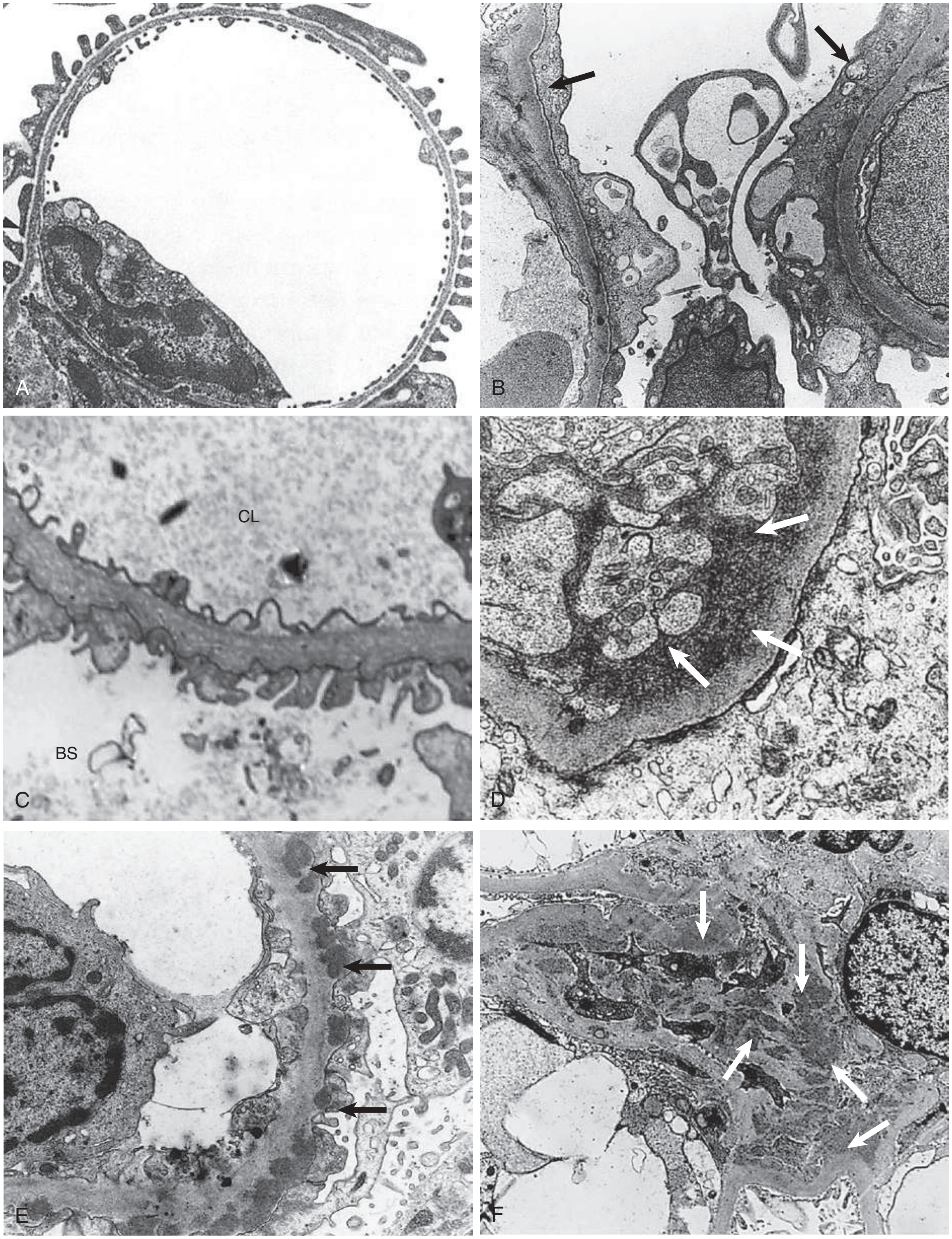

Fig. 16.3 Ultrastructural pathology of glomerular disease. Some characteristic patterns of electron-dense deposits and glomerular basement membrane (GBM) abnormalities seen in glomerular disease. (A) Normal. (B) Foot process effacement: Minimal change disease *(arrows)*. (C) GBM thickening and splitting: Alport syndrome. *BS,* Bowman space; *CL,* capillary lumen. (D) Subendothelial electron-dense deposits *(arrows):* Membranoproliferative glomerulonephritis type I. (E) Subepithelial electron-dense deposits *(arrows):* Membranous nephropathy. (F) Mesangial electron-dense deposits *(arrows):* IgA nephropathy.

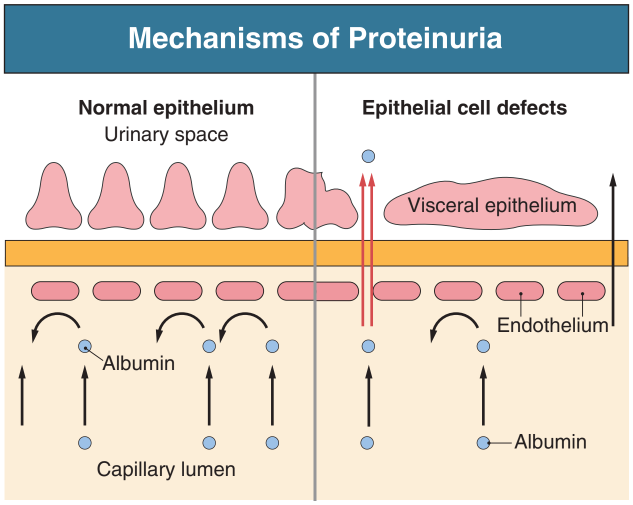

Fig. 16.4 **Mechanisms of proteinuria.** Normally, negatively charged proteins such as albumin *(blue circles)* are repelled by the negatively charged proteins in the endothelium (sialoglycoproteins) and basement membrane (heparan sulfate proteoglycans) as well as by a size barrier in the glomerular basement membrane (GBM) and at the slit diaphragm so that only small amounts of albumin pass into the urinary space. In most proteinuric states, the podocytes are injured, leading to foot process swelling and injury to the slit diaphragm; in these situations, large amounts of protein (albumin) can pass through the GBM and the gaps between the fused foot processes *(red arrows)*.

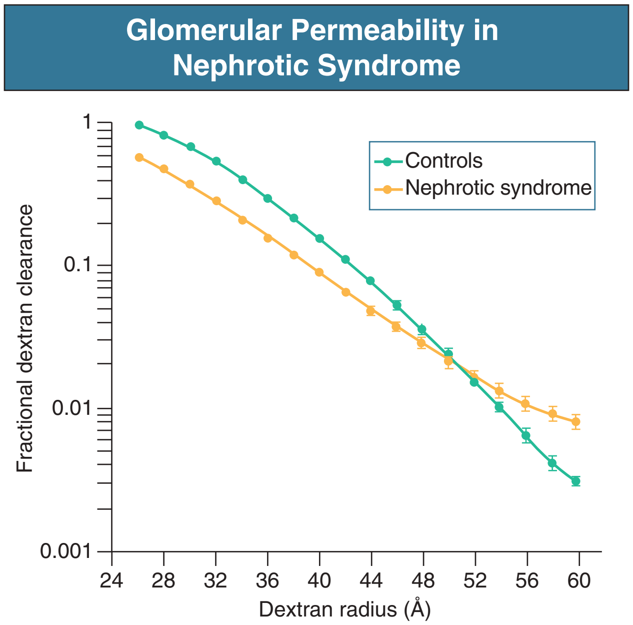

Fig. 16.5 **Glomerular permeability in nephrotic syndrome.** Dextran sieving curve shows the relative glomerular permeability of different-sized dextrans in normal individuals and nephrotic patients with membranous nephropathy and minimal change disease. Nephrotic patients actually have a lower fractional dextran clearance for small dextrans (26 to 48 Å [2.6 to 4.8 nm]) but have an increased clearance for dextrans of larger molecular weight (52 to 60 Å [5.2 to 6.0 nm]). This is consistent with large pores appearing in the glomerular basement membrane. (Modified from reference 4.)

TABLE 16.1 **Antigens Identified in Glomerulonephritis**

Disease	Antigens
Poststreptococcal glomerulonephritis (GN)	Streptococcal pyrogenic exotoxin B (SPEB), plasmin receptor
Anti-GBM disease	α3 Type IV collagen (likely induced by molecular mimicry)
IgA nephropathy	Possibly no antigen but rather polymerized polyclonal IgA (? superantigen driven)
Membranous nephropathy	Phospholipase A_2 receptor Thrombospondin type-1 domain-containing 7A Neutral endopeptidase in podocyte (congenital) HBeAg (hepatitis B virus associated)
Staphylococcus aureus–associated GN	*Staphylococcus* superantigens induce polyclonal response; not necessarily antigen in glomeruli
Membranoproliferative GN (MPGN)	HCV and HBsAg in hepatitis-associated MPGN

ANCA, Antineutrophil cytoplasmic autoantibody (antibody); *GBM,* glomerular basement membrane; *HBsAg,* hepatitis B surface antigen; *HCV,* hepatitis C virus; *IgA.*

immune complexes in patients with GN does not correlate reliably with glomerular events and thus is not typically measured.

In some glomerular diseases, the target antigen has been identified (Table 16.1). In other patients, glomerular disease develops as a result of infection with organisms that release superantigens that cause a polyclonal activation of B cells. The classic organism responsible for superantigen-associated GN is *Staphylococcus aureus,* and the pattern of immune deposits often includes the presence of both IgG and IgA. Some infections initiate an immune response that cross-reacts with endogenous antigens. This type of molecular mimicry may be responsible for Goodpasture disease and certain types of vasculitis[8] (see Table 16.1). Once an immune response is initiated, local injury may lead to the release of additional antigens that extend the immune response (epitope spreading). In Goodpasture disease, in which the antigen is α3 chain of type IV collagen, the antigen is present in the lung alveolar basement membrane but is normally sequestered. In tobacco smokers, however, the inhalation results in oxidative injury with exposure of the α3 chain, allowing the binding of antibody.[9] This may explain why lung involvement rarely occurs in nonsmokers with Goodpasture disease.

Complement

The complement system is often activated in glomerular disease (Fig. 16.6). Complement can be activated through three pathways. *Classic pathway* activation involves the binding of C1q to the Fc region of antibody in IgG- and IgM-containing immune complexes and can result in reduced serum C4 and C3. This is common in lupus nephritis, immune complex–induced GN, and cryoglobulinemic MPGN. Complement may be activated by the *alternative pathway,* which is activated independently of immune complexes and can be triggered by polysaccharide antigens, polymeric IgA, injured cells, bacterial products (e.g., streptococcal antigens), and antibodies to complement pathway components (C3 convertase). The alternative pathway appears to be activated in IgA nephropathy, DDD, and PSGN. Serum complement levels are generally normal in IgA nephropathy; in DDD and PSGN, however, the C3 is typically low but C4 is normal. In DDD as well as in C3-glomerulonephritis (C3-GN) (see Chapter 22), the activation of the alternative pathway

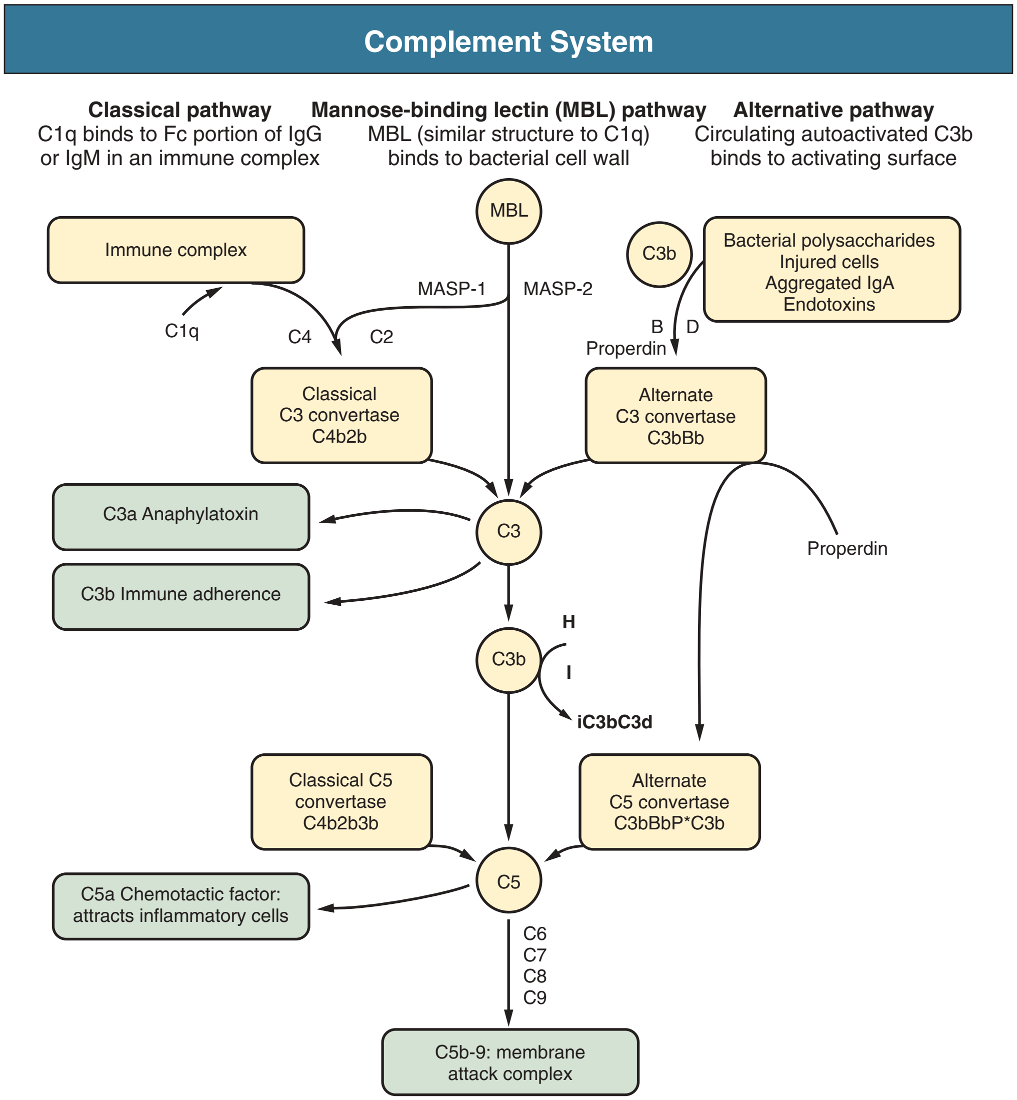
Complement System
Classical pathway
C1q binds to Fc portion of IgG or IgM in an immune complex
Mannose-binding lectin (MBL) pathway
MBL (similar structure to C1q) binds to bacterial cell wall
Alternative pathway
Circulating autoactivated C3b binds to activating surface
MBL
Immune complex
C3b
Bacterial polysaccharides
Injured cells
Aggregated IgA
Endotoxins
MASP-1
MASP-2
C1q
C4
C2
B
D
Properdin
Classical C3 convertase C4b2b
Alternate C3 convertase C3bBb
C3a Anaphylatoxin
C3
Properdin
C3b Immune adherence
H
C3b
I
iC3bC3d
Classical C5 convertase C4b2b3b
Alternate C5 convertase C3bBbP*C3b
C5a Chemotactic factor: attracts inflammatory cells
C5
C6
C7
C8
C9
C5b-9: membrane attack complex

Fig. 16.6 Complement system. The complement system is a self-amplifying cascade of proteins that generates a membrane attack complex, which is cytolytic; the cascade promotes inflammation by the activity of the fragments it produces. The amplifying cascades result from activated fragments of the components combining to make convertase enzymes that degrade C3 and C5. The complement cascade is controlled in part by the short active life of many of its components. There are also inhibitory regulatory proteins, most notably factors H and I inhibiting C3b. Activated fragments of any component are designated *b* (e.g., C3b); anaphylatoxic fragments are designated *a* (e.g., C5a). Inflammatory functions of complement components are shown in green. *IgA,* Immunoglobulin A; *MASP,* MBL-associated serine protease.

may not involve an antigen but rather results from continuous activation of the pathway through altered factor H or an IgG autoantibody (nephritic factor) that stabilizes the C3 convertase (see Chapter 22). Complement also can be activated through the mannose-binding lectin (MBL) pathway initiated by MBL, which has a structure similar to that of C1q. The role of the MBL pathway in GN is emerging in IgA nephropathy and idiopathic membranous nephropathy. However, despite evidence for intraglomerular complement activation in these conditions, serum complement components such as C3 and C4 generally remain in the normal range.

Activation of the complement pathway has several consequences. Leukocyte recruitment is facilitated by the chemotactic factor C5a, and C3b binding is important in the binding and opsonization of the immune complexes by the infiltrating leukocytes. The terminal membrane attack complex of the cascade, C5b-9, inserts into cell membranes, where it can kill cells or more commonly activate them to secrete cytokines, oxidants, and extracellular matrix. C5b-9 likely has a role in mediating injury to the glomerular epithelial cell in membranous nephropathy, in which immune deposits and complement activation occur in the subepithelial space. Complement also can be activated in proteinuric urine because of amidation of C3 by ammonia, which may have a role in mediating tubulointerstitial injury even in conditions not associated with immune complex formation. Experimental studies have emphasized the importance of local synthesis of complement components by the tubular cells as a mechanism that may augment this process.[10]

Activation of complement is controlled by complement regulatory proteins (see Fig. 16.6). A genetic absence or malfunction of factor H or other regulatory proteins can result in increased susceptibility to glomerular endothelial injury, resulting in (HUS; Chapter 29) or less often hereditary forms of GN (see Chapter 22).

Mechanisms of Immune Glomerular Injury

Two major mechanisms account for the presence of immune complexes in glomerular diseases. There may be ineffectual clearance of an antigen from an impaired immune response, as in chronic viral infections caused by hepatitis B or hepatitis C virus (HBV or HCV). Despite a strong humoral response, viral infection persists because the cell-mediated response required for elimination of these viruses is impaired. The consequence is a state of persistent antigenemia with circulating antigen-antibody complexes, which predisposes to glomerular injury. Eradication of the virus with antiviral therapy can be associated with remission of the glomerular disease.

More often, glomerular disease results from autoimmunity. In health, a tension exists between the normal immune response to foreign antigen and tolerance, which is the cellular process that prevents an immune response to self-antigen. Tolerance develops because self-reactive T and B cells are clonally deleted during fetal and neonatal life, although small numbers survive outside the thymus or bone marrow, respectively. Under certain conditions, these peripheral self-reactive cells can be stimulated to generate a cellular and humoral response to a self-antigen. Infection or toxins may play a role in initiating the response by releasing antigens from sequestered sites so they have access to dendritic cells, which carry the antigen to lymph nodes for presentation to T cells, by altering host proteins to make them more immunogenic, or by molecular mimicry, in which antibodies to an exogenous antigen (e.g., those present in infecting organism) cross-react with a native protein.[11] Activation of T cells may be further enhanced by the release of cytokines or endogenous danger-associated molecular patterns, such as Toll-like receptor ligands or inflammasome activators, and the conversion of normally innocuous endogenous renal cells into antigen-presenting cells through the upregulated or de novo expression of human leukocyte antigen (HLA) class II molecules and cytokines.

Regulatory T cells ($CD4^+CD25^+$) have a key role in controlling T cell responses and preventing the development of autoimmunity. However, their role is not well understood and the local regulation of these cells in the kidney by a subset of dendritic cells ($CD103^+$) may be more important than systemic numbers of regulatory T cells.[12]

Variations in HLA molecules and the T cell receptor are under strong genetic influence. Close immunogenetic associations, particularly between HLA expression and various patterns of GN, have been described in IgA nephropathy, membranous nephropathy, and other glomerular diseases. For example, whereas HLA-DR2 identifies a powerful relative risk for the development of Goodpasture disease, some individuals can develop the disease without HLA-DR2, and the vast majority with HLA-DR2 never develop this rare disease. HLA associations also differ among various ethnic groups. To date, HLA associations have no practical diagnostic or therapeutic implications, and HLA typing is not needed in the clinical management of patients with GN.

Inflammation

The presence of glomerular inflammation is largely determined by the site of immune deposits. Immune deposits with direct access to the circulation (subendothelial and basement membrane locations) are usually associated with leukocyte accumulation. Mesangial deposits elicit an intermediate response, whereas immune deposits in the subepithelial space generally are not associated with inflammatory cells.

In GN associated with subendothelial deposits, such as class IV lupus nephritis or MPGN, leukocyte infiltration is common. With acute injury, the predominant infiltrating cells are neutrophils, platelets, and monocytes, and in chronic injury, the predominant cells are monocyte/macrophages and T cells. The primary mechanism for attracting these cells is the secretion of chemokines and the expression of leukocyte adhesion molecules by local endothelial and resident cells; local release of complement activation fragments (C5a) is also important.

Although neutrophils are common with immune complex disease, cell-mediated immunity is important in some glomerular diseases. For example, T cells likely have a role in crescentic nephritis, becoming sensitized to endogenous or exogenous antigen and then recruiting macrophages that mediate crescent formation.

Proliferation, Apoptosis, and Fibrosis

Intrinsic glomerular cells (epithelial, mesangial, and endothelial) are also activated in various glomerular diseases. Mesangial cells can become myofibroblast-like cells that proliferate and produce excessive extracellular matrix. Endothelial cells produce nitric oxide and other antiinflammatory proteins, and injury to this cell population can result in the expression of leukocyte adhesion molecules and activation of the coagulation system. Podocytes are differentiated epithelial cells that when injured undergo shape change (reorganization of the actin filaments) that can lead to disruption of the slit diaphragm, resulting in proteinuria. Interestingly, podocytes also can be induced to express receptors involved in antigen presentation that are similar to those expressed by dendritic cells. Progressive loss of podocytes by apoptosis is associated with the development of glomerulosclerosis. Important growth factors associated with glomerular injury include transforming growth factor β (TGF-β), which mediates matrix deposition; platelet-derived growth factor (PDGF), which mediates mesangial cell proliferation; and vascular endothelial growth factor (VEGF), required for endothelial health.

Crescent formation represents a severe cellular response and is initiated by cytokine-driven proliferation, particularly of the parietal epithelial cells. Local breaks in the GBM or Bowman capsule, mediated by activated leukocytes, are followed by macrophage infiltration, proliferation of parietal epithelial cells and podocytes, and local fibrin deposition (Fig. 16.7).

Glomerular scarring is characterized by proliferation of mesangial cells with loss (apoptosis) of endothelial cells and podocytes. Tubulointerstitial fibrosis also accompanies progressive glomerular disease and correlates with both renal function and prognosis. Proteinuria has been shown to activate tubular cells and induce toxicity, either directly or through the generation of oxidants (from iron proteins excreted in urine) or from complement activation, which can be shown in proteinuric urine. Tubulointerstitial ischemia after loss of glomerular and peritubular capillaries also may drive fibrosis. Finally, loss of renal function may result from leakage of plasma ultrafiltrate into the peritubular space, resulting in a scarring response (misdirected filtration), or stenosis/occlusion of the opening of the proximal tubule from Bowman space, resulting in nonfunctional (atubular) glomeruli. A detailed discussion of current mechanisms involved in glomerulosclerosis is presented in Chapter 78. Specific pathogenic mechanisms in the different patterns of glomerular disease are discussed in subsequent Section IV chapters.

PATHOGENESIS OF SPECIFIC GLOMERULAR SYNDROMES

Minimal Change Disease

Minimal change disease (MCD) is a steroid-sensitive nephrotic syndrome in which the only structural abnormality is podocyte swelling and fusion of foot processes on EM (see Chapter 17). For many years, the podocyte injury in MCD was thought to be caused by a cytokine released from T cells. T cells are activated in MCD, and T cell hybridomas from these patients were reported to secrete a factor that provokes heavy proteinuria in rats.[13] One candidate cytokine is interleukin-13 (IL-13), which is expressed by T cells in patients with MCD, and overexpression of IL-13

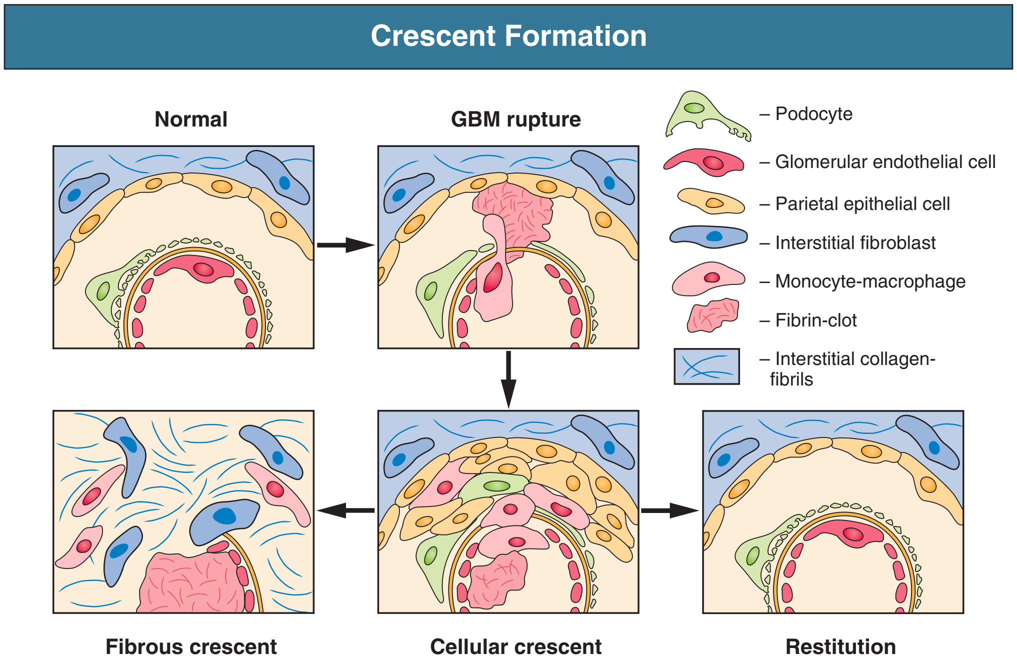

Fig. 16.7 Crescent formation. In early crescent formation, cytokines and growth factors cross the glomerular basement membrane *(GBM)* to initiate proliferation of the parietal epithelial cells. Small breaks in the GBM occur secondary to injury from oxidants and proteases from neutrophils and macrophages, thus allowing the macrophage to enter Bowman space, where it can proliferate. Breaks in Bowman capsule secondary to the periglomerular inflammation also occur, allowing the entrance of more inflammatory cells as well as fibroblasts. The proliferation of parietal and visceral epithelial cells and macrophages is associated with fibrin deposition, slowly choking the glomerular tuft until filtration becomes impossible. In the late stages, the crescent becomes fibrotic and the glomerulus end stage. Alternatively, in less severe cases, complete restitution of the glomerular tuft can occur.

causes nephrotic syndrome and histologic changes consistent with MCD in rats. However, proteinuria can be induced in immunodeficient mice using CD34-positive hematopoietic bone marrow cells of patients with MCD and recurrent FSGS but not by their T cells.[14] Thus the role of T cells in this disorder remains to be clarified.

Evidence also suggests that the podocyte injury is associated with overexpression of angiopoietin-like-4, which is associated with a proteinuric response.[15] This overexpression can be reduced with corticosteroids and *N*-acetyl-D-mannosamine. In addition, patients with MCD show high levels of CD80 (also known as B7.1) in urine and in podocytes, and the level of urinary CD80 correlates with disease activity. CD80 is an antigen that is normally expressed by dendritic cells and B cells.

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is a generic term to describe a pattern of glomerular scarring and is therefore nonspecific. Focal segmental sclerosing lesions in the absence of nephrotic syndrome can occur in a range of contexts, including GN, chronic hypertension, obesity, and progressive renal disease of any etiology. These lesions are particularly common in African Americans; recent findings suggest this susceptibility relates to increased frequency of a genetic polymorphism in *APOL1,* a gene coding for a circulating lipoprotein.

When the histologic pattern of FSGS is seen in association with the nephrotic syndrome, immune deposits are absent, but as with MCD, there is a generalized capillary wall defect with foot process fusion (also termed *effacement*) on EM (see Chapter 18). However, unlike MCD, there is segmental scarring (sclerosis) in some glomeruli with FSGS. Some forms of FSGS result from mutations of podocyte proteins (see Chapter 19), whereas others are believed to originate from a circulating factor; cardiotrophin-like cytokine 1 is one candidate molecule, but others are also being investigated as potential circulating factors that may mediate FSGS (see Chapter 18). Although it is unproven, some consider that MCD and FSGS share similar pathogenic mechanisms and are part of a spectrum in which MCD has lower levels of the circulating factor and is therefore more sensitive to corticosteroids. These forms of FSGS may be particularly prone to rapid recurrence, sometimes within hours, after renal transplantation.

A variant of FSGS is *collapsing* FSGS, in which there is proliferation of the normally quiescent podocyte, leading to collapse of the glomerular tuft, often in association with massive proteinuria. The pathogenesis may involve production by the podocyte of growth factors such as VEGF or local inhibition of cell cycle proteins that normally maintain the podocyte in a nonproliferative state.[16]

Membranous Nephropathy

In membranous nephropathy (MN), immune deposits are localized to the subepithelial space, where they had long been considered to represent autoantibody binding to an intrinsic podocyte antigen (see Chapter 20). This antigen has now been identified as the M-type phospholipase A_2 receptor (PLA_2R) in as many as 70% of cases of idiopathic MN.[17] Antibodies to PLA_2R are specific for MN. Circulating anti-PLA_2R reflects the immunologic activity of the disease and may be useful to monitor the clinical course, including patient response to treatment. Other autoantibodies have been found, albeit much less frequently, including those against thrombospondin type-1 domain-containing 7A,[18] against neutral endopeptidase (in the very rare neonatal MN), or against bovine serum albumin (BSA).[19] Some cases of MN may be caused by low-avidity immune complexes, which may dissociate and then re-form at the subepithelial space; this may be a mechanism for some MN caused by viruses such as HBV.

Most cases of idiopathic MN caused by anti-PLA_2 antibodies are associated with IgG4 deposition, which is an isoform of IgG that does not activate the classic complement pathway. However, there is evidence that the IgG4-PLA_2 complex can activate complement through the MBL complement pathway, resulting in local generation of the membrane attack complex (C5b-9), which may insert into the podocyte to cause activation, injury, and proteinuria.

Membranoproliferative Glomerulonephritis

In MPGN type I, the immune deposits localize to both the mesangium and the subendothelial space (see Chapter 21). A similar pattern is observed in cryoglobulinemic GN, in which the immune complexes contain a monoclonal IgM or polyclonal IgM that acts as a rheumatoid factor by binding to the IgG in the immune complex. In both cases, the disease is thought to occur by passive deposition from the circulation, and the antigen is often a component of the HCV virus, especially in adults. When this pattern is seen in lupus nephritis, it may be facilitated by the binding of extracellular nucleosomes to the complexes. Nucleosomes are cationic nuclear proteins that can interact with the negatively charged proteins within the glomerulus.

Studies in experimental models suggest that the intraglomerular immune complexes cause local complement activation with the generation of chemotactic factors, including C5a, chemokines, and leukotrienes. Leukocyte adhesion molecules on endothelial cells are upregulated (intracellular adhesion molecule 1) or expressed de novo (E- and P-selectin). Proinflammatory cytokines (IL-1 and tumor necrosis factor α) are generated locally and augment the inflammatory response. Neutrophils, platelets, and monocytes/macrophages then localize in the glomerulus and release oxidants, particularly hypohalous acids generated by neutrophil myeloperoxidase, and proteases (elastase, cathepsin G, metalloproteinases) that cause local cellular injury and GBM degradation.

Dense Deposit Disease and C3 Glomerulonephritis

In contrast to MPGN type I, immune complexes are absent in glomeruli of patients with DDD and C3-GN. Initiation results from spontaneous intraglomerular activation of the alternative complement pathway. The most common cause is nephritic factor, an autoantibody that activates the alternative pathway. Some cases may be caused by mutations of the complement regulatory factor H, in which case the location of the mutation within the gene determines whether the disease manifests as DDD or atypical HUS.[20]

Mesangial Proliferative Glomerulonephritis

A mesangial proliferative GN, IgA nephropathy, is the most common type of glomerulonephritis (see Chapter 23). Production of an abnormally glycosylated IgA, possibly by a bacterial superantigen,[21] or perhaps from an altered mucosal immune system, may lead to IgA polymers that deposit in the mesangium; the glomerular capillary wall is relatively spared. Marked yet usually non-nephrotic proteinuria is a common feature of the clinical presentation. Mesangial cell injury may be mediated by binding of the IgA-containing immune complexes to Fcα or other IgA receptors on the mesangial cell, resulting in the release of chemokines and growth factors that provokes leukocyte infiltration as well as mesangial cell proliferation and mesangial matrix production.

Poststreptococcal Glomerulonephritis

Poststreptococcal GN has long been considered the human equivalent of acute serum sickness in rabbits (see Chapter 55). It is observed only in patients infected with specific (nephritogenic strains) of group A streptococci. One antigen responsible for some cases of PSGN, streptococcal pyrogenic exotoxin B, enters the circulation and localizes to glomeruli, resulting in a brisk inflammatory reaction with local endothelial and mesangial cell proliferation and manifestations of nephritic syndrome. Complement activation occurs through the alternative pathway and may result from direct activation of the pathway by streptococcal antigens. Some deposits ("humps") also form in the subepithelial space and may represent the translocation of immune complexes across the GBM.

Goodpasture Disease

Goodpasture disease (anti-GBM disease) is caused by an autoantibody to the α3 chain of type IV collagen present in the GBM and alveolar basement membrane (see Chapter 24). The autoantibody develops in genetically susceptible individuals because of molecular mimicry between the type IV collagen antigens and certain bacterial antigens.[8] Binding of antibody results in complement activation with the infiltration of inflammatory cells, causing local capillary wall damage and proteinuria. Crescent formation also usually occurs and may be mediated by both T cells and macrophages.

Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A severe form of segmental necrotizing glomerular injury, often in association with crescents, can be observed with vasculitis (see Chapter 25). The two most common types of vasculitis causing this type of injury are granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis) and microscopic polyangiitis (MPA). Both are associated with circulating antibodies against neutrophil cytoplasmic antigens (ANCAs), with antibodies to endopeptidase (proteinase) 3, which give a cytoplasmic pattern by staining (c-ANCA) in most patients with GPA granulomatosis, and antibodies to myeloperoxidase, which give a perinuclear staining pattern (p-ANCA) in subjects with MPA. Experimental evidence suggests that ANCAs are pathogenic by activating neutrophils within the vasculature. The mechanism responsible for triggering autoantibodies to neutrophil antigens remains unclear, although geographic and temporal clustering suggest a role for infection or antigen exposure that may induce an autoimmune response.[11]

Further discussion of specific pathogenic mechanisms in the different patterns of glomerular disease can be found in Chapters 17 to 29.

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SELF-ASSESSMENT QUESTIONS

1. Membranous nephropathy (MN) may result from all the following *except:*
   - **A.** Anti–phospholipase A_2 receptor antibodies
   - **B.** Thrombospondin type-1 domain-containing 7A antibodies
   - **C.** Antibodies to cationic bovine serum albumin
   - **D.** Factor H deficiency
   - **E.** Deposition of hepatitis B virus antigens and antibody
2. A low serum C3 level would suggest all the following diseases *except:*
   - **A.** Membranoproliferative glomerulonephritis secondary to hepatitis C virus
   - **B.** Cryoglobulinemic glomerulonephritis accompanying bacterial endocarditis
   - **C.** Class IV lupus nephritis
   - **D.** Goodpasture disease
   - **E.** Class III lupus nephritis
3. Marked proteinuria typically results from damage to which structure?
   - **A.** Mesangial cells
   - **B.** Parietal epithelial cells
   - **C.** Podocytes
   - **D.** Preglomerular arterioles
   - **E.** Loops of Henle
4. Which statement best describes focal segmental glomerulosclerosis (FSGS)?
   - **A.** It is typically a disease of the mesangium.
   - **B.** It usually results in nephrotic syndrome.
   - **C.** FSGS can result from a circulating factor.
   - **D.** FSGS is an autoimmune disease.
   - **E.** Most FSGS cases result from mutations.

Minimal Change Disease

Gabriel Cara-Fuentes, Eduardo H. Garin, Richard J. Johnson, Jürgen Floege

Minimal change disease (MCD), previously known as *lipoid nephrosis* or *minimal lesion*, represents the most common type of nephrotic syndrome in children (~80%), whereas in adults it accounts for 10% to 20% of cases. MCD refers to nephrotic syndrome in which glomeruli appear normal or with very subtle morphologic changes under light microscopy, with podocyte foot process fusion or effacement found on electron microscopy. MCD displays a higher rate of remission after corticosteroid treatment, has better long-term renal outcomes, and has an earlier onset than other patterns of nephrotic syndrome.

EPIDEMIOLOGY

The largest epidemiologic study carried out in children with nephrotic syndrome was the International Study of Kidney Disease in Children (ISKDC).[1] In this study, 363 of 471 (77%) children presenting with nephrotic syndrome had MCD as the underlying histologic diagnosis. MCD accounted for 94% of cases in patients younger than 6 years of age who responded to an 8-week course of oral steroids. In older children with nephrotic syndrome, the proportion with MCD decreases steadily, reaching about 50% of all cases between 8 and 16 years of age. More recent studies, based on smaller populations than that included in ISKDC, found a rising proportion secondary to focal segmental glomerulosclerosis (FSGS) relative to MCD.[2]

The incidence of MCD in children ranges from 1.2 to 7 per 100,000 cases and has a seasonal influence with a greater incidence during winter and shows great variability among different populations.[3] Thus MCD is reported to be as low as 1 per million of the population in the United Kingdom and up to 27 per million in the United States. It is more common in South Asians and Native Americans but is much rarer in African Americans, in whom nephrotic syndrome is much more likely to be caused by FSGS.[4] The prevalence of MCD is approximately 16 in 100,000. MCD is more common in boys (2:1) during childhood but is equally common in male and female adolescents.

ETIOLOGY

Few children have an underlying disease or condition leading to MCD. When it occurs, secondary MCD may be clinically indistinguishable from idiopathic MCD. A list of secondary causes is summarized in Box 17.1. Of these, Hodgkin disease, atopy, exposure to allergens (vaccinations, insect stings, foods), and nonsteroidal antiinflammatory drugs (NSAIDs) (particularly fenoprofen) seems to have a strong clinical association with MCD. The latter is an idiosyncratic reaction and is usually associated with chronic NSAID use that has occurred for several weeks or months. Unlike classic MCD, this syndrome is usually associated with massive nephrotic syndrome with impaired renal function, and renal biopsy shows MCD with features of an acute interstitial nephritis with T cell infiltration.

MCD is the most common type of nephrotic syndrome in patients with Hodgkin disease, but its incidence is low (<1%).[5] In these patients a protein known as C-MIP is overexpressed in Reed-Steinberg cells and podocytes. C-MIP appears to mediate podocyte injury by preventing the interaction of nephrin with the tyrosine kinase Fyn, resulting in decreased phosphorylation of nephrin, which in turn, could lead to cytoskeleton rearrangement and proteinuria.[6]

Relapses of MCD can follow exposure to bee sting, foods, and viral or bacterial respiratory tract infections (URIs). The association of bee sting and MCD is limited to few anecdotal case reports. Food allergens have been reported as triggers of MCD relapses in numerous case reports. This clinical association led to introduction of allergen-free diets for patients with MCD, and case reports and case series have reported that a gluten-free diet, elemental diets, or skin desensitization may result in a decrease in proteinuria.[7] Well-designed, controlled studies are needed to validate these observations.

Rare cases of familial MCD have been reported in Europe but may more likely represent an underlying mutation in genes encoding for slit diaphragm proteins instead of primary or idiopathic MCD (see Chapter 19).[8]

PATHOGENESIS

The pathogenesis of proteinuria in MCD is unknown. Shalhoub,[9] in 1974, proposed that MCD is caused by a circulating factor, thought to be a cytokine, that increases the permeability of the glomerular basement membrane (GBM) to plasma proteins. He suggested that MCD might represent a T cell disorder based on the lack of immune deposits, the rapid response to corticosteroids, the association with Hodgkin disease (a T cell neoplasm), and the observation that remission often occurred during resolution of measles infection, which is associated with a transient inhibition of cell-mediated immunity. This hypothesis remains dominant, although neither the circulating factor nor a T cell–dependent mechanism has been identified. However, several potential pathways that result in podocyte activation and proteinuria have been identified (Fig. 17.1).

Circulating Factor(s)

Several candidate molecules have been considered as possible circulating factors.

Cytokines

Cytokines have been measured in serum, urine, supernatants of peripheral blood mononuclear cells, and mRNA levels in circulating T cells

BOX 17.1 Secondary Causes of Minimal Change Disease

Drugs
- Nonsteroidal antiinflammatory drugs
- Interferon-α
- Lithium: Rare (usually causes chronic interstitial nephritis)
- Gold: Rare (usually causes membranous nephropathy)

Allergy
- Pollens
- House dust
- Insect stings
- Immunizations
- Poison Oak

Malignancy
- Hodgkin disease
- Mycosis fungoides
- Chronic lymphocytic leukemia: Uncommon (usually associated with membranoproliferative glomerulonephritis)

or leukocyte populations. Although some patterns have been observed, especially related to an increase in Th2-derived cytokines (that are associated with allergy), no definitive confirmed pattern has emerged.[10]

Some groups have administered or overexpressed cytokines in laboratory animals to determine if they can induce nephrotic proteinuria. Rats were infused with interleukin-8 (IL-8) to achieve levels found in serum in MCD patients, with a concomitant increase catabolism of GBM heparan sulfate, but the proteinuria was in the non-nephrotic range.[11] In a transgenic rat model that developed elevated serum IL-13 levels, there was an increased podocyte CD80 overexpression attributed to IL13, as well as nephrotic proteinuria.[12] However, the role of IL-13 in MCD patients is debatable because although some MCD patients have elevated IL-13 in serum during relapse, most patients have serum IL-13 levels either within the normal range or even undetectable in serum.

Hemopexin

Hemopexin is synthesized in the liver and is present in human plasma of patients with MCD, which, when infused into the isolated rat kidney, induced proteinuria.[13] However, its role in disease remains controversial because only 50% of the proteinuria was due to albumin; this is a

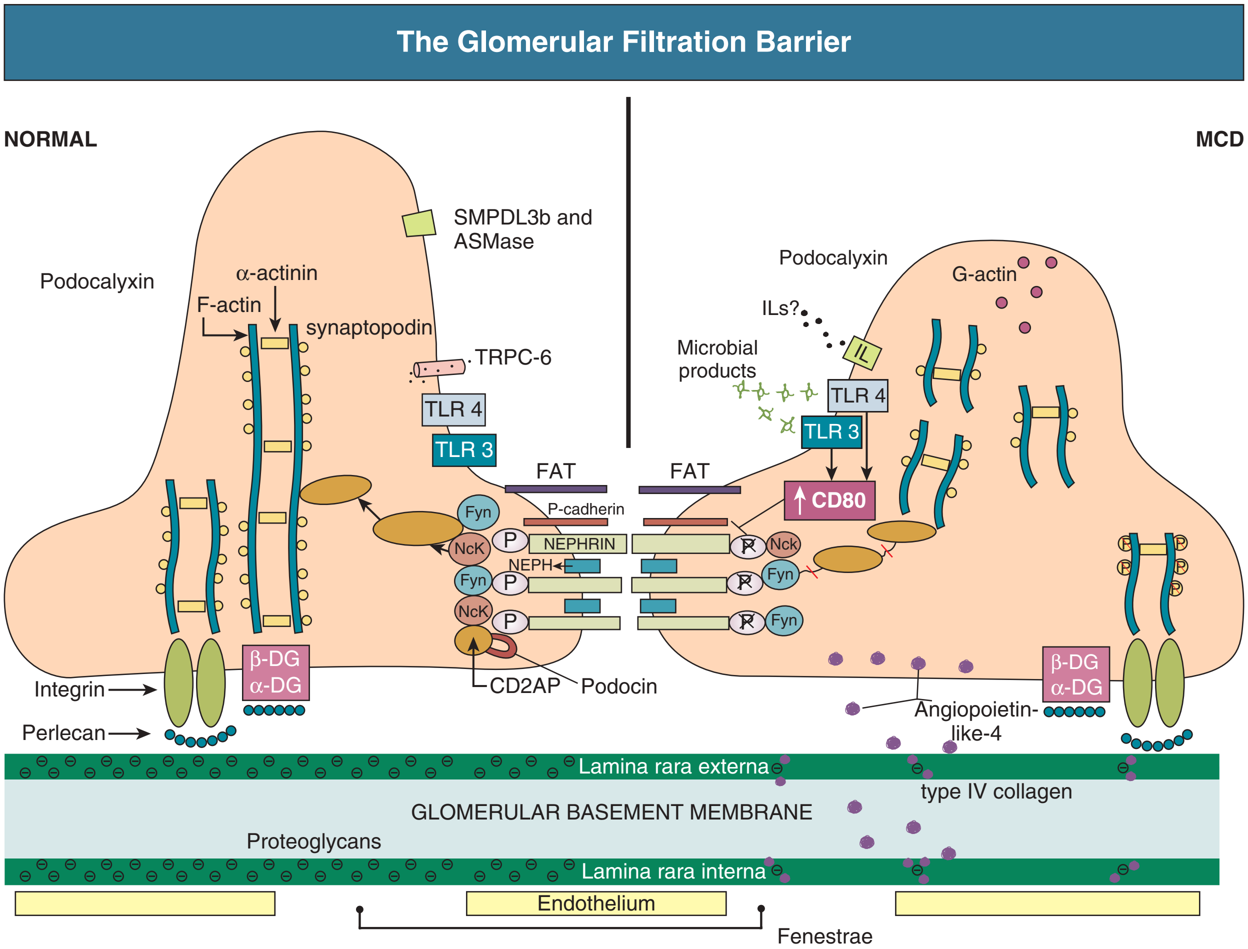
The Glomerular Filtration Barrier
NORMAL
MCD
SMPDL3b and ASMase
Podocalyxin
α-actinin
F-actin
synaptopodin
TRPC-6
TLR 4
TLR 3
FAT
P-cadherin
Fyn
NcK
P
NEPHRIN
NEPH
Fyn
P
NcK
P
CD2AP
Podocin
Integrin
Perlecan
β-DG
α-DG
Podocalyxin
G-actin
ILs?
IL
Microbial products
TLR 4
TLR 3
FAT
↑ CD80
Nck
Fyn
Fyn
P
P
β-DG
α-DG
Angiopoietin-like-4
Lamina rara externa
type IV collagen
GLOMERULAR BASEMENT MEMBRANE
Proteoglycans
Lamina rara interna
Endothelium
Fenestrae

Fig. 17.1 Glomerular filtration barrier in healthy state *(left)* and in minimal change disease *(MCD)* during relapse *(right)*. In MCD, microbial products and/or interleukins *(ILs)* bind to Toll-like receptors *(TLRs)* or IL receptors leading to *CD80* expression, which in turn, may interfere with nephrin expression/phosphorylation. Angiopoietin-like-4 is thought to induce proteinuria by reducing anionic sites at the glomerular basement membrane level. *DG,* Dystroglycans.

different pattern from that of MCD because the filtration fraction also contains other protein and MCD patients have low serum levels of hemopexin, likely as a result of urinary losses, and no hemopexin has been detected in their kidneys.

Microbial Products

A role for microbial products as circulating factors is attractive because 70% of MCD patients with relapse have documented viral or bacterial respiratory infections.[14] Two Toll-like receptor (TLR) ligands, lipopolysaccharide (LPS), a component of the outer membrane of gram-negative bacteria, and polyinosinic-polycytidylic acid (poly IC), a viral-like particle, bind to TLR-4 and TLR-3 on podocytes, respectively, and cause proteinuria in animals with podocyte expression of CD80 and increased urinary CD80 excretion, mimicking findings observed in MCD patients during relapse.[15,16]

Mechanism(s) of Proteinuria

Loss of Anionic Charges in the Glomerular Filtration Barrier as a Cause of Minimal Change Disease

Proteinuria in MCD has been proposed to result from a loss of proteins carrying negative charges in the glomerular capillary wall, resulting in disruption of the charge barrier and allowing albumin (which is negatively charged) to pass across in excess quantities.[17] Heparan sulfate proteoglycans, which are the major source of anionic sites in the GBM, are reported to be low or normal in the GBM of MCD patients. Nevertheless, experimental studies in which the charge barrier of the GBM has been altered do not confirm a loss of the charge barrier as a major cause of proteinuria.[18]

Podocyte Dysfunction as a Cause of Minimal Change Disease

More recent studies have focused on podocyte dysfunction in the mechanism of proteinuria. Several suggestions have been proposed, including alteration of slit diaphragm proteins such as reduced nephrin phosphorylation[19] and alteration in integrin-mediated podocyte adhesion. Decreased expression of acid sphingomyelinase-like phosphodiesterase 3b (SMPDL3b), a protein mainly localized in podocytes' lipid rafts, also has been associated with FSGS, although no data are available in MCD.[20] Podocyte expression of two molecules, CD80 (also known as B7.1) and angiopoietin-like-4 (Angptl-4) also have been proposed (see Fig. 17.1).[21,22]

CD80. A major discovery was that the podocyte can become an antigen-presenting cell and can express proteins normally expressed by dendritic cells, such as CD80.[15] CD80 is a costimulatory molecule present on antigen-presenting cells that was found to be expressed on podocytes in children with MCD.[21] It also can be induced in podocytes both in vitro and in vivo by TLR ligands, with the development of transient proteinuria and focal foot process effacement.[15,16] Serum from patients with MCD who are in relapse induces CD80 expression in cultured podocytes but not serum from MCD patients in remission. High levels of CD80 also can be found in the urine of children with steroid-sensitive MCD, and levels decrease to normal with remission.[23] CD80 is regulated by cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), which is a molecule also expressed by podocytes. The administration of CTLA-4 immunoglobulin to a child with recurrent steroid-dependent MCD resulted in rapid decrease in urinary CD80, with the development of remission within 72 hours.[23]

These observations led to the hypothesis that MCD relapse may develop after viral infection in which viral components stimulate TLR-3 podocyte receptors, resulting in overexpression of podocyte CD80. Because of an inadequate CTLA4 response by the podocyte, the increased expression of CD80, by interfering with phosphorylation of nephrin, could lead to changes in podocyte shape affecting the "size barrier," allowing protein to pass through larger physical gaps in the continuity of the podocyte barrier. Consistent with this hypothesis, glomerular nephrin phosphorylation is decreased in MCD.[19]

CD80 is also expressed in glomeruli in other glomerular diseases, and not all studies have observed high glomerular expression in subjects with MCD as well as in other glomerulopathies.[24] However, urinary CD80 is significantly higher in persons with MCD compared with FSGS or other conditions, suggesting that although CD80 may be expressed in many diseases, its expression is greatest in MCD. Indeed, CTLA4 immunoglobulin (Ig) does not appear to be effective in inducing remission in FSGS.[23]

Angptl-4. Angptl-4 is a glycoprotein that has been proposed as a mediator of proteinuria in MCD.[22] In a transgenic rat model characterized by glomerular overexpression of angptl4 and podocin, rats had a marked loss of GBM heparan sulfate proteoglycans, podocyte foot process effacement, and albuminuria.

Nevertheless, data on angptl4 in MCD are scarce. Our group found urinary angptl4 levels to be elevated not only in MCD but also in other nephrotic glomerular diseases (MCD, FSGS, membranous nephropathy) consistent with it being a marker of proteinuria.[25] In addition, angptl4 expression in glomeruli could not be confirmed in glomeruli of MCD subjects in a recent study.[25] Further studies on the role of angptl4 and CD80 in MCD are needed.

PATHOLOGY

MCD received its name because of the minimal, if any, glomerular abnormalities present by light microscopy. Mild changes such as a slight increase in mesangial matrix and hypercellularity may occasionally be observed. A small percentage (<10%) of glomeruli may display global, but not segmental, glomerular sclerosis, which may reflect the natural senescence of glomeruli observed in young adults. In a few cases, minor focal tubular atrophy with segmental interstitial fibrosis may be present. Fat and hyaline droplets also may be found in the proximal tubule.

By immunofluorescence, immunoglobulins or complement deposits are rarely found. If present, deposits are limited to the mesangium. There is a small subset of patients who have IgM deposits, which has been considered by some clinicians to represent an entity distinct from MCD, known as IgM nephropathy and characterized by a poorer clinical outcome. Although mesangial IgM has been considered "passive trapping" and of no pathogenic significance, recent studies suggest IgM may be directed against mesangial antigens and contribute to proteinuria. Some case series have found mesangial C1q deposits, which may be associated with worse outcomes, leading to the concept of C1q nephropathy (see Chapters 22 and 28). However, it remains controversial whether the long-term prognosis is dictated by the presence of C1q deposits or, most likely, by the presence or lack of glomerular sclerosis on light microscopy. Likewise, the mechanism by which C1q would trigger or accelerate podocyte injury is unknown.

Electron microscopy demonstrates podocyte foot process effacement or fusion (Fig. 17.2). Although fusion of foot processes is observed in other nephrotic conditions, in the absence of light microscopy glomerular changes, the finding is pathognomonic for MCD. The GBM is normal, and no electron-dense deposits are observed.

CLINICAL MANIFESTATIONS

Edema is the first sign and is noticeable after a weight gain of at least 5% to 7% of a patient's dry weight. The edema is pitting, worse in the lower extremities, and typically of rapid onset. Some patients present with bilateral periorbital edema, often misinterpreted as an allergic process.

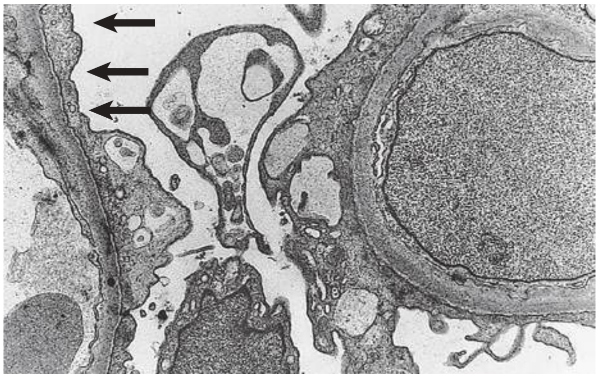

Fig. 17.2 Podocyte foot process fusion in minimal change disease. The epithelial cells *(arrows)* are completely effaced along the glomerular basement membranes. (Electron micrograph; magnification ×6000.) The normal appearance of epithelial cell foot processes is shown in Chapter 1, Figs. 1.6 and 1.7.

Edema may be mild and associated only with fatigue or may be severe, presenting as anasarca with pleural effusions and ascites. Bowel edema may manifest as diarrhea. The mechanism(s) of edema formation in MCD is not fully understood, but may be due to both a decrease in oncotic pressure and an increase in sodium reabsorption in the distal tubule (see Chapter 15).

In contrast with other glomerular diseases, MCD is associated with normal blood pressure. Some patients may develop transient renin-mediated hypertension during relapse from hypovolemia and renal hypoperfusion. Paradoxically, blood pressure will normalize after albumin infusion as the intravascular compartment is restored. Hypertension also can be iatrogenic, secondary to use of steroids, cyclosporine, or tacrolimus. Sustained hypertension questions the diagnosis of MCD.

Abdominal pain and nausea are common manifestations in MCD. Pain is usually dull because of massive ascites and bowel hypoperfusion. This pain resolves after albumin is administered. Severe pain may be due to peritonitis or acute pancreatitis. Hepatomegaly is common in children but may be overlooked in the presence of ascites.

Macroscopic hematuria is not seen in MCD unless there is a complication such as renal venous thrombosis.

Less commonly, patients with MCD may develop “white nails,” sometimes in bands (Muehrcke lines) correlating with periods of clinical relapse (see Fig. 15.4). Adults may develop xanthomas and xanthelasmas, especially on the eyelids (see Fig. 15.5).

LABORATORY FINDINGS

Nephrotic syndrome is defined by the combination of nephrotic-range proteinuria, hypoalbuminemia, hyperlipidemia, and edema. In children, nephrotic-range proteinuria is defined as greater than 50 mg/kg/24 h, greater than 40 mg/h/m^2 (urinary specimens collected overnight), 200 mg protein/mmol urine creatinine, or a ratio of urinary protein to creatinine (uPCR) greater than 3 mg/mg.[1] In adolescents and adults, nephrotic-range proteinuria is defined as greater than 3.5 g/24 h. The uPCR in a random sample correlates moderately with proteinuria measured in urine collected over 24 hours from patients with glomerular disease. In MCD, proteinuria is not only massive but selective (see Chapter 15). Urine microscopy shows hyaline casts and fat bodies, as well as microhematuria in 20% of patients.

Hypoalbuminemia is defined by a serum level of albumin below 2.5 g/dl. It is the result of the increased glomerular filtration permeability to plasma proteins. It remains controversial whether there is also an increased catabolism of filtered albumin by proximal tubule cells. The current evidence suggests that albumin is reabsorbed intact at that level. The liver production of albumin is increased in MCD patients, and gastrointestinal losses are minimal. Massive edema usually develops with serum albumin levels below 2 g/dl.

Hyperlipidemia (elevated total cholesterol and low-density lipoprotein [LDL] cholesterol) is a universal feature of patients with MCD in relapse, and if massive proteinuria is persistent, triglycerides and very-LDL (VLDL) are also elevated. Hyperlipidemia results from increased hepatic synthesis of cholesterol and triglycerides and decreased activity of lipoprotein lipase. In addition, urinary losses of lecithin cholesterol acyltransferase lead to a reduction of chylomicrons and VLDL clearance. The hyperlipidemia resolves after resolution of proteinuria.

Renal function is commonly normal. Some patients have transient acute kidney injury (AKI) with oliguria during relapse secondary to reduction of intravascular compartment. AKI is more common in adolescents and young adults than children. Similarly to persistent hypertension and macroscopic hematuria, sustained renal injury should raise a concern for a complication such as renal venous thrombosis, interstitial nephritis (i.e., secondary to drugs), or a different glomerular disease.

Mild hyponatremia is common during relapse and may represent pseudohyponatremia as a result of hyperlipidemia. Indirect ion-sensitive electrode only measures the aqueous phase of the plasma specimen in contrast to direct ion-sensitive electrode. If the latter is not available, a fast way to determine whether the patient has true hyponatremia or pseudohyponatremia is by measuring plasma osmolality.

Total serum calcium and vitamin D levels may be low because of hypoalbuminemia with decreased protein-bound calcium and lower circulating levels of vitamin D–binding proteins as a result of loss in the urine, respectively, and ionized calcium is usually normal and no treatment is indicated. Bone disease, however, may develop if prolonged courses of steroids are required.

Elevated hemoglobin and hematocrit levels and thrombocytosis are usually found in MCD patients during relapse as result of plasma volume contraction.

Other Presentations (Complications)

MCD patients exhibit an increased risk for infections (sepsis, peritonitis, cellulitis, and pneumonia). Low serum IgG (but not IgM) may be present in patients with persistent proteinuria or frequent relapses secondary to excessive urinary losses. This together with the urinary losses of factor B and properdin may predispose MCD patients to infections caused by encapsulated organisms. Serum C3 levels are elevated in MCD. *Streptococcus pneumoniae, Haemophilus influenza,* and other encapsulated bacteria are the most common cause of peritonitis in these patients. Therefore clinicians must ensure that patients are properly immunized. Peritonitis is rare in adults, who usually have developed protective antibodies. Varicella may develop a severe course in those patients receiving immunosuppressive therapy.

The combination of a hypercoagulability state (decreased anti–thrombin III and proteins C and S and increased fibrinogen, coagulation factors V, VII, VIII, X, and XII, and platelet aggregability among others), along with immobilization (in the setting of anasarca) and the presence of hypovolemia (and thrombocytosis as a result), put MCD patients at high risk for thrombosis, including pulmonary emboli, sagittal venous thrombosis, renal vein thrombosis, or peripheral venous thrombosis and less frequently arterial thrombosis.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

MCD is the most common type of idiopathic nephrotic syndrome in children. So, renal biopsy is not routinely done in children (younger than 10 years of age) presenting with idiopathic nephrotic syndrome. However, if there are features that are not characteristic for MCD, such as hypertension, red cell casts, gross hematuria, or renal dysfunction (estimated glomerular filtration rate persistently <80 ml/min/1.73 m^2), renal biopsy is performed at presentation. In addition, for children who fail to respond to a 4- to 6-week course of corticosteroids, a renal biopsy is performed. These steroid-resistant cases almost never have MCD and more likely represent a form of hereditary nephrotic syndrome (see Chapter 19).

In adults, in whom there is a wide differential diagnosis for nephrotic syndrome and corticosteroid responsiveness is less likely, a renal biopsy is required to establish the diagnosis.

Pathologic findings need to be carefully interpreted, along with the response to steroids. A patient with normal-appearing glomeruli who is not responding could have a hereditary disease associated with a podocyte mutation (e.g., congenital nephrotic syndrome, see Chapter 19). Some patients may have FSGS and may have a relatively low percentage of glomeruli showing FSGS that is not evident on the initial biopsy sample because of a sampling error. Indeed, there is an ongoing debate about whether MCD and FSGS represent different diseases or whether they are the same disease at different stages. MCD patients with steroid dependence or resistance often have findings consistent with FSGS in subsequent kidney biopsies.

NATURAL HISTORY

Children and adults with MCD classically present with nephrotic syndrome with normal renal function, and spontaneous remission is low in the absence of corticosteroid treatment. Corticosteroid treatment is usually effective in inducing remission, but relapse is common and repeated therapy often required. Among children with MCD, 25% never relapse, 25% relapse infrequently, and 50% have numerous relapses. The last group are classified as frequent relapsers if they have at least four relapses per year and steroid dependent if relapse occurs during the steroid taper or soon after it is stopped (Table 17.1).

There is no support for the concept that disease resolves during puberty, and it is not unusual to see children with MCD undergoing relapses during adulthood. However, is claimed that patients in remission for more than 5 years are less likely to relapse.[26]

Two thirds of relapses occur during an upper or lower respiratory infection. A short course (5 days) of prednisolone started at the clinical onset of URI decreases the rate of relapse (from 59% to 34%) and the number of relapses per patient.[27]

Long-term renal function in MCD patients is normal unless renal venous thrombosis develops. This is in contrast to the decreased function leading to renal failure in FSGS patients. Hence, MCD can be viewed as having a good long-term prognosis.

TREATMENT

General Considerations

Management of nephrotic syndrome follows standard approaches, as discussed in Chapter 15, including a low-sodium diet to control edema. Bed rest should be avoided because of the increased risk for thromboembolic events. Diuretics are infrequently used in children because of potential further volume depletion, but diuretics are often used to control extracellular fluid volume in adults, in whom hypovolemia before treatment is less common. In patients with pronounced hypoalbuminemia (i.e., serum albumin <2 g/dl) and in those with prolonged nephrotic syndrome, thrombosis prophylaxis may be considered. Treatment of hyperlipidemia with statins is rarely necessary because of the rapid response to corticosteroids.

TABLE 17.1 Definition of Terms Used in Nephrotic Syndrome in Adults and Children

Classification	Definition
Nephrotic syndrome	Edema, uPCR ≥2000 mg/g (≥200 mg/mmol), or ≥3.5 g/day proteinuria, or 3+ protein on urine dipstick, hypoalbuminemia ≤2.5 g/dl (≤25 g/l)
Complete remission	uPCR <200 mg/g (<20 mg/mmol) or <1+ of protein on urine dipstick for 3 consecutive days (children) Reduction of proteinuria to ≤0.20 g/day and serum albumin >3.5 g/dl (adults)
Partial remission	Proteinuria reduction of 50% or greater from the presenting value and absolute uPCR between 200 and 2000 mg/g (20-200 mg/mmol) (children) Reduction of proteinuria to between 0.21 g/day and 3.4 g/day ± decrease in proteinuria of ≥50% from baseline (adults)
No remission	Failure to reduce urine protein excretion by 50% from baseline or persistent excretion uPCR >2000 mg/g (>200 mg/mmol)
Initial responder	Attainment of complete remission within initial 4 wk of corticosteroid therapy
Initial nonresponder/ steroid resistance	Failure to achieve complete remission after 8 wk of corticosteroid therapy (children) Persistence of proteinuria despite prednisone therapy, 1 mg/kg/day for 16 wk (adults)
Relapse	uPCR ≥2000 mg/g (≥200 mg/mmol) or ≥3+ protein on urine dipstick for 3 consecutive days (children) Proteinuria ≥3.5 g/day occurring after complete remission obtained for >1 month (adults)
Infrequent relapse	One relapse within 6 mo of initial response, or one to three relapses in any 12-mo period
Frequent relapse	Two or more relapses within 6 mo of initial response, or four or more relapses in any 12-mo period
Steroid dependence	Two consecutive relapses during corticosteroid therapy, or within 14 days of completing corticosteroid therapy
Late nonresponder	Persistent proteinuria during ≥4 wk of corticosteroids after one or more remissions

Modified from reference 53.
uPCR, Ratio of urine protein to creatinine.

Treatment of Children

Initial Treatment

Corticosteroids are the first-line therapy to induce remission in children with idiopathic nephrotic syndrome and biopsy-proven MCD (Fig. 17.3), because 95% of MCD patients respond to this therapy. In patients with a contraindication for steroids (e.g., patients with diabetes), cyclosporine has been used as initial therapy.

The induction phase consists of administering prednisone 60 mg/day/m^2 (equivalent to 2 mg/kg, with a maximum of 60 mg/day for children and 80 mg/day for adolescents) for 4 weeks. Although the

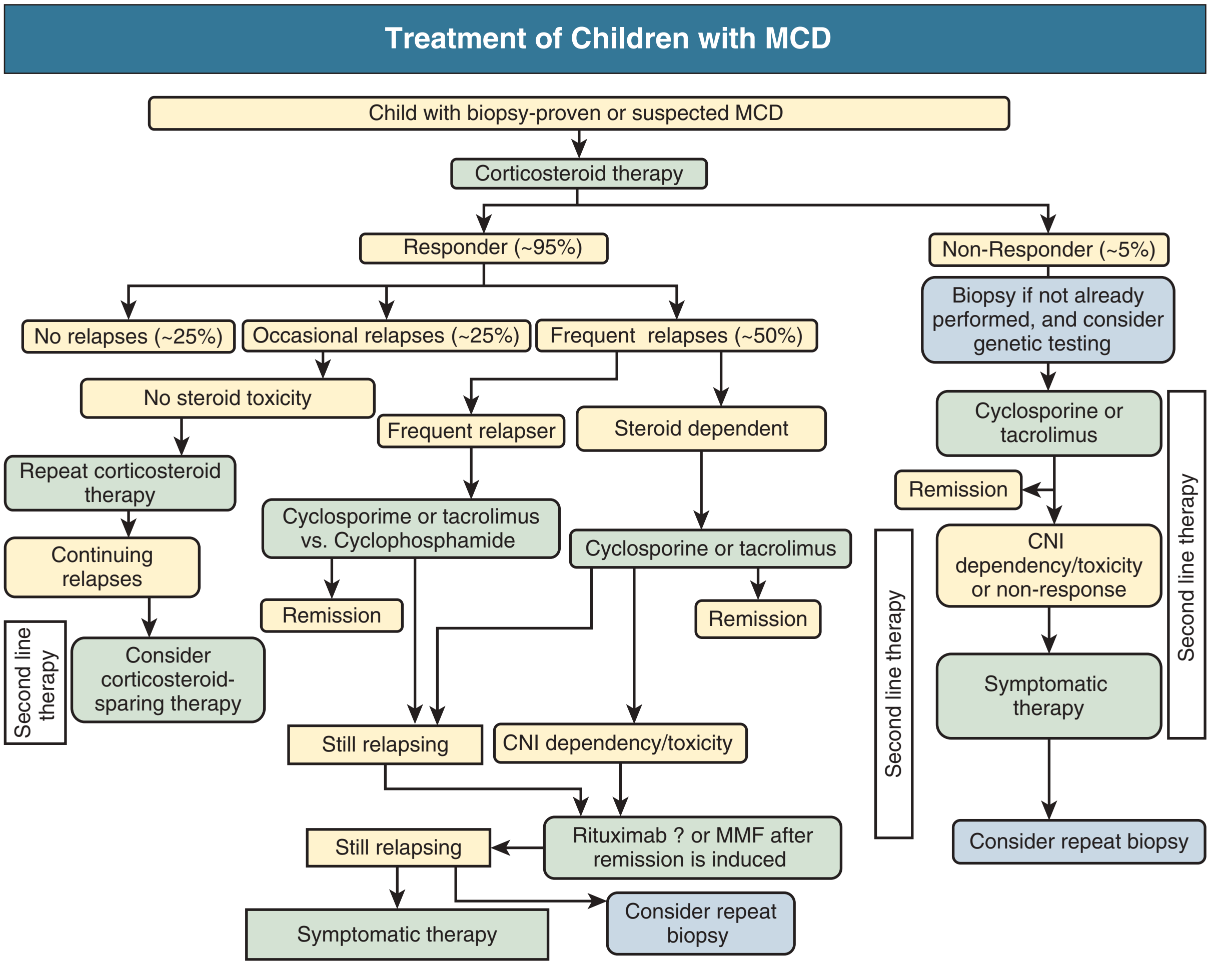
Treatment of Children with MCD
Child with biopsy-proven or suspected MCD
Corticosteroid therapy
Responder (~95%)
Non-Responder (~5%)
No relapses (~25%)
Occasional relapses (~25%)
Frequent relapses (~50%)
Biopsy if not already performed, and consider genetic testing
No steroid toxicity
Frequent relapser
Steroid dependent
Cyclosporine or tacrolimus
Repeat corticosteroid therapy
Cyclosporime or tacrolimus vs. Cyclophosphamide
Remission
Cyclosporine or tacrolimus
Continuing relapses
Remission
Remission
CNI dependency/toxicity or non-response
Second line therapy
Second line therapy
Second line therapy
Consider corticosteroid-sparing therapy
Symptomatic therapy
Still relapsing
CNI dependency/toxicity
Rituximab ? or MMF after remission is induced
Still relapsing
Consider repeat biopsy
Symptomatic therapy
Consider repeat biopsy

Fig. 17.3 Algorithm for treatment of childhood minimal change disease. For definitions, see Table 17.1. The patient or parents should be involved in the decision after the potential side effects of the second-line treatment are considered in the rare patient who is a nonresponder to standard corticosteroid therapy and by definition "corticosteroid resistant." *CNI*, Calcineurin inhibitor; *MMF*, mycophenolate mofetil.

ISKDC recommends dosing in 3 divided doses per day, most nephrologists administer 2 mg/kg of prednisone as a single morning daily dose based on evidence that it provides equal efficacy,[28] because single dosing results in less adrenal insufficiency and better adherence.

Whether the initial dosing of 60 mg/day/m^2 should be for 4 weeks ("short duration", ISKDC recommendation) or 6 weeks ("extended therapy") was addressed by the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN).[29] The cumulative rate of patients with sustained remission after 2 years was significantly higher in the extended therapy group than the short regimen. In addition, the frequent relapsing pattern was observed more often in patients under the short compared with the extended prednisone regimen (57% and 29%, respectively). However, these results were not confirmed by the Southwest Pediatric Nephrology Study Group (SWPNS).[30] At the end of the SWPNS study, the relapse rate was not statistically different between patients receiving the short versus extended induction therapy with prednisone.

Given these results, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment of the initial episode of nephrotic syndrome in children with daily oral prednisone or prednisolone at 60 mg/m^2/day or 2 mg/kg/day (maximum 60 mg/day) as induction therapy for 4 to 6 weeks.[31] The addition of cyclosporine to full dose of prednisone in the induction phase did not increase the remission rate or shorten the timing of remission.[29]

Most children will undergo remission during the induction phase, but treatment is continued to the 4-week or 6-week time point and then there is a tapering phase in which prednisone is slowly reduced to lower the risk for side effects. During the tapering phase, it is widely accepted that prednisone should be administered on alternate days. Similar to the induction phase, there is no agreement on the duration of the tapering phase or the dose of prednisone. Thus the tapering duration varies from a 4-week period followed by abrupt discontinuation as proposed by the ISKDC to a slow tapering that ranged from 6 weeks to 7 months.

A Cochrane systematic review in 2015 concluded, based on three well-designed randomized controlled trials (RCTs), that a 6-month prednisone course does not reduce the risk for relapse compared with a 2- or 3-month course in children aged 1 to 17 years at presentation.[32] The 2012 KDIGO guidelines for children with idiopathic nephrotic syndrome recommend, based on these studies, to give oral prednisone at 40 mg/m^2 or 1.5 mg/kg on alternate days and continue for 2 to 5 months with tapering of the dose.

Treatment of Relapses

Similar to the treatment of the initial episode, there is no consensus on the use of prednisone in the induction and tapering phases. The ISKDC recommends prednisone at 60 mg/m^2/day until response (maximum of 4 weeks) followed by prednisone 40 mg/m^2/day for 3 consecutive days in a week for a total of 4 weeks.[1] The ISKDC provided arbitrary definitions regarding the relapse pattern, grouping patients as steroid dependent and frequent relapsers (see Table 17.1).[1] These are widely used, but the distinction between steroid dependent and frequent relapser should be made carefully, to select appropriate therapy based on the available studies. Definitions of steroid dependence can vary among different centers. For example, longer tapering schedules (>8 weeks) will lead to a higher number of patients with a steroid-dependent pattern. In addition, the definition of steroid dependence does not take into consideration the role of URI as triggers of nephrotic syndrome.

Whereas initial treatment of relapsing patients usually involves repeated courses of corticosteroids, repeated or prolonged course of steroids can be associated with significant toxicity, including behavioral changes, growth impairment, and diabetes. This led to the use of alternative therapies in MCD patients who are steroid dependent and relapse frequently.

Chlorambucil 0.15 mg/kg/day for 56 days or cyclophosphamide 2 mg/kg/day orally for 56 days used in combination with low-dose prednisone can induce sustained remission (72% patients at 30 months after cytotoxic drug) in MCD patients with multiple relapses.[33] The ISKDC found fewer episodes of relapse (48% vs. 88% at 22 months) among patients with multiple relapses treated with a 6-week course of cyclophosphamide 5 mg/kg/day until induction of cytopenia, followed by 1 to 3 mg/kg/day along with prednisone 10 mg/m^2/day for 10 days compared with those on an intermittent dose of prednisone 40 mg/m^2 for 3 of 7 days for 6 months.[34] Cyclophosphamide should not be started until the patient has achieved complete remission with prednisone to avoid hemorrhagic cystitis. In addition, to avoid gonadal toxicity, it is recommended not to exceed a cumulative dose of 168 and 8 mg/kg, respectively, for cyclophosphamide and chlorambucil. Second courses of these medications should not be administered.

The optimal length of cyclophosphamide therapy is debatable. The APN reported a higher probability of remission after 2-year follow-up in patients receiving cyclophosphamide for 12 weeks compared with those treated for 8 weeks (67% vs. 22%, respectively).[35] No such difference was observed after 5 years in another study (24% vs. 25%, respectively).[36]

These prior studies did not differentiate between steroid-dependent patients and frequent relapsers, but the response to cyclophosphamide is better for those with a frequent relapsing pattern (70% remission) versus those who are steroid dependent (38% remission).[37] Therefore we do not recommend the routine use of either cyclophosphamide or chlorambucil in the steroid-dependent MCD patient.

Cyclosporine and tacrolimus may be considered as alternative therapeutic agents in MCD patients who relapse frequently. Treatment with cyclosporine results in a similar rate of remission compared with cyclophosphamide and chlorambucil. However, its long-term efficacy is hampered by frequent relapse shortly after calcineurin inhibitor (CNI) withdrawal.[38] Cyclosporine is recommended at an initial dose of 5 mg/kg/day with dose adjustment to maintain trough serum levels between 100 and 150 ng/ml. The length of therapy varies from 12 to 24 months. Mild to moderate cyclosporine-associated nephrotoxicity has been reported in up to one third of MCD patients treated with cyclosporine for more than 3 years. Tacrolimus appears to have efficacy similar to that of cyclosporine.[39]

Mycophenolate mofetil (MMF) has been used in MCD patients with multiple relapses in RCTs but is less efficacious than cyclosporine.[40,41] An RCT also concluded that azathioprine has no effect in the relapse rate of children with steroid-sensitive nephrotic syndrome.[42] Likewise, levamisole is an anthelminthic agent that was found to possibly reduce the risk for relapse in patients with frequent relapse and steroid-dependent nephrotic syndrome in single-center studies.[43] However, the use of levamisole is hampered by the lack of a large multicenter RCT confirming its efficacy and because in drug users it has been associated with development of antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis.

More recently, rituximab has been used for steroid-dependent nephrotic syndrome in children.[44-46] Rituximab and lower doses of prednisone and CNIs were not inferior to standard doses of steroids in patients with steroid-dependent nephrotic syndrome.[44] Nevertheless, 75% of patients in the rituximab group had relapsed at 1-year follow-up. In a second study, children received a single dose of rituximab while in remission. Proteinuria was lower at 3 months in the rituximab group, although it did not reach statistical significance. Only 34% of patients in the rituximab group relapsed at 1 year in contrast with the 75% previously reported by the same group. Iijima and colleagues[46] studied patients with “complicated” steroid-dependent or frequently relapsing nephrotic syndrome. Patients were administered rituximab for 4 weeks after remission had been induced. Those who received rituximab had a significantly longer relapse-free period and fewer relapses compared with those patients receiving placebo. Unfortunately, although initial response showed a better response for rituximab, most patients relapsed (17 of 20 vs. 23 of 23, rituximab vs. control, respectively) by the end of the study, and it is unclear whether frequently relapsing and steroid-dependent patients had a similar response to rituximab. In summary, whether rituximab is beneficial in MCD is not conclusive. Rituximab may prolong remission, but RCTs with a larger and well-defined cohort of patients and long-term follow-up (>1 year) are needed to assess the efficacy and safety of rituximab before its widespread use in children MCD.

Treatment of Adults

Initial Treatment

Studies comparing different corticosteroid regimens in adults with MCD are limited, and the treatment recommendations given here are in line with KDIGO guidelines[47] (Fig. 17.4) and are extrapolated from successful approaches in children with steroid-sensitive nephrotic syndrome, although often with slightly lower doses of oral prednisolone (1 mg/kg/day, up to maximum 80 mg/day). There is no good evidence that alternate-day corticosteroids (prednisolone 2 mg/kg, up to maximum 120 mg) offer any clinical advantages over daily dosing; however, induction with methylprednisolone pulses may lead to more rapid responses and fewer relapses.[48]

Response is often delayed in comparison with that in children, and 25% fail to remit after 3 to 4 months[49] (Fig. 17.5). Although unclear, the reason may be that adults are often given a smaller dose of corticosteroids or that a greater proportion of adults have FSGS, missed on the original biopsy, which is more likely to be corticosteroid resistant.

Based on meta-analyses of pediatric studies, the recommended corticosteroid treatment should be at least 3 to 4 months (KDIGO recommends up to 6 months, but based on very-low-grade evidence). The initial high dose of corticosteroids, if tolerated, should be maintained for a minimum of 4 weeks if complete remission is achieved and for a maximum of 16 weeks if complete remission is not achieved. The rate of dose tapering and total length of treatment of the initial episode may need to be reduced in individual patients if steroid toxicity is significant (e.g., uncontrolled diabetes, psychiatric complications, patient with severe osteoporosis). If the patient has not responded after 12 to 16 weeks, consideration should be given to adherence with corticosteroid treatment or failure of absorption. The latter is unusual unless the patient is vomiting or has diarrhea, in which case some recommend intravenous methylprednisolone, with anecdotal success, although initial treatment with pulse methylprednisolone and lower doses of oral corticosteroid does not seem to be beneficial. A repeat biopsy should be considered in patients failing to respond.

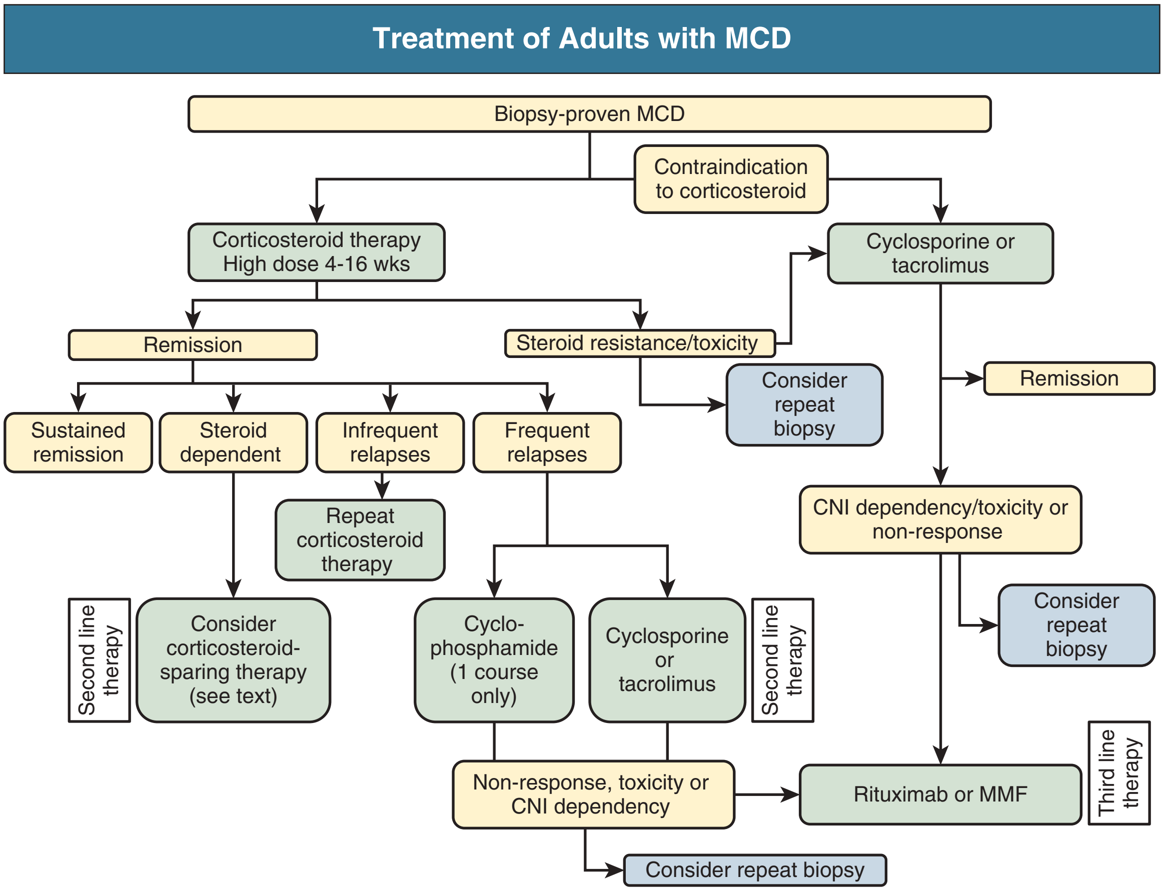
Treatment of Adults with MCD
Biopsy-proven MCD
Contraindication to corticosteroid
Corticosteroid therapy High dose 4-16 wks
Cyclosporine or tacrolimus
Remission
Steroid resistance/toxicity
Consider repeat biopsy
Remission
Sustained remission
Steroid dependent
Infrequent relapses
Frequent relapses
Repeat corticosteroid therapy
CNI dependency/toxicity or non-response
Consider repeat biopsy
Second line therapy
Consider corticosteroid-sparing therapy (see text)
Cyclo-phosphamide (1 course only)
Cyclosporine or tacrolimus
Second line therapy
Third line therapy
Non-response, toxicity or CNI dependency
Rituximab or MMF
Consider repeat biopsy

Fig. 17.4 Algorithm for treatment of adult minimal change disease. *CNI,* Calcineurin inhibitor; *MMF,* mofetil mycophenolate.

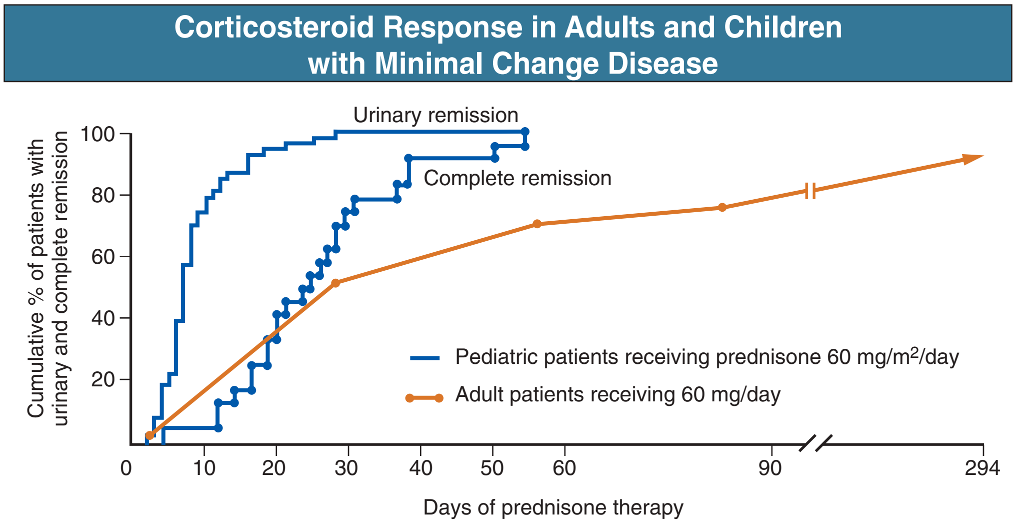

Fig. 17.5 Corticosteroid response in adults and children with minimal change disease (MCD). Adults with nephrotic syndrome and MCD take longer to respond than children and are less likely to remit. *Orange line* shows the cumulative percentage of adults with complete remission (i.e., reduction of proteinuria ≤0.2 g/day and serum albumin concentration >35 g/l). *Blue lines* show the cumulative percentage of pediatric patients with urinary remission and with complete remission.

Infrequent relapses should be treated in the same way as the initial presentation, but there is even less evidence that a prolonged course of corticosteroids is beneficial in reducing the frequency of subsequent relapse. Therefore steroid tapering can start a week after remission, with a taper to finish over 4 to 6 weeks, although this is not evidence based.

Frequently Relapsing and Corticosteroid-Dependent Minimal Change Disease

Adults relapse less often than children (30% to 50%). Relapse may occur in up to 40% of adults who had MCD in childhood.[50] As in children, some adults have transient non-nephrotic relapses, so it is important to establish that a full relapse has developed with persistent heavy proteinuria, a low albumin level, and fluid retention before recommencing steroids. Frequently relapsing and corticosteroid-dependent patients should receive second-line therapy with cyclophosphamide or cyclosporine, but the timing of this decision will vary between physicians and patients. Many factors will influence the decision to abandon repeated corticosteroid courses, including steroid toxicity and tolerance and level of steroid dependence; 5 to 10 mg/day may be acceptable for several months, but more than 20 mg/day would not. The patient should be involved in the decision after explanation of the relative risks with further courses of corticosteroids and the alternative treatments.

A 12-week course of oral cyclophosphamide 2 to 2.5 mg/kg/day induces a permanent remission more often in adults than children (75% and 66% at 2 and 5 years, respectively).[51] Although there are no satisfactory studies comparing 8-week and 12-week courses in adults, the 12-week course is logical on the basis of the pediatric experience. If this treatment is selected, the opportunity for banking sperm or retrieval of ova should be considered before treatment, although the azoospermia or amenorrhea risk at this dose is low. Intravenous cyclophosphamide has been recommended to limit the cumulative dose: intravenous cyclophosphamide 0.5 g/m^2 per month adjusted upward to 1 g/m^2 on the basis of the leukocyte count after 2 weeks with a target nadir of 3000 cells/mm^3.

Some nephrologists prefer calcineurin inhibitors before cyclophosphamide, especially in younger adults and those who want to maximize future fertility. Cyclosporine 4 to 6 mg/kg/day, aiming for trough whole-blood levels of 50 to 150 ng/ml for at least 12 months, is effective, but relapse usually follows dose reduction or withdrawal. Cyclosporine is a good short- to medium-term management strategy because remission occurs in 50% to 75% of patients.[52] However, careful monitoring is required because nephrotoxicity is common after more than 1 year of therapy.[53]

Tacrolimus has effectiveness similar to that of cyclosporine and may have a more favorable side-effect profile. Initial target levels are 4 to 8 ng/ml, but higher levels may be required to maintain remission. A Chinese randomized trial found in 119 adults with MCD that 10 days of methylprednisolone 0.8 mg/kg/day followed by tacrolimus was as effective as a purely corticosteroid-based first-line therapy and led to fewer adverse events.[54] Thus tacrolimus may be particularly attractive as first- or second-line therapy in patients with contraindications for or intolerance of high-dose corticosteroids.

Several uncontrolled reports suggest that MMF may have a place in management of corticosteroid- and cyclosporine-dependent patients, but more data on efficacy, dosage, and duration of treatment are needed before these could be widely recommended. However, MMF did not appear as efficacious as cyclosporine in controlled trials in children.[40,41]

Rituximab has been reported to induce remission in adults with frequently relapsing disease unresponsive to other treatments, but some caution is needed because RCTs have not been performed. Two non-randomized studies in adults with corticosteroid-dependent or frequently relapsing MCD suggested that rituximab is beneficial, with an up to 10-fold reduction in annual relapse rate.[55,56] Whether a dosing regimen of 1 or 2 infusions of 1 g rituximab or up to 4 infusions of 375 mg/m^2 is superior, remains to be established.

Minimal Change Disease With Non-Nephrotic Proteinuria

In patients with well-documented MCD who have the rare relapse in which the proteinuria is non-nephrotic, treatment does not require corticosteroids but rather can include angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy. If there is any question as to diagnosis, repeated biopsy may be indicated because other conditions can mimic MCD.

Treatment of Secondary Minimal Change Disease

MCD secondary to NSAIDs requires discontinuation of the offending medication. Many patients are treated with a course of corticosteroids for MCD (higher dose) or for acute interstitial nephritis (see Chapter 60), but evidence of benefit is uncertain. Secondary MCD from Hodgkin disease usually responds to treatment of the lymphoma. Some patients will also receive a drug regimen for MCD as adjunctive therapy in addition to the chemotherapy directed at the tumor in particular if MCD remission does not occur quickly with adequate chemotherapy.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following conditions or drugs has *not* been associated with minimal change disease (MCD) in children or adults?
   - **A.** Asthma
   - **B.** Hodgkin disease
   - **C.** Interferon-α
   - **D.** Rhabdomyosarcoma
   - **E.** Eczema
2. Which of the following factors has been implicated in the pathogenesis of nephrotic-range proteinuria in MCD?
   - **A.** CD4
   - **B.** Interleukin-1 (IL-1)
   - **C.** Vascular endothelial growth factor
   - **D.** CD80/B7.1
   - **E.** Hepcidin
3. Which of the following statements regarding the therapy of MCD in adults is correct?
   - **A.** Adults usually achieve remission with relatively low doses of prednisolone (maximum 20 mg every other day).
   - **B.** Good evidence suggests that alternate-day corticosteroids are more effective than daily dosing.
   - **C.** Spontaneous remission is rare.
   - **D.** The total length of corticosteroid therapy should not exceed 1 month.
   - **E.** Patients with infrequent relapses should receive a 12-week course of oral cyclophosphamide (2-2.5 mg/kg/day)

18

Primary and Secondary (Non-Genetic) Causes of Focal and Segmental Glomerulosclerosis

Gerald B. Appel, Vivette D. D'Agati

Focal segmental glomerulosclerosis (FSGS), a histologic pattern of glomerular injury, defines a number of clinicopathologic syndromes that may be primary (idiopathic) or secondary to diverse causes[1-4] (see Chapter 19). Early in the disease process, the pattern of glomerulosclerosis is focal, involving a minority of glomeruli, and segmental, involving a portion of the glomerular tuft.[4] Alterations of podocyte cytoarchitecture on electron microscopy (EM) are relatively diffuse, underscoring the pathogenetic importance of podocyte injury. As FSGS progresses, more diffuse and global glomerulosclerosis evolves.[4] Although it accounts for only a small percentage of cases of nephrotic syndrome in young children, FSGS represents as many as 35% of cases in adults[1,2] and is a major cause of end-stage renal disease (ESRD) in certain populations.[5]

Diverse pathogenetic mechanisms have been identified and often manifest as particular histologic subtypes of disease. Through podocyte depletion and dysregulation, structural deterioration of the glomerular tuft leads to FSGS as a final common pathway.[4,6] Although primary (idiopathic) FSGS is potentially treatable and curable in many patients, the optimal type and duration of immunosuppressive, as well as adjunctive therapy, remain controversial. For secondary FSGS, effective therapies exist to slow or modify the disease course (see Chapter 79).

ETIOLOGY AND PATHOGENESIS

FSGS represents a common phenotypic expression of diverse clinicopathologic syndromes with distinct causes (Box 18.1). Causes include genetic mutations in podocyte components (see Chapter 19), circulating permeability factors, viral infections, drug toxicities, maladaptive responses to a reduced number of functioning nephrons, and hemodynamic stress placed on an initially normal nephron population. In all these forms of FSGS, injury directed to or inherent within the podocyte is a central pathogenetic mediator.[1,4,6] These injuries promote altered cell signaling, reorganization of the actin cytoskeleton, and resulting foot process effacement. Critical levels of injury cause podocyte depletion through detachment or apoptosis. Stress placed on the remaining podocytes may lead to local propagation of damage (see Chapter 78). Injury to podocytes may spread to adjacent podocytes by reduction in supportive factors such as nephrin signaling, increased toxic factors such as angiotensin II (Ang II), or mechanical strain on remnant podocytes.[6-8] Cell-to-cell spread of podocyte injury until the entire glomerular lobule is captured could explain the characteristic segmental nature of the sclerosing lesions.[7,8]

Minimal Change Disease Versus Focal Segmental Glomerulosclerosis

By definition, the etiology of idiopathic or primary FSGS is unknown. Some clinical data support etiologic factors similar to those at work in minimal change disease (MCD; see Chapter 17). Certain corticosteroid-responsive patients who exhibit MCD on initial biopsy subsequently relapse and display FSGS on repeated biopsy. In some, this may simply represent a sampling error in the initial biopsy. In others with well-documented repeated relapses and responses of the nephrotic syndrome and multiple biopsies over years, FSGS truly appears to have evolved from an initial MCD pattern. Moreover, the pathologic changes in the nonsclerotic glomeruli of idiopathic FSGS resemble glomeruli of MCD.[4] In addition, sequential biopsy samples of recurrent FSGS in the allograft show it may pass through an early stage that mimics MCD.[9] Thus MCD and FSGS are often considered together under the rubric of "podocytopathies."

Both MCD and primary FSGS are thought to be mediated by circulating permeability factors.[10] Recent studies suggested the permeability factors in FSGS and MCD differ and that the diseases can be distinguished using biomarkers. Elevated CD80 (also known as B7-1), a costimulatory factor expressed on podocytes and B cells, is found in the urine of corticosteroid-sensitive MCD[11] but not in FSGS. Angiopoietin-like-4, a podocyte-secreted glycoprotein, is upregulated in podocytes and is elevated in the serum of animal models and patients with MCD.[12] In animal models, induction of urokinase plasminogen activator receptor (uPAR), derived from immature myeloid cells of the bone marrow, produces podocyte effacement, proteinuria, and FSGS.[13,14] In initial studies, patients with primary FSGS were reported to have higher levels of circulating soluble uPAR (suPAR) than equally proteinuric patients with MCD or membranous nephropathy (MN), and treatment-induced reduction in proteinuria was associated with reduction in suPAR levels in patients with FSGS.[13] Moreover, patients with recurrent FSGS in the allograft also had high circulating suPAR levels, which were reduced by plasma exchange in parallel with reductions in proteinuria.[13] However, subsequent studies found that higher suPAR levels correlated with lower glomerular filtration rate (GFR) irrespective of the underlying kidney disease and the induction of proteinuria by suPAR was not confirmed.[15,16] Thus the balance of evidence does not support suPAR as a specific mediator or biomarker of FSGS.

More recently, B7-1 (also known as CD80) has been proposed as a podocyte biomarker and potential therapeutic target in FSGS.[17] Initial studies suggested that abatacept (CTLA4-Ig) bound to induced podocyte B7-1 and led to remission of proteinuria in native kidneys with FSGS and recurrent FSGS in the allograft.[17] However, other investigators have not been able to identify B7-1 expression by podocytes in experimental models of FSGS or human FSGS and could not demonstrate therapeutic efficacy of abatacept in patients with recurrent FSGS in the allograft.[18,19] Given these limitations, podocyte B7-1 expression cannot currently be considered a biomarker or a proven therapeutic target in FSGS.

Alterations in glomerular capillary wall permeability may occur in response to circulating "humoral" substances that act on the podocyte

BOX 18.1 Etiologic Classification of Focal Segmental Glomerulosclerosis

Primary (Idiopathic) FSGS

- Probably mediated by circulating/permeability factor(s)

Secondary FSGS

Familial/Genetic*

- Mutations in nephrin *(NPHS1)*
- Mutations in podocin *(NPHS2)*
- Mutations in α-actinin 4 *(ACTN4)*
- Mutations in transient receptor potential cation channel *(TRPC6)*
- Mutations in Wilms tumor suppressor *(WT1)*
- Mutations in inverted formin-2 *(INF2)*
- Mutations in phospholipase C epsilon 1 *(PLCE1)*
- Risk alleles for apolipoprotein L1 *(APOL1)*

Virus Associated

- HIV-1 (HIV-associated nephropathy)
- Parvovirus B19
- Simian virus 40 (SV40)
- Cytomegalovirus (CMV)

Drug Induced

- Heroin ("heroin-nephropathy")
- Interferon
- Lithium
- Pamidronate
- Sirolimus
- Anabolic steroids
- Tyrosine kinase inhibitors

Mediated by Adaptive Structural-Functional Responses

Reduced Renal Mass

- Oligomeganephronia
- Very low birth weight
- Unilateral renal agenesis
- Renal dysplasia
- Reflux nephropathy
- Sequela to cortical necrosis
- Surgical renal ablation
- Chronic allograft nephropathy
- Any advanced renal disease with reduction in functioning nephrons

Initially Normal Renal Mass

- Hypertension
- Atheroemboli or other acute vaso-occlusive processes
- Obesity
- Increased lean body mass
- Cyanotic congenital heart disease
- Sickle cell anemia

*For complete list of genetic causes see Chapter 19.

to promote foot process effacement. Circulating permeability factors that enhance in vitro permeability of glomeruli to albumin have been found in some FSGS patients. The presence of such permeability factors has been used to predict the recurrence of FSGS in transplanted FSGS patients.[10] Some patients with FSGS with recurrence of nephrotic syndrome after transplantation achieve remissions of nephrotic syndrome after plasma exchange or use of a protein A adsorption column, supporting the role of a circulating factor[1,10,20] (see Chapter 111). However, none of several candidate proteins, including suPAR, B7-1, or cardiotrophin-like cytokine 1 (CLC1), a member of the IL-6 family of interleukins, has been proven to be the permeability factor in human FSGS.[21]

In contrast to MCD, the proteinuria in FSGS is usually nonselective, including albumin and higher-molecular-weight macromolecules. In human FSGS and toxin-induced animal models of FSGS, such as puromycin or doxorubicin (Adriamycin) nephrosis, nonselective proteinuria develops in conjunction with detachment of podocyte foot processes from the glomerular basement membrane (GBM), a finding not seen in MCD.[1,6] The susceptibility gene to doxorubicin toxicity in Balb/c mice has been identified as *PRKDC,* required for double-stranded DNA break repair. Animals deficient in this DNA repair machinery develop mitochondrial DNA depletion after doxorubicin exposure, leading to podocyte cell death and FSGS.[1] This mechanism illustrates how long-lived cells such as podocytes, which lack the ability to repair themselves by cell division, are especially vulnerable to genotoxic stress. In humans, repeated and diverse stresses to the podocyte could explain the development of FSGS pattern of injury in age-related nephrosclerosis and glomerular senescence.[1,6]

Glomerular hypertrophy (or glomerulomegaly) may identify children with MCD at risk for development of FSGS. In early idiopathic FSGS and in many secondary forms of FSGS, such as obesity related, there is initially glomerular hypertrophy and a high GFR, supporting roles for hyperfiltration and increased intracapillary glomerular pressures (glomerular hypertension).[1,21] Similarly, in secondary forms of FSGS with reduced nephron numbers, maladaptive hemodynamic alterations may be associated with glomerular hyperfiltration. Intraglomerular coagulation and abnormalities of lipid metabolism may also contribute to glomerulosclerosis in these patients (see Chapter 78). Although IgM and C3, commonly found in all forms of FSGS, are generally regarded as nonspecifically trapped in areas of sclerosis, recent murine evidence suggests they may actively contribute to glomerular injury through activating complement and binding antigens.[22,23] Recent studies document both reparative and sclerosing roles for parietal epithelial cells in FSGS. In vivo microscopy has illustrated the ability of parietal cells to rapidly cover sites of podocyte denudation and depletion in FSGS, but there is limited contribution to podocyte regeneration.[24,25] They also may directly contribute to glomerulosclerosis by migrating onto the glomerular tufts and synthesizing extracellular matrix proteins, as shown in both animal models and human biopsy samples with forms of primary and secondary FSGS.[1,26]

Genetic Variants of Focal Segmental Glomerulosclerosis

Genetic and familial forms of FSGS are covered in detail in Chapter 19. Many cases of apparently primary FSGS may harbor unidentified mutations or polymorphisms in podocyte genes that go unrecognized because of lack of genetic testing. In primary FSGS, a genetic predisposition may underlie the susceptibility to a "second hit," whereby viral factors or other immune stimuli lead to the initiation of disease. Mutations in podocyte genes also may predispose to FSGS induced by such secondary causes as obesity, systemic hypertension, and infectious agents, allowing multifactorial podocyte stress. For example, genetic studies have identified *APOL1* gene variants, encoding for apolipoprotein L-1, as a major predisposing factor for FSGS, as well as for HIV nephropathy, chronic hypertensive nephrosclerosis, and progressive lupus nephritis among African Americans.[27] G1 and G2 mutations in *APOL1* are protective against infection by *Trypanosoma brucei,* the parasite that causes African sleeping sickness. Similar to the gene for sickle cell disease, which confers selective advantage against malaria, this genetic mutation became prevalent in a population because it was protective against an infectious pathogen. Although *APOL1* is expressed by glomerular endothelial cells and podocytes, it is not entirely clear how sequence variations in *APOL1* mechanistically cause glomerulosclerosis.[28] In vitro studies have proposed increased podocyte membrane pores promoting intracellular potassium depletion and induction of stress-activated protein kinases.[29] A recent podocyte-specific inducible transgenic model of *APOL1*-associated FSGS suggests impairment of podocyte endocytic functions and autophagy.[30]

Viral Induction of Focal Segmental Glomerulosclerosis

Although a number of studies have noted a relationship between prior viral infection with parvovirus or other viruses and FSGS, in particular collapsing FSGS, these data have not been consistent.[31] By contrast, the role of HIV infection in the pathogenesis is well established (see Chapter 56).

Drug-Induced Focal Segmental Glomerulosclerosis

A number of drugs and medications have been associated with the FSGS phenotype, including heroin, lithium, pamidronate, sirolimus, calcineurin inhibitors, tyrosine kinase inhibitors, and interferons α, β, and γ[1,32,33] (see Box 18.1). Heroin has been associated with the nephrotic syndrome and FSGS (heroin nephropathy), although its incidence has diminished markedly in the modern era. Pamidronate, a bisphosphonate used to prevent bone resorption in myeloma and metastatic tumors, has been associated with both collapsing FSGS and MCD.[33] Stabilization of renal function and resolution of nephrotic syndrome may follow withdrawal of the offending medication (e.g., interferon, heroin, pamidronate). Long-term anabolic steroid abuse among bodybuilders has been associated with the development of FSGS.[34] Many of these individuals also consume high-protein diets and potentially injurious supplements, including growth hormone. Putative mechanisms of glomerular injury include direct toxic effects of anabolic steroids on glomerular cells, as well as adaptive responses to a very elevated lean body mass.[34] Patients who develop FSGS secondary to interferon therapy have been shown to carry double *APOL1* risk alleles and to activate a viral innate immunity program in podocytes upon interferon exposure, supporting a two-hit model of podocyte injury.[35]

Structural Maladaptation Leading to Focal Segmental Glomerulosclerosis

Many secondary forms of FSGS are mediated by adaptive structural-functional responses.[1,2,4] These adaptive forms include patients with both congenital and acquired reduction in the number of functioning nephrons, whereas other secondary forms are associated with hemodynamic stress placed on an initially normal nephron population (see Box 18.1). Obesity-related glomerulopathy (ORG), is increasingly common worldwide and may be associated with metabolic syndrome, including hypertension, diabetes, and hyperlipidemia. In most studies obesity has been defined by a body mass index (BMI) greater than 30 kg/m^2, although some Chinese studies have used a definition of greater than 28 kg/m^2. ORG usually lacks the full nephrotic syndrome and has a low risk for progression to ESRD.[21] Secondary FSGS resembling ORG in nonobese, highly muscular body builders may be mediated in part by hyperfiltration as well as direct podocyte effects of anabolic steroids.[34] Low birth weight associated with prematurity and reduced nephron endowment also may lead to glomerular hypertrophy, with secondary FSGS developing in adolescence or adulthood.[36] Biopsy specimens with secondary adaptive FSGS typically show glomerulomegaly and perihilar lesions of segmental sclerosis and hyalinosis. These conditions resemble experimental models of renal ablation in which the surgical reduction in renal mass causes functional hypertrophy of remnant nephrons with increased glomerular plasma flows and pressures. Whereas these changes are initially "adaptive," the resultant hyperfiltration and increased glomerular pressure become "maladaptive" and serve as mechanisms for progressive glomerular damage.[4,6]

Pathogenesis of Progressive Renal Failure in Focal Segmental Glomerulosclerosis

Although much attention has been focused on the pathogenesis of proteinuria in FSGS, the segmental and eventual global glomerulosclerosis in association with interstitial fibrosis and tubular atrophy clearly underlie the progression to renal failure. Podocytes in some forms of FSGS, such as the collapsing variant, display a dysregulated phenotype with dedifferentiation, proliferation, and apoptosis.[37] Such biopsy samples have altered podocyte expression of cell cycle–related proteins.[38] In renal biopsy specimens of patients with FSGS, the expression levels of transforming growth factor (TGF) β1, thrombospondin-1, and TGF-β2 receptor proteins are all increased, as are podocyte markers of the phosphorylated Smad2/Smad3 signaling pathway.[38] Reduction in vascular endothelial growth factor synthesis after podocyte loss and increased parietal cell coverage may contribute to capillary collapse. Thus pathways that promote podocyte depletion and overproduction of extracellular matrix (ECM) converge to produce a sclerosing phenotype.

EPIDEMIOLOGY

There is a large variability in the frequency of various primary glomerular diseases between different geographic and among racial populations.[1,2,39,40] The exact reasons for these differences may be multifactorial (e.g., bias in referral patterns and who undergoes biopsy, environmental or racial predispositions such as the presence of *APOL1* genetic variants in people of African descent). Some studies of renal biopsies show an increasing prevalence of FSGS in both adults and children in a number of countries on different continents.[1,2,40] For example, in Brazil, FSGS is the most common primary renal disease.[1,2] In the United States, one study found FSGS to be the most common lesion in adults with idiopathic nephrotic syndrome.[40] An analysis of the prevalence of ESRD in the United States caused by FSGS during a 21-year period shows an increase from 0.2% in 1980 to 2.3% in 2000, and FSGS is the most common primary glomerular disease leading to ESRD.[1,2,5] Although some changes in prevalence may relate to changes in biopsy practice or disease classification, the true frequency of FSGS has likely increased over time.

Primary FSGS is slightly more common in males than females, and the incidence of ESRD secondary to FSGS in males of all races is 1.5 to 2 times higher than in females. The incidence in both children and adults is higher in African Americans than in Whites and those of Asian descent.[1,3] This most likely relates to the presence of G1 and G2 variants of the apolipoprotein L1 genes in African Americans.[27,41] In the United States, FSGS is the most common cause of idiopathic nephrotic syndrome in adult African Americans.[1,2,40,41] African Americans have a fourfold greater risk for ESRD from FSGS than Whites. Even in an almost entirely White U.S. population, a clear increase in the incidence of FSGS has been documented over a 30-year period,[42] whereas this has not been the case in some White populations in Europe.[43]

CLINICAL MANIFESTATIONS

Patients with primary FSGS can present with asymptomatic proteinuria or the full nephrotic syndrome.[1-3] In some countries where routine medical checks are more common, 10% to 30% of children with asymptomatic proteinuria are detected in school and sports physical examinations; in adults, asymptomatic detection occurs at military induction examinations, obstetric checkups, and insurance or employment physical examinations. The incidence of nephrotic-range proteinuria at onset in children is 70% to 90%, whereas only 50% to 70% of adults with FSGS present with nephrotic syndrome. Secondary forms of FSGS associated with hyperfiltration typically have lower levels of proteinuria, and many such patients have subnephrotic proteinuria and a normal serum albumin concentration.[1-3,21]

Hypertension is found in 30% to 65% of children and adults with FSGS at diagnosis. Microhematuria is found in 30% to 75% of these patients, and a decreased GFR is noted at presentation in 20% to 50%.[1-3] Daily urinary protein excretion ranges from less than 1 to more than 30 g/day. Proteinuria is typically nonselective. Complement levels and other serologic test results are normal. Occasional patients will have glycosuria, aminoaciduria, phosphaturia, or a concentrating defect indicating functional tubular damage and glomerular injury.

Different histologic patterns of FSGS may display different clinical features. Patients with the tip variant of FSGS have clinical features more similar to those of MCD.[44] They often present with an abrupt clinical onset of the full nephrotic syndrome (almost 90%), shorter time course from onset to renal biopsy, more severe proteinuria, and less chronic tubulointerstitial disease than in FSGS not otherwise specified (NOS).[44,45] The cellular variant also typically manifests with greater proteinuria and higher incidence of nephrotic syndrome than FSGS NOS.[46] The collapsing variant usually manifests with greater proteinuria, more full-blown nephrotic syndrome, and lower GFR.[45-48]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

With the exception of genetic forms of FSGS, it is impossible to establish a firm diagnosis without a renal biopsy. Tests for permeability factors are neither reliable nor available in routine clinical practice. In children with FSGS, most of whom present with nephrotic syndrome, the major differential is between MCD and other variants of corticosteroid-resistant nephrotic syndrome. In adults with subnephrotic proteinuria, the differential includes almost all glomerular diseases without positive serologic results. In adults with nephrotic syndrome, MN and MCD may present in an identical manner, and only a renal biopsy will clarify the diagnosis. Focal sclerosing lesions caused by other glomerulopathies (e.g., segmental scarring from chronic glomerulonephritis) must be excluded pathologically. Moreover, because the defining glomerular lesion of FSGS is focal and may be confined to deeper juxtamedullary glomeruli early in the disease, it may not be sampled on renal biopsy. A large glomerular sample of more than 20 glomeruli for light microscopy increases the likelihood of identifying the diagnostic segmental lesions.

Even after the diagnosis of FSGS is established, the primary (idiopathic) form must be distinguished from secondary forms by careful clinicopathologic correlation (see Box 18.1). In general, many forms of adaptive FSGS have lower levels of proteinuria than primary FSGS, a lower incidence of hypoalbuminemia, and, on biopsy, lesser degrees of foot process effacement. In patients younger than 25 years and especially in those with a family history of FSGS, genetic screening for mutations in podocin, TRPC6, α-actinin-4, inverted formin 2, or other podocyte genes may be useful (see Chapter 19). However, in adults with sporadic FSGS genetic testing is currently not recommended given a very low detection rate of pathogenetic mutations.

PATHOLOGY

The pathologic manifestations of FSGS are heterogeneous, both qualitatively and with respect to the location of lesions within the glomerular tuft.[1,4] A classification of FSGS by histologic variants (Box 18.2) can be applied to both primary and secondary forms of FSGS (see Box 18.1).[49] Subtypes include *classic,* or NOS; *perihilar* variant, in which more than 50% of glomeruli with segmental lesions display hyalinosis and sclerosis involving the vascular pole region; *cellular* variant, manifesting endocapillary hypercellularity; *collapsing* variant, in which at least one glomerulus has global collapse and overlying visceral cell hypertrophy and hyperplasia; and *tip* variant, with segmental lesions involving the tubular pole. This working classification has been applied successfully to retrospective and prospective biopsy series. Other, more controversial histologic variants of FSGS include FSGS with diffuse mesangial hypercellularity and C1q nephropathy (see Chapter 28). Some think these are distinct disease entities, whereas others think they are merely subgroups of FSGS.[50,51]

BOX 18.2 Morphologic Variants of Focal Segmental Glomerulosclerosis

- FSGS, not otherwise specified (NOS; also known as classic FSGS)
- FSGS, perihilar variant
- FSGS, cellular variant
- FSGS, collapsing variant (also known as collapsing glomerulopathy)
- FSGS, tip variant

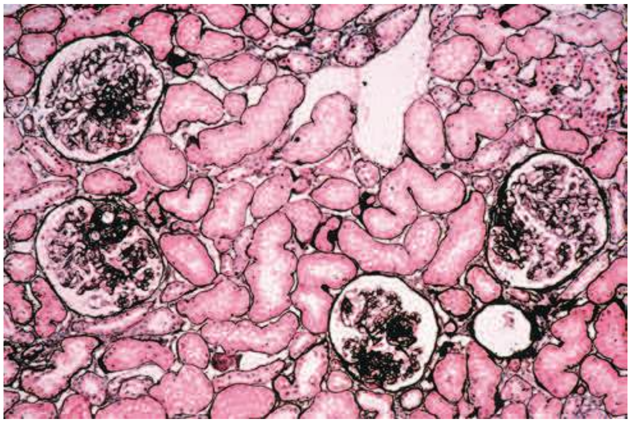

Fig. 18.1 Focal segmental glomerulosclerosis, not otherwise specified (FSGS NOS). A low-power view shows four glomeruli with discrete lesions of segmental sclerosis involving a portion of the tuft. The adjacent nonsclerotic capillaries are unremarkable. In this example, there is no evidence of tubulointerstitial injury. (Jones methenamine silver stain; magnification ×100.)

Classic Focal Segmental Glomerulosclerosis (FSGS Not Otherwise Specified)

FSGS NOS is the common generic form of the disease. FSGS NOS requires exclusion of the more specific subtypes described later. It is defined by accumulations of ECM that occlude glomerular capillaries, forming discrete segmental solidifications (Fig. 18.1).[49] There may be hyalinosis (plasmatic insudation of amorphous glassy material beneath the GBM), endocapillary foam cells, and wrinkling of the GBM (Fig. 18.2). Adhesions or synechiae to the Bowman capsule are common, and overlying visceral epithelial cells often appear swollen and form a cellular “cap” over the sclerosing segment. Glomerular lobules unaffected by segmental sclerosis appear normal on light microscopy, except for mild podocyte swelling. Tubular atrophy and interstitial fibrosis are commensurate with the degree of glomerulosclerosis. Immunofluorescence

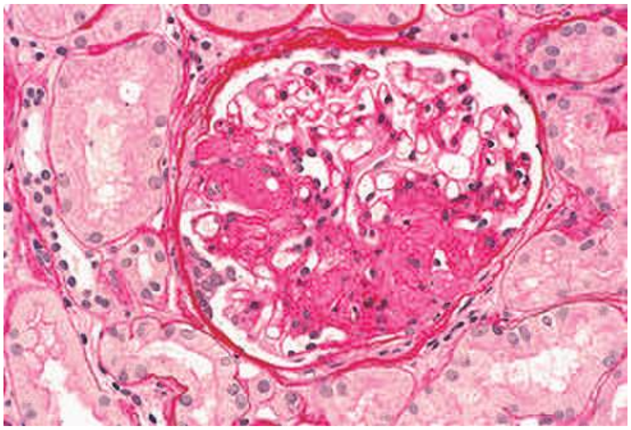

Fig. 18.2 **Focal segmental glomerulosclerosis, not otherwise specified.** The lesions of segmental sclerosis display increased extracellular matrix and hyalinosis. There is adhesion to the Bowman capsule without significant podocyte hypertrophy. The nonsclerotic capillaries have glomerular basement membranes of normal thickness and mild podocyte swelling. (Periodic acid–Schiff [PAS] reaction; ×400.)

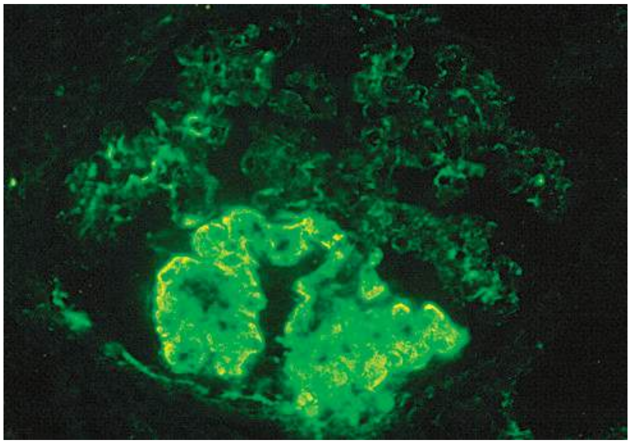

Fig. 18.3 **Focal segmental glomerulosclerosis, not otherwise specified.** The lesions of segmental sclerosis contain deposits of immunoglobulin M (IgM) corresponding to areas of increased matrix and hyalinosis. Weaker staining for IgM is also seen in the adjacent mesangium. (Immunofluorescence micrograph; ×400.)

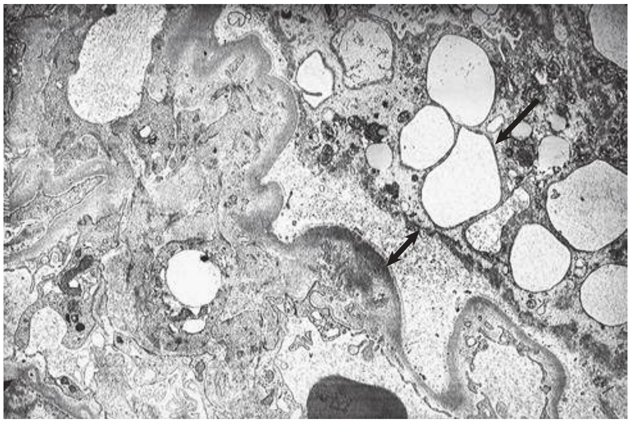

Fig. 18.4 **Focal segmental glomerulosclerosis, not otherwise specified.** Electron micrograph illustrates the lesion of segmental sclerosis with obliteration of the glomerular capillaries by increased extracellular matrix with wrinkled and retracted glomerular basement membranes. The overlying podocytes are detached, with complete effacement of foot processes *(double-headed arrow)* and numerous electron-lucent intracellular transport vesicles *(arrow)*. (×2500.)

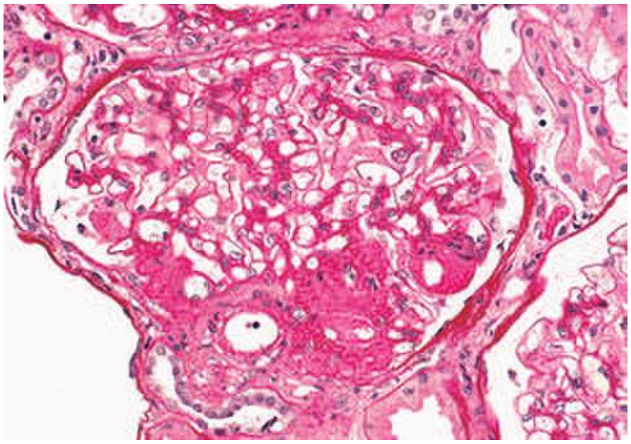

Fig. 18.5 **Focal segmental glomerulosclerosis (FSGS), perihilar variant.** A discrete lesion of segmental sclerosis and hyalinosis is located at the glomerular vascular pole (i.e., perihilar). The glomerulus is hypertrophied. The patient had secondary FSGS in the setting of solitary kidney as a result of contralateral renal agenesis. (PAS; ×250.)

(IF) typically reveals focal and segmental granular deposition of immunoglobulin M (IgM), C3, and more variably C1q in the distribution of the segmental glomerular sclerosis (Fig. 18.3). On EM, segmental sclerotic lesions exhibit increased ECM, wrinkling and retraction of the GBM, accumulation of inframembranous hyaline, and resulting narrowing or occlusion of the glomerular capillary lumina (Fig. 18.4). No electron-dense deposits are found. Overlying the segmental sclerosis, there is often podocyte detachment with parietal cell coverage. The adjacent nonsclerotic glomerular capillaries show foot process effacement with variable microvillous transformation (slender projections resembling villi along the surface of podocytes). This is the most frequent variant and may occur in primary or secondary forms of FSGS, including genetic forms.

Perihilar Variant of Focal Segmental Glomerulosclerosis

The perihilar variant is defined as perihilar hyalinosis and sclerosis involving more than 50% of glomeruli with segmental lesions.[49] This category requires exclusion of the cellular, tip, and collapsing variants. Podocyte hyperplasia is uncommon. Although the perihilar variant may occur in primary FSGS, it is particularly frequent in secondary forms of FSGS mediated by adaptive structural-functional responses, accompanied by glomerular hypertrophy (glomerulomegaly) and relatively mild foot process effacement (Fig. 18.5). In this setting, reflex dilation of the afferent arteriole and the greater filtration pressures at the proximal end of the glomerular capillary bed may favor the development of lesions at the vascular pole.[1,4,21]

Cellular Variant of Focal Segmental Glomerulosclerosis

The cellular variant is characterized by focal and segmental endocapillary hypercellularity that may mimic a form of focal proliferative glomerulonephritis.[46,49] Glomerular capillaries are segmentally occluded by endocapillary hypercellularity, including foam cells, infiltrating leukocytes, karyorrhectic debris, and hyaline (Fig. 18.6). There is often hyperplasia of the visceral epithelial cells, which may appear swollen, sometimes forming pseudocrescents. Foot process effacement is typically severe. This variant requires that tip lesions and collapsing lesions

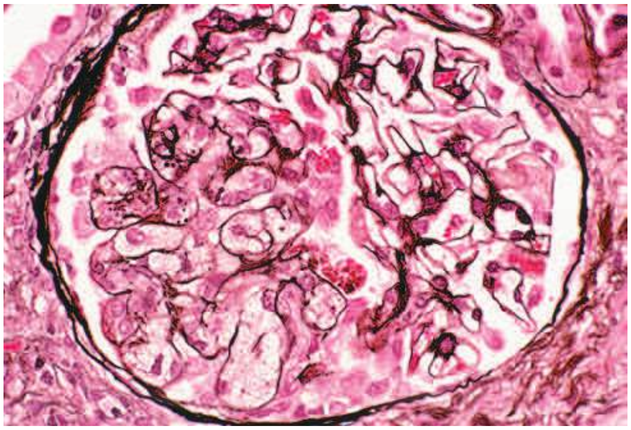

Fig. 18.6 Focal segmental glomerulosclerosis, cellular variant. The glomerular capillary lumina are segmentally occluded by endocapillary cells, including foam cells, infiltrating mononuclear leukocytes, and pyknotic debris. The findings mimic a proliferative glomerulonephritis because of the hypercellularity and absence of extracellular matrix material. There are hypertrophy and hyperplasia of the overlying visceral epithelial cells, some of which contain protein resorption droplets. (Jones methenamine silver; ×400.)

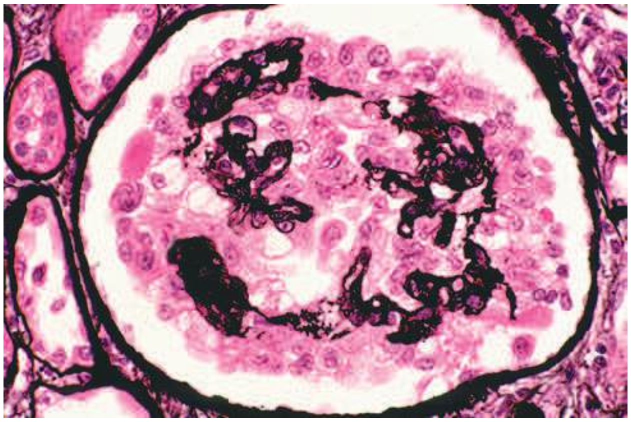

Fig. 18.7 Focal segmental glomerulosclerosis, collapsing variant. There is global implosive collapse of the glomerular tuft with obliteration of capillary lumina. The overlying visceral epithelial cells appear hypertrophied and hyperplastic with enlarged nuclei and nucleoli. There are no adhesions to the Bowman capsule. (Jones methenamine silver; ×400.)

be excluded. Cellular FSGS is thought to represent an early stage in the development of segmental lesions and is usually primary.

Collapsing Variant of Focal Segmental Glomerulosclerosis

The collapsing variant is defined by at least one glomerulus with segmental or global collapse and overlying hypertrophy and hyperplasia of visceral epithelial cells (Fig. 18.7). In these areas, there is occlusion of glomerular capillary lumina by implosive GBM wrinkling and collapse.[47-49] The collapsing lesion is more often global than segmental. Overlying visceral epithelial cells display hypertrophy and hyperplasia and express proliferation markers. Glomerular epithelial cells often contain prominent intracytoplasmic protein resorption droplets and may fill the Bowman space, forming pseudocrescents (Figs. 18.8 and 18.9). Although visceral cell hyperplasia is found in both the collapsing and the cellular variant of FSGS, collapsing glomerulopathy is distinguished by the absence of endocapillary hypercellularity. Studies suggest that dysregulated podocytes, activated parietal cells (expressing claudin and CD44), and progenitor cells (expressing stem cell markers CD133 and CD24) that line the Bowman capsule contribute to the glomerular epithelial cell hyperplasia and glomerulosclerosis.[4,6,37,52]

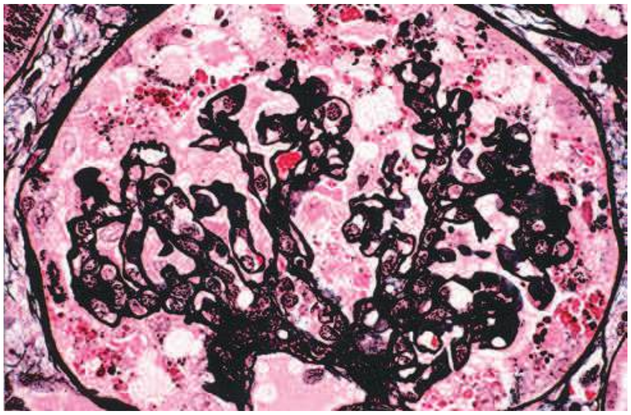

Fig. 18.8 Focal segmental glomerulosclerosis, collapsing variant. In this example, exuberant proliferation of glomerular epithelial cells forms a pseudocrescent that obliterates the urinary space. The pseudocrescent lacks the spindle cell morphology, ruptures of the Bowman capsule, or pericellular matrix typically seen in true inflammatory crescents of parietal epithelial origin. (Jones methenamine silver; ×400.)

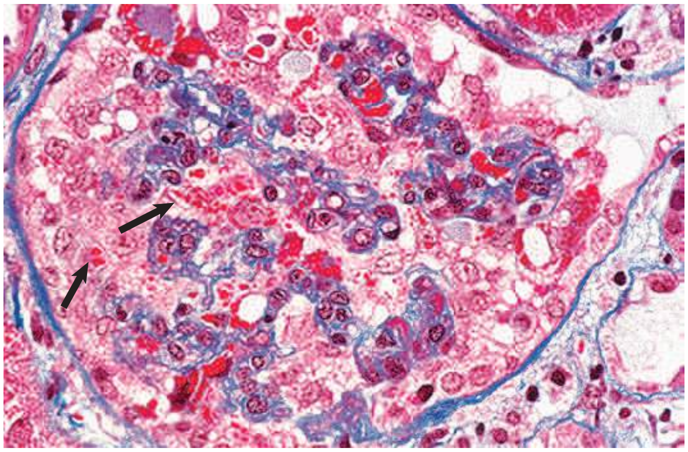

Fig. 18.9 Focal segmental glomerulosclerosis, collapsing variant. The crescent-like proliferation of glomerular epithelial cells contains numerous intracytoplasmic vacuoles and trichrome-red protein resorption droplets *(arrows)*. (Masson trichrome; ×400.)

In collapsing FSGS, there is prominent tubulointerstitial disease, including tubular atrophy, interstitial fibrosis, interstitial edema, and inflammation. A distinctive feature is the presence of dilated tubules forming microcysts that contain proteinaceous casts. On EM, there is typically severe foot process effacement affecting both collapsed and noncollapsed glomeruli (Fig. 18.10). Collapsing glomerulopathy may occur as a primary form of FSGS.[1,47] It is also frequently observed in secondary FSGS caused by HIV infection, parvovirus B19 infection, lupus podocytopathy, hemophagocytic syndrome, interferon therapy, tyrosine kinase inhibitor use, or pamidronate toxicity[1,2,31-33] (Fig. 18.11). The presence of endothelial tubuloreticular inclusions helps identify collapsing glomerulopathy secondary to HIV-associated nephropathy, lupus podocytopathy, or interferon therapy.

Tip Variant of Focal Segmental Glomerulosclerosis

The tip variant is defined by the presence of at least one segmental lesion involving the tip domain, the outer 25% of the tuft next to the

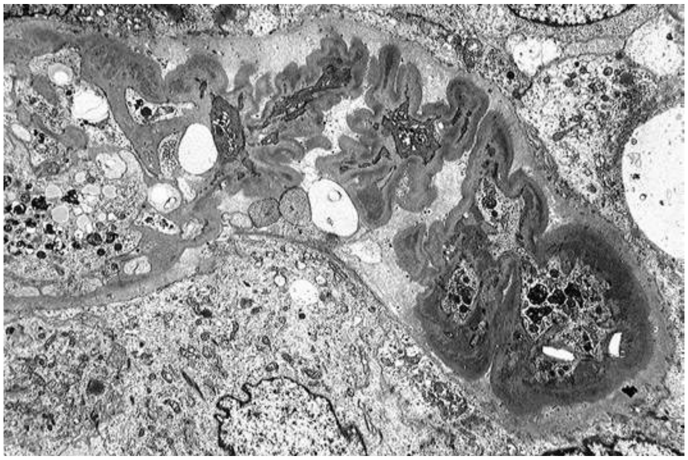

Fig. 18.10 Focal segmental glomerulosclerosis, collapsing variant. On electron microscopy, there is tight collapse of the glomerular capillaries with corrugated glomerular basement membrane. The overlying visceral epithelial cells appear detached and hypertrophied, with complete loss of foot processes. (×2500.)

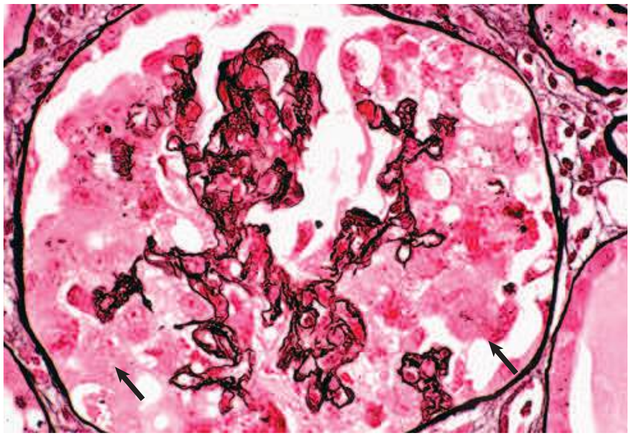

Fig. 18.11 Focal segmental glomerulosclerosis, collapsing variant, from pamidronate toxicity. The glomerular tuft is retracted, without appreciable increase in matrix material. The overlying visceral epithelial cells are enlarged and hyperplastic *(arrows),* with numerous intracytoplasmic vacuoles and protein resorption droplets. (Jones methenamine silver; ×400.)

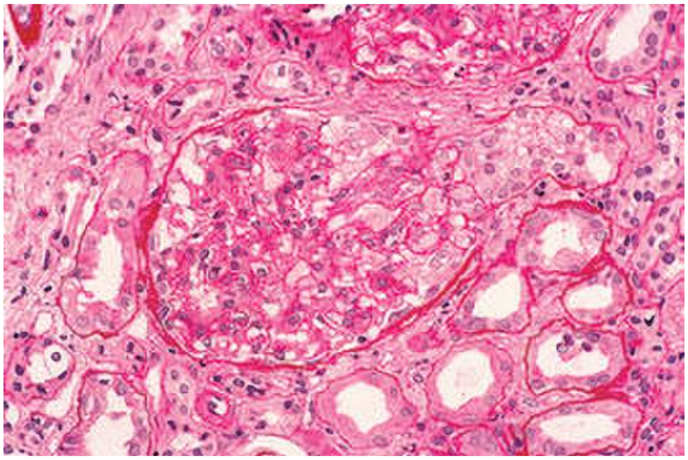

Fig. 18.12 Focal segmental glomerulosclerosis, tip lesion variant. A cellular tip lesion displays engorgement of glomerular capillaries by foam cells and adhesion of the involved segment to the origin of the proximal tubule (tubular pole). (PAS; ×250.)

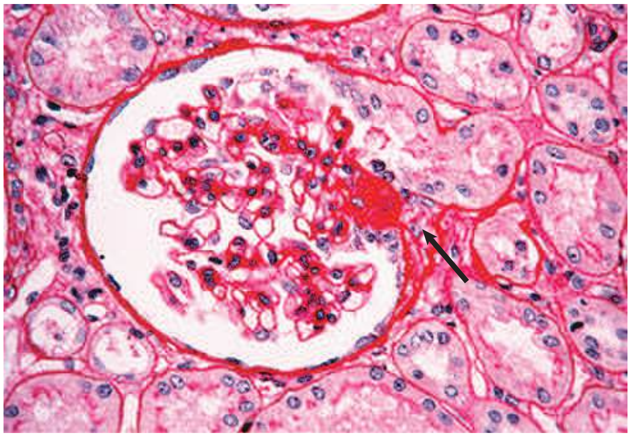

Fig. 18.13 Focal segmental glomerulosclerosis, tip lesion variant. A sclerosing tip lesion forms an adhesion to the tubular pole *(arrow).* (PAS; ×250.)

origin of the proximal tubule.[44,45,49] There is either adhesion between the tuft and Bowman capsule or confluence of swollen podocytes with parietal or tubular epithelial cells at the tubular lumen or neck. The segmental lesions may be cellular or sclerosing (Figs. 18.12 and 18.13). These lesions may evolve more centrally. The presence of perihilar sclerosis or collapsing sclerosis rules out the tip variant. In one study of FSGS tip lesions, biopsy specimens had glomerular tip lesions alone in 26% and glomerular tip lesions plus other peripheral FSGS lesions in the other 74%.[44] The degree of foot process effacement is usually severe. Most cases are primary and resemble MCD clinically. Higher shear stress and tuft prolapse at the tubular pole are likely to play a role in the morphogenesis of this lesion.[4]

Other Variants of Focal Segmental Glomerulosclerosis

Two histologic variants often included within the FSGS spectrum are FSGS with diffuse mesangial hypercellularity and C1q nephropathy (see Chapter 28).[1,50,51] FSGS with *diffuse mesangial hypercellularity* has lesions of FSGS on a background of generalized hypercellularity. By IF, there is diffuse mesangial positivity for IgM, with more variable mesangial staining for C3. EM reveals extensive foot process effacement without glomerular electron-dense deposits. This variant occurs almost exclusively in young children.

C1q nephropathy is defined by dominant or codominant IF staining for C1q, mesangial electron-dense deposits, and light microscopic findings resembling FSGS or MCD with variable mesangial hypercellularity. In one study, 17 patients had a light microscopic appearance of FSGS (including six collapsing and two cellular) and three of MCD.[50] In addition to C1q staining, biopsy specimens may show deposition of other immunoglobulins (particularly IgG) and complement components (C3), making it important to exclude other clinical disease such as lupus nephritis. In C1q nephropathy, electron-dense deposits are typically located in the paramesangial region subjacent to the GBM reflection. There is variable foot process effacement. The largest series of C1q nephropathy supports that many cases represent a subgroup of primary FSGS or MCD, whereas others are an idiopathic immune complex–mediated glomerulonephritis.[51]

Distinguishing Pathologic Features of Secondary Focal Segmental Glomerulosclerosis

Although the pathology of some secondary forms of FSGS resembles closely that of primary FSGS, there are several noteworthy differences.

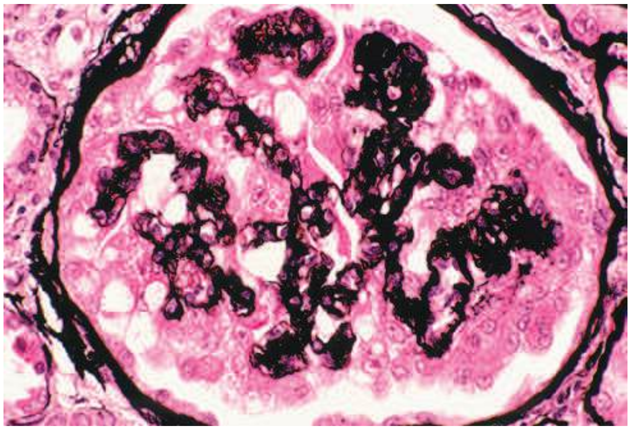

Fig. 18.14 HIV-associated nephropathy. A globally collapsed glomerulus shows marked visceral cell hypertrophy and hyperplasia. (Jones methenamine silver; ×400.)

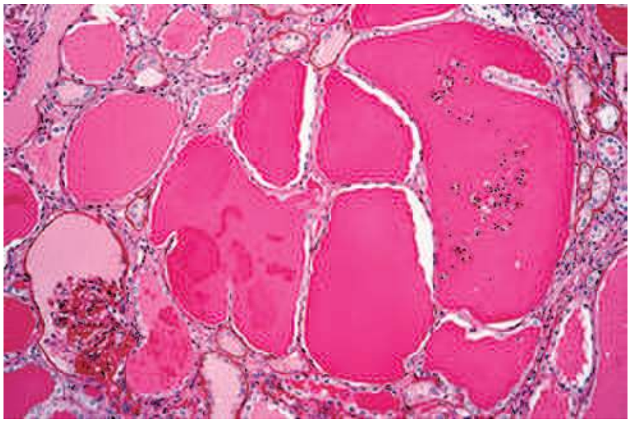

Fig. 18.15 HIV-associated nephropathy. At low power, the renal parenchyma contains abundant tubular microcysts with proteinaceous casts. The glomerulus is collapsed with dilated urinary space. (PAS; ×80.)

Whereas the light microscopic findings in HIV-associated nephropathy are similar to those of primary collapsing FSGS (Fig. 18.14), tubular microcysts are particularly common (Fig. 18.15). On EM, a major difference is the abundance of tubuloreticular inclusions in the glomerular endothelial cells of HIV-associated nephropathy. These "interferon footprints" consist of 24-nm interanastomosing tubular structures located within dilated cisternae of endoplasmic reticulum (Fig. 18.16). Tubuloreticular inclusions have become less frequent in patients treated with antiretroviral therapy.[53]

In secondary adaptive forms of FSGS, renal biopsy typically shows glomerulomegaly and predominantly perihilar lesions of segmental sclerosis and hyalinosis. In secondary FSGS resulting from loss of renal mass, such as from reflux nephropathy or hypertensive arterionephrosclerosis, FSGS is usually seen on a background of extensive global glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. In secondary FSGS related to sickle cell disease, glomerular hypertrophy and sclerosis are associated with capillary congestion by sickled erythrocytes and double contours of the GBM resembling those seen in chronic thrombotic microangiopathy. Importantly, in adaptive forms of FSGS, the degree of foot process effacement tends to be relatively mild, affecting less than 50% of the total glomerular capillary surface area, with correspondingly shorter foot process width (Fig. 18.17). In one study, a cutoff of more than 1500 nm for mean foot process width was able to distinguish primary from adaptive FSGS.[54]

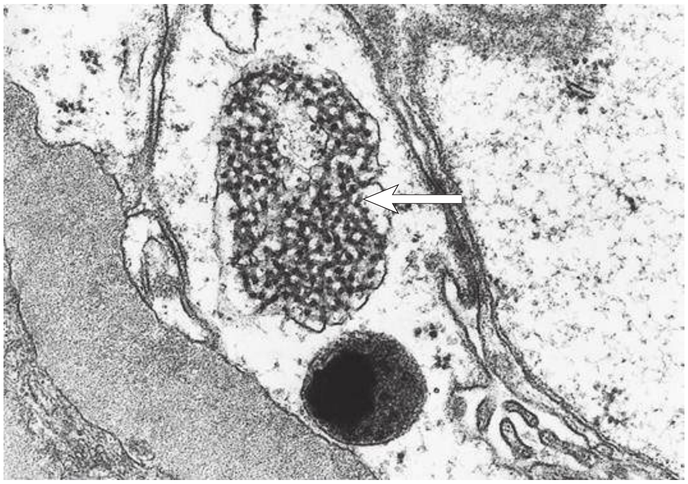

Fig. 18.16 HIV-associated nephropathy. The glomerular endothelial cell pictured here contains a large intracytoplasmic tubuloreticular inclusion ("interferon footprint"; *arrow*) composed of interanastomosing tubular structures within a dilated cisterna of endoplasmic reticulum. (Electron micrograph; ×15,000.)

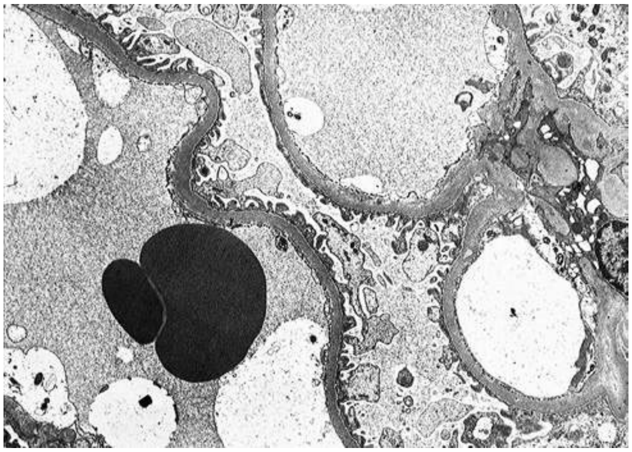

Fig. 18.17 Secondary focal segmental glomerulosclerosis (FSGS) from obesity. This patient with morbid obesity had glomerular hypertrophy and predominantly perihilar lesions of segmental sclerosis and hyalinosis on light microscopy. The foot processes show mild effacement involving approximately 20% of the glomerular capillary surface area despite the presence of nephrotic-range proteinuria. This mild degree of foot process effacement is less than that usually seen in primary FSGS. (Electron micrograph; ×2500.)

NATURAL HISTORY AND PROGNOSIS

The natural history of FSGS is varied.[31] Without response to therapy, the majority of patients with primary FSGS experience a progressive increase in proteinuria and progression to renal failure. Although some untreated patients undergo a spontaneous remission of proteinuria,[1,2] most unresponsive children and adults have a similar course and develop ESRD 5 to 20 years from presentation, with approximately 50% of such patients reaching ESRD by 10 years[1,2,55-57] (Fig. 18.18).

Certain epidemiologic, clinical, and histologic findings at diagnosis help predict the long-term course of patients with FSGS[1-3] (Box 18.3). Even after controlling for severity of proteinuria, hypertension, and other features, African Americans with FSGS experience a more rapid progression to ESRD than people of other races. At biopsy, reduced GFR, greater degrees of proteinuria, and greater degrees of interstitial

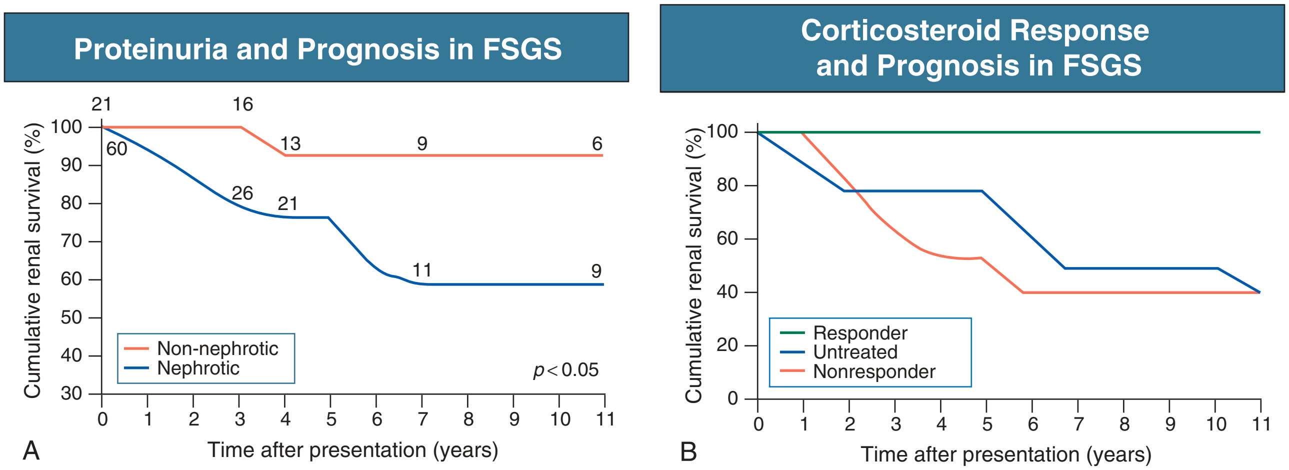

Fig. 18.18 **Prognosis in primary focal segmental glomerulosclerosis (FSGS).** (A) The risk for development of renal failure is related to the extent of proteinuria. Those with nephrotic-range proteinuria are much more likely to develop renal failure than those with low-grade proteinuria. The figures indicate the number of at-risk patients at different time points. (B) Corticosteroid-responsive patients are significantly less likely to develop renal failure than nonresponders and untreated patients. (Modified from reference 73.)

BOX 18.3 Risk Factors for Progressive Renal Disease in Focal Segmental Glomerulosclerosis

Clinical Features at Biopsy

- Severity of nephrotic-range proteinuria
- Elevated serum creatinine
- Black race

Histopathologic Features at Biopsy

- Collapsing variant
- Tubulointerstitial fibrosis

Clinical Features During Disease Course

- Failure to achieve partial or complete remission

fibrosis predict a more progressive course.[1,2,56] The degree of glomerulosclerosis has been much less consistent as a prognostic finding. Patients who experience a remission of proteinuria and the nephrotic syndrome have much better renal survival than those who do not.[1-3,48,57] Even patients with a partial remission of nephrotic syndrome have a lower rate of long-term renal failure.[57]

In general, outcomes are best for tip variant and worst for collapsing variant of primary FSGS, with intermediate outcome in FSGS NOS.[1,2,45,46] These differences held true even in a cohort of children and young adults with initially corticosteroid-resistant FSGS.[56] In a comparative series, the percentage of complete and partial remission was greatest for tip lesion (76%), lowest for collapsing variant (13%), and intermediate for cellular (44%) and FSGS NOS (39%).[46] There was a strong inverse correlation between remission rates and progression to ESRD among these subgroups. Accordingly, the likelihood of ESRD was greatest for collapsing variant (65%), lowest for tip lesion (6%), and intermediate for cellular variant (28%) and FSGS NOS (35%).[46] Although collapsing variant has the worst outcome among the FSGS variants, when patients with collapsing variant are matched with patients with FSGS NOS for baseline levels of renal function, proteinuria, and immunosuppression, responses to treatment are similar, highlighting the importance of early detection and aggressive therapy.[48]

TREATMENT

There is considerable debate about the appropriate treatment of patients with primary FSGS[1-3,59,60] (Fig. 18.19). In part, this relates to confusion between primary and secondary forms of the disease, including unrecognized genetic variants. Even after biopsy, it is not always clear whether an obese person with glomerulomegaly, FSGS, and nephrotic-range proteinuria has secondary or primary disease. Given any doubts, most clinicians would favor attempting to treat patients with nephrotic FSGS as if they had primary disease as long as the treatment does not have undue side effects. Moreover, the course of FSGS is variable, and only recently have clear prognostic features, such as histologic pattern, degree of proteinuria and presence of nephrotic syndrome, and degree of interstitial fibrosis, been defined.[45,46,56] Finally, although FSGS is common in adults, there are many therapeutic options with few randomized controlled trials (RCTs) on which to base judgment.[59] However, almost all patients with FSGS will benefit from good supportive care (e.g., blockade of the renin-angiotensin-aldosterone system), as described in Chapter 79.

In early studies, only 10% to 30% of patients with FSGS treated with corticosteroids or other immunosuppression for short periods experienced a remission of proteinuria and the relapse rate was high. Thus many nephrologists considered FSGS to be untreatable. A classic study documented that 44% of children with FSGS treated with immunosuppressive agents experienced a remission.[55] Although the response rate for treated adults was similar (39%), most of the adults never received immunosuppressive therapy. In general, in most patients with nephrotic syndrome, treatment will potentially benefit from a trial of immunosuppressive therapy.[58,60] However, benefit from use of immunomodulatory medicines in patients with asymptomatic proteinuria or sub-nephrotic proteinuria is unproven. Recent retrospective studies support the use of corticosteroids and other immunosuppressive agents over no treatment in preventing ESRD in FSGS.[58]

Corticosteroids

In trials using 6 months or longer courses of corticosteroids in primary FSGS, many patients experience a remission of nephrotic syndrome. In adults, therapy is usually with prednisone or prednisolone 1 mg/kg/day (maximum of 80 mg/day) or 1.5 to 2 mg/kg (maximum of 120 mg) every other day, for an initial period of 4 to 8 weeks, with subsequent

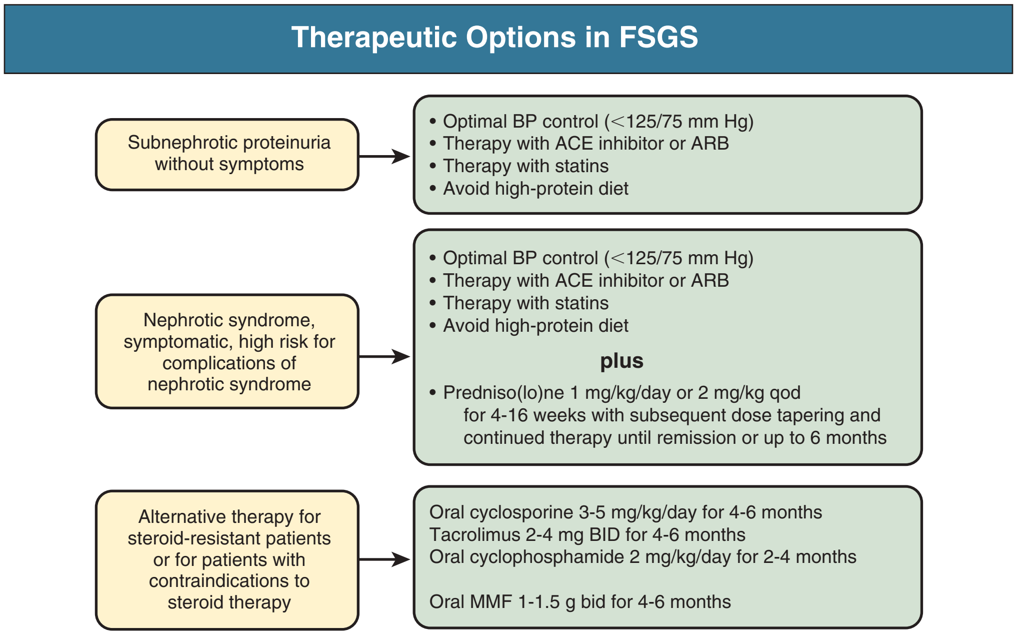
Therapeutic Options in FSGS
Subnephrotic proteinuria without symptoms
• Optimal BP control (<125/75 mm Hg)
• Therapy with ACE inhibitor or ARB
• Therapy with statins
• Avoid high-protein diet
Nephrotic syndrome, symptomatic, high risk for complications of nephrotic syndrome
• Optimal BP control (<125/75 mm Hg)
• Therapy with ACE inhibitor or ARB
• Therapy with statins
• Avoid high-protein diet
plus
• Predniso(lo)ne 1 mg/kg/day or 2 mg/kg qod for 4-16 weeks with subsequent dose tapering and continued therapy until remission or up to 6 months
Alternative therapy for steroid-resistant patients or for patients with contraindications to steroid therapy
Oral cyclosporine 3-5 mg/kg/day for 4-6 months
Tacrolimus 2-4 mg BID for 4-6 months
Oral cyclophosphamide 2 mg/kg/day for 2-4 months
Oral MMF 1-1.5 g bid for 4-6 months

Fig. 18.19 **Therapeutic options in focal segmental glomerulosclerosis (FSGS).** Treatment of secondary FSGS should be directed at the underlying cause whenever possible. For HIV-associated nephropathy, treatment with highly active antiretroviral therapy (HAART); for pamidronate nephrotoxicity, discontinue the medication; and for obesity-related glomerulopathy, weight loss. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *MMF,* mycophenolate mofetil.

tapering of the dose.[1-3,60] Initial response rates range from 40% to 80%. Nephrotic children typically receive an empiric 4- to 6-week course of prednisone (60 mg/m^2 body surface area) before a renal biopsy is performed if there is no remission. In children with biopsy-documented FSGS, 20% to 25% will achieve a complete remission with a short course of corticosteroids, but as many as 50% will remit with more intensive therapy. In adults, although no large prospective RCTs are available, more prolonged use of corticosteroids has led to much higher remission rates of nephrotic syndrome than in earlier studies.[1,2,60] The median duration of corticosteroid treatment for complete remission to be achieved is 3 to 4 months; most patients respond by 6 months. Thus most clinicians would treat all adult patients with nephrotic primary FSGS and those at risk for progressive disease with a prolonged course (at least 6 months) of daily or every-other-day corticosteroid therapy or other immunosuppressive medication in the hope of inducing a remission of nephrotic syndrome and preventing eventual ESRD. The Kidney Disease: Improving Global Outcomes (KDIGO) study guidelines recommend initial prednisone therapy in nephrotic patients with primary FSGS, with the high dose to be continued for a minimum of 4 weeks and a maximum of 16 weeks, with a slow taper over 6 months after achieving complete remission.[60] If there is no remission or significant reduction in proteinuria, many clinicians would rapidly taper off the daily prednisone or just discontinue the alternate-day corticosteroids without taper and proceed to another therapy.

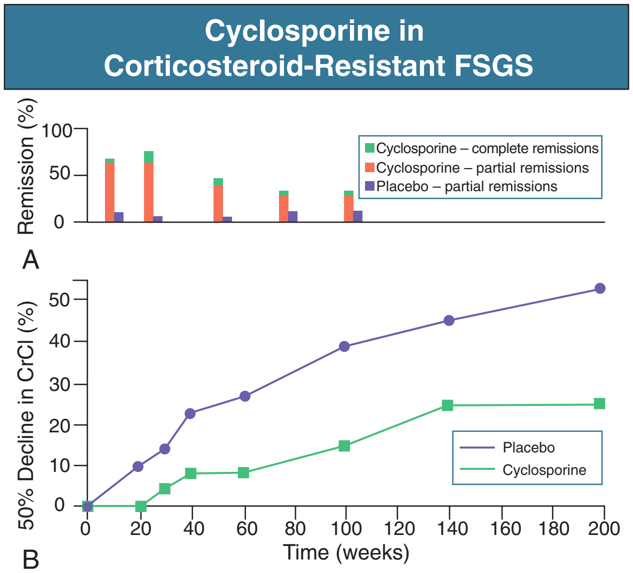

Fig. 18.20 **Cyclosporine in corticosteroid-resistant focal segmental glomerulosclerosis (FSGS).** Randomized controlled trial of 6 months of treatment with prednisolone and either cyclosporine or placebo. (A**)** Cyclosporine induces a partial or complete remission significantly more often than placebo. (B**)** Cyclosporine treatment results in a lower rate of decline in renal function than with placebo, even after 4 years; *CrCl,* creatinine clearance. (Modified from reference 54.)

Other Immunosuppressive Agents and Corticosteroid Resistant Patients

For many years, either chlorambucil or cyclophosphamide combined with corticosteroids was the treatment of choice for corticosteroid-resistant FSGS.[1,60,61] However, KDIGO guidelines specifically suggest that cyclophosphamide not be given to children with corticosteroid-resistant nephrotic syndrome and to use alternative medicines such as calcineurin inhibitors (CNIs) or mycophenolate mofetil.[60] In adults with FSGS treated with oral cyclophosphamide or chlorambucil, pooled data showed a high response rate for patients with corticosteroid dependence or intolerance, but a remission rate of less than 20% for corticosteroid-resistant patients.

Several studies have used low-dose cyclosporine, 3 to 6 mg/kg/day for 2 to 6 months, to treat corticosteroid-resistant FSGS[58,60,61] (Fig. 18.20). Complete plus partial remission has been achieved in 60% to 70% with cyclosporine versus only 17% to 33% in the placebo groups. In North

America, steroid-resistant adult patients with FSGS randomized to either cyclosporine with low-dose corticosteroids or the same low dose of corticosteroids alone for a 6-month period exhibited a much higher remission rate (12% complete and >70% complete or partial) in the group treated with cyclosporine.[60,61] Despite some relapses after cyclosporine discontinuation, the treated group still had significantly more remitters and better preserved GFR at long-term follow-up. Because there is a high relapse rate when cyclosporine is discontinued after only 6 months, many clinicians use a 1-year course with slow taper in patients who have had a favorable reduction of proteinuria with cyclosporine.[1,2,60] Although data on tacrolimus are more limited, results have been similar.[62] Because the major side effects of nephrotoxicity, hypertension, and hyperkalemia are the same for both cyclosporine and tacrolimus, choice may depend on other less severe, adverse side effects (e.g., gum swelling, tremor, hirsutism). Tacrolimus has been effective in some patients who are resistant to or intolerant of cyclosporine. Although CNIs are used to treat many patients with FSGS, almost all studies deal with corticosteroid-resistant patients, and there are no large RCTs comparing the two regimens. One recent large retrospective study of children and adults with FSGS found 173 treated with corticosteroids, 90 treated with CNIs with or without corticosteroids, and 183 not treated with immunosuppression.[53] Therapy with either corticosteroids or CNIs was associated with better renal survival than no immunosuppression. However, despite a suggestion of lower likelihood of ESRD in patients treated with other immunosuppression versus corticosteroids, the superiority of CNIs over corticosteroids could not be proven.[58] Additional studies are needed to determine whether CNI therapy for FSGS is superior to corticosteroids as a first-line therapy.[59]

Mycophenolate mofetil (MMF; mycophenolic acid) has been used successfully in several uncontrolled series of patients with FSGS.[63] A multicenter prospective RCT compared cyclosporine and a regimen of oral MMF plus dexamethasone in 138 children and adults up to age 40 who had corticosteroid-resistant FSGS.[64] The partial or complete remission rates were not significantly different. KDIGO guidelines suggests MMF and dexamethasone be considered for corticosteroid-resistant patients who do not tolerate CNIs.[60]

The use of sirolimus has been limited since the drug was reported to induce proteinuria and FSGS lesions in kidney transplant patients. In one series, sirolimus was associated with worsening of renal function, episodes of acute kidney injury, and no remissions of the nephrotic syndrome.[65] The addition of plasma exchange to immunosuppressive medications, which has been successful in treating some patients with recurrent FSGS in the renal allograft (see Chapter 111), has given mixed results in patients with disease in their native kidneys.[60] Likewise, use of low-density lipoprotein apheresis and galactose (a monosaccharide sugar with a high affinity for CLC1, a putative permeability factor in patients with FSGS) have been anecdotal.

Rituximab has been used in several studies of small numbers of patients with FSGS who have either failed other treatments or become dependent on these therapies.[66-68] It has proved more successful for steroid-dependent than steroid-resistant patients. Rituximab has not yet been studied in an RCT of patients with FSGS. Abatacept, which has proved effective in inducing remissions of nephrotic syndrome in only some patients with FSGS, is currently being studied in patients with resistant MCD and FSGS in a controlled cross-over trial.[17] Corticotropin (adrenocorticotropic hormone) has been beneficial in small numbers of patients with FSGS resistant to multiple other immunosuppressive agents, but it also has not been studied in large RCTs.[69]

Other Forms of Therapeutic Interventions

The role of immunosuppressive agents in the treatment of patients with sub-nephrotic levels of proteinuria and little damage on renal biopsy is unclear. Most nephrologists would not use corticosteroids to treat these patients. However, most would treat all patients with FSGS who have no contraindications with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), as well as statins, similar to other progressive glomerular diseases (see Chapter 79).

How best to prevent renal fibrosis in patients with FSGS is of particular interest. Neither pirfenidone, an oral TGF-β inhibitor, nor a monoclonal antibody against TGF-β have proven safe and effective in preventing progressive renal disease in FSGS.[70]

For patients with secondary forms of FSGS, attempts to treat the underlying cause should be the initial step in management. Patients with FSGS secondary to obesity and heroin nephropathy have had remissions of proteinuria after weight reduction or cessation of heroin use, respectively. In HIV-associated nephropathy, therapy with highly active antiretroviral drugs and blockers of the renin-angiotensin system has proven useful (see Chapter 56). The role of immunosuppression has not yet been proven in RCTs in any form of secondary FSGS. In all forms of secondary FSGS, supportive therapy as outlined in Chapter 79 is essential to prevent progressive renal disease. In patients with primary idiopathic or a secondary form of FSGS who remain nephrotic, fluid retention and edema can be managed with salt restriction and diuretics (see Chapter 15).

TRANSPLANTATION

Approximately 30% of patients with primary FSGS who develop ESRD and undergo renal transplantation develop recurrent FSGS in the allograft.[1,9,71,72] Children with early-onset FSGS, those with more severe proteinuria and a more rapid course to renal failure in their native kidneys, and, in the United States, White patients are all at greater risk for recurrence. In other countries non-Whites have a greater recurrence rate.[71,72] Those who have lost a prior allograft due to recurrent FSGS are at highest risk for recurrence. Recurrent FSGS is further discussed in Chapter 111.

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SELF-ASSESSMENT QUESTIONS

1. Use of which of the following medications has *not* been associated with proteinuria and the histologic pattern of focal segmental glomerulosclerosis (FSGS)?
   - **A.** Interferon β
   - **B.** Pamidronate
   - **C.** Sirolimus
   - **D.** Amlodipine
   - **E.** Lithium
2. Which histologic feature on renal biopsy suggests a "secondary" FSGS pattern related to "structural-functional adaption"?
   - **A.** Adhesions or synechiae to the Bowman capsule
   - **B.** Glomerulomegaly and perihilar segmental sclerosis and hyalinosis
   - **C.** Hypertrophy and hyperplasia of the visceral epithelial cells
   - **D.** Diffuse mesangial hypercellularity
   - **E.** Collapse of part of or all the glomerular tuft
3. Which of the following statements about the prognosis of idiopathic focal segmental glomerulosclerosis is *true*?
   - **A.** The outcome is worse for patients with the "tip" variant versus other patterns.
   - **B.** The outcome is better for patients with the collapsing variant versus other patterns.
   - **C.** Remission of proteinuria is a strong predictor of a favorable outcome.
   - **D.** African Americans have a prognosis similar to that of Whites if controlling for hypertension and degree of proteinuria.
   - **E.** The degree of glomerular sclerosis is the strongest histologic predictor of a poor renal outcome.

19

Inherited Causes of Nephrotic Syndrome

Shazia Ashraf, Friedhelm Hildebrandt

CLINICAL FEATURES OF NEPHROTIC SYNDROME

Nephrotic syndrome (NS) is caused by malfunction of the glomerular filter that leads to significant proteinuria (>3.5 g/day) with hypoalbuminemia, which in turn causes edema.[1,2] NS is classified by response or lack of response to a standardized corticosteroid therapy into steroid-sensitive (SSNS) versus steroid-resistant nephrotic syndrome (SRNS), respectively. SRNS accounts for approximately 15% of childhood cases with NS and frequently leads to chronic kidney disease (CKD).[3–6] SRNS constitutes the second most frequent cause of CKD in children.[6a] It carries a 33% risk for relapse in a renal transplant, thereby causing recurrence of CKD.[2] Adult-onset NS is heterogeneous and may include causes such as diabetic nephropathy, amyloid nephropathy, etc. SRNS manifests histologically as focal segmental glomerulosclerosis (FSGS), a lesion characterized by sclerosis and podocyte foot process effacement in a few capillary segments of a fraction of glomeruli.[7] Diffuse mesangial sclerosis (DMS) is a pathogenic finding that may occur in patients with early-onset NS. In DMS, light microscopy shows podocyte hypertrophy, mesangial matrix expansion, thickened basement membranes, and decreased size of glomerular capillary lumina. SRNS may rarely be associated with extrarenal manifestations such as neurologic defects[8] (Fig. 19.1).

MONOGENIC CAUSES OF NEPHROTIC SYNDROME ELUCIDATE ITS PATHOGENESIS

In the last 15 years, more than 44 recessive and 8 dominant genes have been discovered to cause NS in humans, if mutated[6] (Tables 19.1 and 19.2, Fig. 19.2). Identification of these single-gene causes of NS has revealed that the glomerular podocyte and the glomerular slit membrane that it maintains are the primary sites at which the pathogenesis of NS unfolds.[1,9] The power of identification of such single-gene causes of NS lies in the fact that recessive mutations almost always convey full penetrance and thereby represent the cause of NS (i.e., the etiology) rather than representing only an increased risk for acquiring disease (Box 19.1). Thus, if strict genetic criteria are being followed for the decision, in which mutations in the 52 monogenic genes are considered causative (Boxes 19.1 and 19.2), identification of the causative mutation allows for (1) unequivocal molecular genetic diagnosis, (2) establishment of genotype–phenotype correlations, (3) transfer of mutations into genetic animal models with detailed study of their detrimental effects, (4) etiologic stratification of participants for therapeutic studies by specific causative gene and mutation, and (5) discovery of distinct mutations that may be amenable to treatment.[6]

The capillary tuft of the renal glomerular filtering apparatus consists of four major components: (1) the fenestrated endothelial cell layer, (2) the glomerular basement membrane (GBM), (3) the epithelial podocyte layer, and (4) the mesangial cells that help shape the glomerular tuft (see Fig. 19.2) (see Chapter 1). Interdigitations of podocyte foot processes form the glomerular slit membrane between them, which is critical for the filtering process and retention of protein in the blood stream.[9a] The integrity of the glomerular slit membrane is lost in NS. Thus identification of monogenic causes of NS revealed dozens of proteins, each of which is an indispensable component of glomerular function, because loss of their function in a monogenic form of NS inescapably leads to proteinuria and FSGS. Therefore the discovery of genes that, if mutated, cause monogenic forms of NS significantly increased our understanding of glomerular filtration barrier physiology and of pathogenic mechanisms of NS.

This discovery started with the genes encoding the slit membrane proteins nephrin *(NPHS1),*[10] podocin *(NPHS2),*[11] and phospholipase C epsilon 1 (*PLCE1*).[12] In the meantime, acceleration of whole-exome sequencing and next-generation sequencing has permitted identification of more than 52 monogenic causes of NS, and this number is rapidly increasing (see references in Tables 19.1 and 19.2) (see Fig. 19.2). The majority of the patients with NS, in whom a single-gene cause is detected, show no response to steroid treatment. The encoded proteins map back onto distinct structural protein complexes and signaling pathways that reveal what is essential for glomerular function (see Fig. 19.2). These functional complexes include proteins involved in coenzyme Q_{10} (CoQ_{10}) biosynthesis, sphingosine-1-phosphate (S1P) metabolism, nuclear transcription factors, nucleoporins, lysosomal proteins, actin-regulating small GTPases of the Rho/Rac/Cdc42 family, glomerular slit membrane–associated components, actin-binding proteins, tRNA modification (KEOPS complex) and laminin/integrin receptors (focal adhesions) (see Fig. 19.2). Very recently, six genes *(EMP2, TNS2, DLC1*, *CDK20, ITSN1, ITSN2)* were identified in which recessive mutations surprisingly caused partially treatment-sensitive NS (see Table 19.1).[13,42]

GENOTYPE PHENOTYPE CORRELATIONS

Recessive Versus Dominant Steroid-Resistant Nephrotic Syndrome

One of the most important genotype–phenotype correlations in SRNS is the distinction between recessive versus dominant SRNS genes (see Tables 19.1 and 19.2). In recessive mutations, family history is most likely negative, because parents of individuals with recessive mutations will be healthy heterozygous carriers, and no one in the ancestry will have had the disease. If there is any inherited mutation, it will be occurring heterozygous only in ancestors. However, in dominant disease, one of the parents of an affected individual will most likely be affected, and the disease may have been handed down through multiple generations

BOX 19.1 Assignment of Autosomal Recessive Mutations as Disease Causing

Basic assumptions: (1) Defined clinical phenotype. (2) Known genes with similar phenotype have been excluded. (3) "Mutation" implies that an allele causes a disease phenotype. (4) Full penetrance (age related). (5) Two mutated alleles present, because disease genes are recessive.

Include Allele as Disease Causing if:

- Truncating mutation (stop, abrogation of start or stop, obligatory splice, frame-shift) in an expressed gene (well annotated mRNA, conservation, protein expression) or:
- Missense mutation if:
  - Continuously conserved at least up to *Danio rerio (zebrafish)* OR:
  - Loss of function in human allele is supported by functional data AND
  - Allele segregates with the affected status in the family.

Exclude Allele as Disease Causing if:

- Heterozygous allele frequency >1% (in EVS server: 13,000 control chromosomes) or reported homozygous in ExAC (The Exome Aggregation Consortium).
- Nonsegregation (e.g., "compound heterozygous" in cis; *affected* family member is *without* the variant; *unaffected* parent has homozygous variant).

Modified from Lovric et al, NDT 2015.

Alleles considered as disease causing for recessive (Box 19.1) and dominant (Box 19.2) genes are then confirmed via Sanger sequencing for segregation with the phenotype within the family.

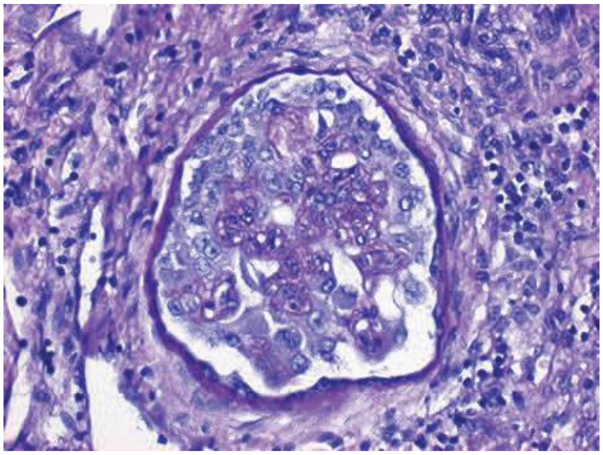

Fig. 19.1 Renal histologic image of an individual with steroid-resistant nephrotic syndrome. Periodic acid–Schiff (PAS) reaction staining reveals diffuse mesangial sclerosis (DMS). (Original magnification, ×40.) (Courtesy Prof. Kerstin Amann, University of Erlangen, Germany.)

(except for situations of incomplete penetrance or in the case of de novo mutations). Therefore the detection of dominant mutations has important clinical implications, such as in situations of a planned living-related donor kidney transplantation. Here, it will be important to exclude the presence of the disease-causing mutation in the related donor, in whom SRNS may not yet have manifested because of incomplete penetrance, which can be a feature of autosomal dominant inheritance.

BOX 19.2 Assignment of Autosomal Dominant Mutations as Disease Causing

Include Allele as Disease Causing if:

- Truncating mutation (stop, abrogation of start or stop, obligatory splice, frame-shift) in an expressed gene (well annotated mRNA, conservation, protein expression) or:
- Missense mutation if:
  - Continuously conserved at least up to *Danio rerio (zebrafish)* OR:
  - Loss of function in human allele is supported by functional data AND:
  - Allele segregates with the affected status in the family AND:
  - Mutations in known genes with similar phenotype have been excluded.

Exclude Allele as Disease Causing if:

- Reported homozygous or heterozygous (allele frequency >0.1%) in ExAC (The Exome Aggregation Consortium).
- Nonsegregation (e.g., *affected* family member is *without* the variant; but if an affected family member is with the allele, consider "incomplete penetrance" and "variable expressivity").

Modified from Lovric et al, NDT 2015.

Gene-Specific Phenotypes

Specific SRNS genes or distinct mutations (alleles) in the same SRNS gene may cause characteristic phenotypes, and this may pertain to age of onset of disease.[5,14] A recent study employed next-generation sequencing and tested a large international cohort of patients with SRNS manifesting before 25 years of age (1783 families).[5] The diagnostic panel included 21 genes with a recessive mode of inheritance and 6 genes with a dominant mode of inheritance. A genetic diagnosis was established in 526 of 1783 families (29.5%) in whom the condition manifested before 25 years of age.[5] Stringent criteria for calling mutations "disease causing" were applied (see Boxes 19.1, 19.2). This study showed that four genes were major SRNS genes: *NPHS2* (9.93%), *NPHS1* (7.34%), *WT1* (4.77%), and *PLCE1* (2.17%). The highest rate of mutation detection of 69.4% was in the youngest group of patients (0 to 3 months), and this percentage decreased with older age (Fig. 19.3). The second important finding from this study was that mutations in some recessive genes such as *NPHS1, LAMB2,* or *PLCE1* caused onset of NS in early childhood, whereas other recessive genes, such as *NPHS2,* lead to onset in later childhood (see Fig. 19.3). There is a tendency that mutations in dominant SRNS genes (*TRPC6, INF2, ANLN,* and *ARHGAP24*) cause adult-onset SRNS,[15–18] with the exception of *WT1*,[5] whereas mutations in recessive genes cause childhood-onset of NS. In this study, mutations in *WT1* showed a biphasic distribution with a first peak at 4 to 12 months and a second peak for age of onset beyond 18 years (see Fig. 19.3).[5] The most prevalent SRNS dominant genes are *INF2, TRPC6,* and *ACTN4* (see Fig. 19.3).[14]

Allele-Specific Phenotypes

"Multiple allelism" is a genetic mechanism in which specific mutations within the same gene may determine a phenotypic range, such as for age of onset of SRNS. For instance, in *NPHS2* mutations, the mutation R138Q causes onset in early childhood,[19,20] whereas the mutation R229Q in compound heterozygosity with specific second mutations causes later onset SRNS.[21] Currently only "strong" mutations are labeled disease causing (see Boxes 19.1 and 19.2), but it is very likely that a high percentage of adult-onset SRNS is caused by "weak" recessive alleles, which have not yet been revealed as deleterious (such as the allele R229Q of

TABLE 19.1 **Forty-Four Recessive Genes That Cause Monogenic Steroid-Resistant or Steroid-Sensitive or Dependent Nephrotic Syndrome, If Mutated.**

Gene Symbol*	Protein	Pathogenic Pathway (Comments)	Reference(s)
Autosomal Recessive, Steroid-Resistant NS			
ADCK4	AarF domain containing kinase 4	CoQ_{10} biosynthesis	Ashraf et al, J Clin Invest. 2013
ARHGDIA	Rho GDP dissociation inhibitor (GDI) α	RHO GTPase signaling	Gee et al, J Clin Invest. 2013
AVIL	Advillin	Actin regulation	Rao et al., J Clin Invest. 2017
CD2AP	CD2-associated protein	—	Lowik et al, Kid Int. 2007
COQ2	Coenzyme Q_{10} 4-hydroxybenzoate Polyprenyltransferase-2	CoQ_{10} biosynthesis	Diomedi-Camassei et al, J Am Soc Nephrol. 2007
COQ6	Coenzyme Q_{10} monooxygenase-6	CoQ_{10} biosynthesis	Heeringa et al, J Clin Invest. 2011
CRB2	Crumbs homolog 2	Tight junction protein	Ebarasi et al, Am J Hum Genet. 2015
CUBN	Cubilin (intrinsic factor-cobalamin receptor)	Tubular proteinuria	Ovunc et al. J Am Soc Nephrol. 2011
DGKE	Diacylglycerol kinase, epsilon	5 (Glomerular microangiopathy)	Ozaltin et al, J Am Soc Nephrol. 2013
FAT1	FAT tumor suppressor homolog 1	6 (Glomerulotubular nephropathy)	Gee et al, Nat Commun. 2016
ITGA3	Integrin, α3 (antigen CD49C, α 3 subunit of VLA-3 receptor)	GBM architecture	Has et al, N Engl J Med. 2012
ITGB4	Integrin, β4	GBM architecture	Kambham et al, Am J Kid. Dis 2000
KANK1	KN motif and ankyrin repeat domain containing protein 1	RHO GTPase signaling	Gee et al, J Clin Invest. 2015
KANK2	KN motif and ankyrin repeat domain containing protein 2	RHO GTPase signaling	Gee et al, J Clin Invest. 2015
KANK4	KN motif and ankyrin repeat domain containing protein 4	RHO GTPase signaling	Gee et al, J Clin Invest. 2015
LAGE3	L antigen family member 3	(GMS)	Unpublished
LAMB2	Laminin, β2	Abnormal GBM (Pierson syndrome)	Zenker et al, Hum Mol. Genet 2004
MAGI2	Membrane associated guanylate kinase, WW and PDZ domain containing 2	RhoA regulation/signaling	Unpublished
MT-TL1	Mitochondrially encoded tRNA leucine 1	Mitochondrial function	Yasukawa et al, J Biol Chem. 2000
MYO1E	*Homo sapiens* myosin 1E (MYO1E)	(Childhood familial FSGS)	Mele et al, N Engl J Med. 2011
NPHS1	Nephrin	Slit diaphragm (CNS, Finnish type)	Kestila et al, Mol Cell. 1998
NPHS2	Podocin	Slit diaphragm	Boute et al, Nat Genet. 2000
NUP85	Nucleoporin 85 kDa	Nucleoporins	Unpublished
NUP93	Nucleoporin 93 kDa	Nucleoporins, SMAD signaling	Braun et al, Nat Genet. 2016
NUP107	Nucleoporin 107 kDA	nucleoporins	Miyake et al, Am J Hum Genet. 2015
NUP133	Nucleoporin 133 kDA	nucleoporins	Unpublished
NUP205	Nucleoporin 205 kDA	nucleoporins, SMAD signaling	Braun et al, Nat Genet. 2016
OSGEP	O-sialoglycoprotein endopeptidase	tRNA modification (GMS)	Unpublished
PDSS2	Prenyl (decaprenyl) diphosphate synthase, subunit 2	—	Lopez et al, Am J Hum Genet. 2006
PLCE1	Phospholipase C, epsilon 1	(Isolated DMS)	Hinkes et al, Nat Genet. 2006
PTPRO	Protein tyrosine phosphatase, receptor type, O	—	Ozaltin et al, Am J Hum Genet. 2011
SCARB2	Scavenger receptor class B, member 2	7 (Myoclonus epilepsy and glomerulosclerosis)	Berkovic et al, Am J Hum Genet. 2008
SGPL1	sphingosine phosphate lyase 1	Sphingosine-1-phosphate (S1P) metabolism	Lovric et al, J Clin Invest. In press
SMARCAL1	SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily a-like 1	(Schimke immuno-osseous dystrophy)	Boerkoel et al, Nat Genet. 2002
TP53RK	TP53-regulating kinase	tRNA modification (GMS)	Unpublished
TPRKB	TP53RK-binding protein	tRNA modification (GMS)	Unpublished
WDR73	WD repeat domain 73	(GMS)	Colin et al, Am J Hum Genet. 2014; Vodopiutz et al, Hum Mut. 2015; and Jinks et al, Brain. 2015

TABLE 19.1 Forty-Four Recessive Genes That Cause Monogenic Steroid-Resistant or Steroid-Sensitive or Dependent Nephrotic Syndrome, If Mutated.—cont'd

Gene Symbol*	Protein	Pathogenic Pathway (Comments)	Reference(s)
XPO5	Exportin 5	SMAD signaling (Nuclear export protein in concert with nucleoporins)	Braun et al, Nat Genet. 2016
Autosomal Recessive, Steroid Sensitive/Dependent NS			
CDK20	Cyclin dependent kinase 20	RhoA regulation/signaling	Unpublished
DLC1	Deleted in liver cancer 1	RhoA regulation/signaling	Unpublished
EMP2	Epithelial membrane protein 2	Increased CAV1	Gee et al, Am J Hum Genet. 2014
ITSN1	Intersectin 1	Cdc42 regulation/signaling	Unpublished
ITSN2	Intersectin 2	Cdc42 regulation/signaling	Unpublished
TNS2	Tensin 2	RhoA regulation/signaling	Unpublished

*Disease caused by mutations in this gene can be found at: http://ncbi.nml.nih.gov/OMIM

CAV1, Caveolin 1; *CNS,* congenital nephrotic syndrome; *CoQ,* coenzyme Q; *DMS,* diffuse mesangial sclerosis; *FSGS,* focal segmental glomerulosclerosis; *GBN,* glomerular basement membrane; *GMS,* Galloway-Mowat syndrome; *NS,* nephrotic syndrome.

TABLE 19.2 Eight Dominant Genes That Cause Monogenic Steroid-Resistant Nephrotic Syndrome, If Mutated

Gene symbol*	Protein	Pathogenic pathway (Comments)	Reference(s)
Autosomal Dominant, Steroid Resistant NS			
ACTN4	Actinin, α4	Abnormal assemble-disassemble of actin (FSGS type 1)	Kaplan et al, Nat Genet. 2000
ANLN	Anillin, actin-binding protein	—	Gbadegesin et al, J Am Soc Nephrol. 2014
ARHGAP24	Rho GTPase-activating protein 24	Increased podocyte membrane ruffling and hypermotility through potentiation of Rac1 activity in vitro	Akilesh et al, J Clin Invest. 2011
INF2	Inverted formin, FH2 and WH2 domain containing	(FSGS type 5)	Brown et al, Nat Genet. 2010
LMX1B	LIM homeobox transcription factor 1, β	(Nail-patella syndrome)	Vollrath et al, Hum Mol Genet. 1998 and McIntosh et al, Am J Hum Genet. 1998
MYH9	Myosin heavy chain 9	Fechtner syndrome	Heath et al, Am J Hum Genet. 2001
TRPC6	Transient receptor potential cation channel, subfamily C, member 6	Increased calcium transients leading to disruption of podocyte structure or function (FSGS type 2)	Winn et al, Science. 2005
WT1	Wilms tumor 1	Abnormal urogenital development (Denys-Drash and Frasier syndromes)	Jeanpierre et al, Am J Hum Genet. 1998

*Disease caused by mutations in this gene can be found at http://ncbi.nml.nih.gov/OMIM.

FSGS, Focal segmental glomerulosclerosis; *NS,* nephrotic syndrome.

NPHS2). One of the most important tasks in the future of renal genetics is to define, using cell-based and animal model systems, deleteriousness of "weak" recessive mutations that cause adult-onset SRNS.

SYNDROMIC PROTEINURIC RENAL DISEASE

Galloway-Mowat Syndrome

Galloway-Mowat syndrome is clinically defined by microcephaly, abnormal cerebral gyral patterns, seizures, psychomotor retardation, cranial dysmorphia, and a renal glomerulopathy that is inherited in an autosomal recessive pattern. The renal disease generally presents as NS within the first few months of life, with rapid progression to ESRD. Most affected children die before age 6 years. Recessive mutations of *WDR73* gene have been identified in patients with Galloway-Mowat syndrome.[22] Very recently, recessive mutations have been identified in KEOPS complex genes (*LAGE3*, *OSGEP*, *TP53RK*, and *TPRKB*) as new monogenic causes of Galloway-Mowat syndrome.[43]

Denys-Drash and Frasier Syndromes

Denys-Drash syndrome (DDS) and Frasier syndrome (FS) are two rare and related conditions caused by mutations of the Wilms tumor gene, *WT1*. The gene responsible for both DDS and Frasier syndrome is *WT1*,

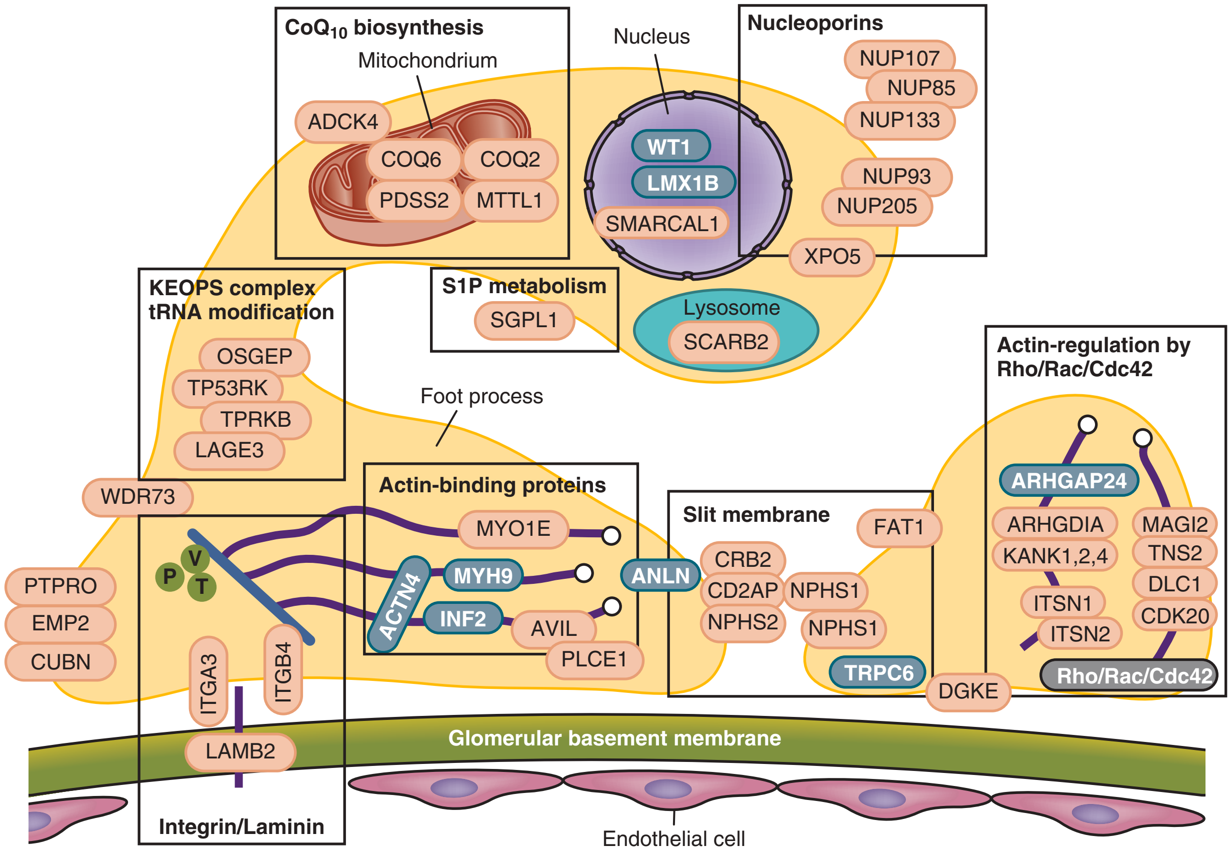
CoQ10 biosynthesis
Mitochondrium
ADCK4
COQ6
COQ2
PDSS2
MTTL1
Nucleus
WT1
LMX1B
SMARCAL1
Nucleoporins
NUP107
NUP85
NUP133
NUP93
NUP205
XPO5
KEOPS complex
tRNA modification
OSGEP
TP53RK
TPRKB
LAGE3
S1P metabolism
SGPL1
Lysosome
SCARB2
Foot process
Actin-regulation by
Rho/Rac/Cdc42
ARHGAP24
ARHGDIA
MAGI2
KANK1,2,4
TNS2
DLC1
ITSN1
ITSN2
CDK20
Rho/Rac/Cdc42
WDR73
Actin-binding proteins
MYO1E
MYH9
ACTN4
INF2
AVIL
PLCE1
ANLN
Slit membrane
FAT1
CRB2
CD2AP
NPHS1
NPHS2
NPHS1
TRPC6
DGKE
PTPRO
EMP2
CUBN
V
P
T
ITGA3
ITGB4
LAMB2
Integrin/Laminin
Glomerular basement membrane
Endothelial cell

Fig. 19.2 Proteins whose genes, if mutated, cause monogenic steroid-resistant nephrotic syndrome define essential podocyte functions. Identification of 52 single-gene (monogenic) causes of steroid-resistant nephrotic syndrome (SRNS) has revealed the renal glomerular epithelial cell, the podocyte, as central to the pathogenesis of SRNS, because all of the related genes are relevantly expressed in podocytes. Identification of genes that, if mutated, cause SRNS revealed distinct proteins and functional pathways as essential for glomerular function, because a mutation in any single one of them is sufficient to cause SRNS. This figure depicts a simplified cross section through a podocyte *(vanilla color)* and a neighboring podocyte foot process, which is attached to the glomerular basement membrane *(green)* by laminin-integrin receptors. Forty-four proteins whose genes, if mutated, cause recessive monogenic forms of SRNS are shown in *red,* and eight proteins whose genes, if mutated, cause dominant forms of SRNS are shown in *blue* (see Tables 19.1 and 19.2). The 52 SRNS-related proteins were found to be part of protein–protein interaction complexes that participate in defined structural components or signaling pathways of podocyte function (shown within *black dashed frames*). These proteins include proteins involved in coenzyme Q_{10} biosynthesis, S1P metabolism, nuclear transcription factors, nucleoporins, lysosomal proteins, actin-regulating small GTPases of the Rho/Rac/Cdc42 family, glomerular slit membrane–associated components, actin-binding proteins, tRNA modification (KEOPS complex), and laminin/integrin receptors (focal adhesions). Proteins that are encoded by recessive NS genes are marked in *red:* ADCK4, aarF domain containing kinase 4; ARHGDIA, Rho GDP dissociation inhibitor (GDI) α; AVIL, advillin; CD2AP, CD2-associated protein; CDK20, cyclin-dependent kinase 20; COQ2, coenzyme Q2 4-hydroxybenzoate polyprenyltransferase; COQ6, coenzyme Q_{10} monooxygenase 6; CRB2, crumbs family member 2; CUBN, cubilin (intrinsic factor-cobalamin receptor); DGKE, diacylglycerol kinase; DLC1, deleted in liver cancer 1; EMP2, epithelial membrane protein 2; FAT1, FAT tumor suppressor homolog 1; ITGA3, integrin, α3; ITGB4, integrin, β4; ITSN1, intersectin 1; ITSN2, intersectin 2; KANK, KN motif and ankyrin repeat domains 1/2/4; LAGE3, L antigen family member 3; LAMB2, laminin, β2; MAGI2, membrane-associated guanylate kinase, WW and PDZ domain containing 2; MTTL1, mitochondrial tRNA leucine 1; MYO1E, *Homo sapiens* myosin 1e; NPHS1, nephrin; NPHS2, podocin; NUP85, nucleoporin 85 kDa; NUP93, nucleoporin 93 kDa; NUP107, nucleoporin 107 kDa; NUP133, nucleoporin 133 kDa; NUP205, nucleoporin 205 kDa; OSGEP, O-sialoglycoprotein endopeptidase; PDSS2, prenyl (decaprenyl) diphosphate synthase, subunit 2; PLCE1, phospholipase C, ε 1; PTPRO, protein tyrosine phosphatase, receptor type O; SCARB2, scavenger receptor class B member 2; SGPL1, sphingosine-1-phosphate lyase 1; SMARCAL1, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1; TNS2, tensin 2; TP53RK, TP53-regulating kinase; TPRKB, TP53RK-binding protein; WDR73, WD repeat domain 73; and XPO5, exportin 5. Proteins that are encoded by dominant NS genes are marked in *blue:* ACTN4, actinin, α4; ANLN, anillin; ARHGAP24, Rho GTPase-activating protein 24; INF2, inverted formin, FH2 and WH2 domain containing; LMX1B, LIM homeobox transcription factor 1-β; MYH9, myosin, heavy chain 9; TRPC6, transient receptor potential cation channel, subfamily C, member 6; WT1, Wilms tumor 1. (Modified from reference 6.)

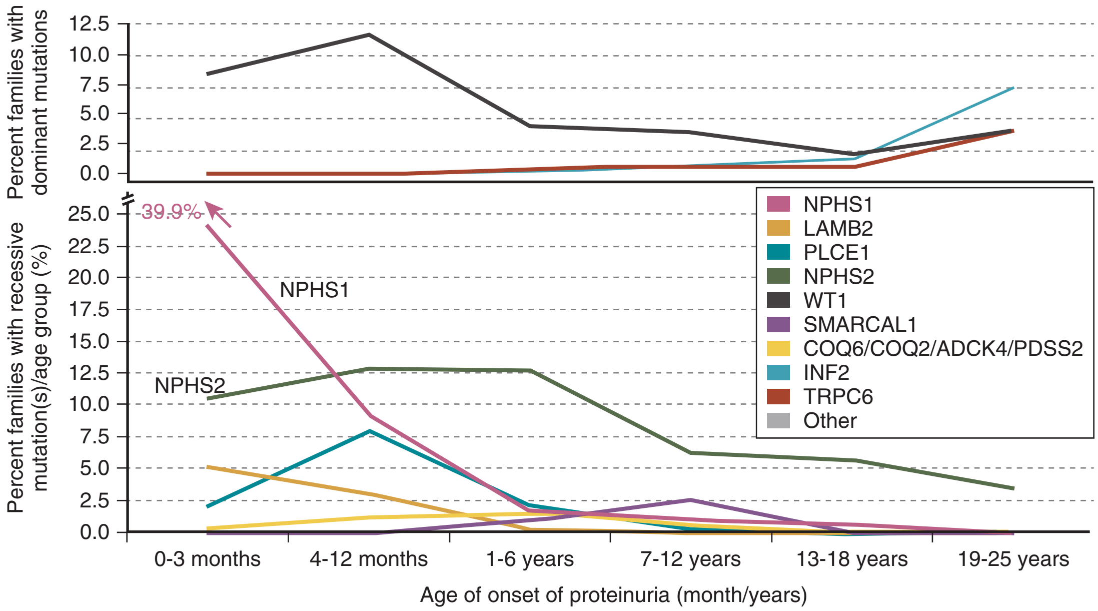

Fig. 19.3 **Relative distribution of SRNS-causing genes by their age of onset.** Percentages of families in an international cohort with SRNS that manifested at 25 years of age and resulted from mutations in monogenic genes are interconnected by lines between age groups and shown in different colors for each causative gene (*lower panel* for recessive genes, *upper panel* for dominant genes). *NPHS1* mutations *(red), LAMB2 (orange),* and *PLCE1 (dark blue)* have early age of onset and are rarely found in patients older than 6 years. The dominant genes *INF2 (light blue)* and *TRPC6 (brown)* manifest in early adulthood and *WT1 (black)* shows a biphasic distribution with a first peak at 4 to 12 months and a second peak for age of onset beyond 18 years *(upper panel).* These findings are compatible with the notion that mutations in recessive disease genes are found more frequently in early-onset disease, whereas mutations in dominant genes more frequently cause adult-onset disease. (Modified from reference 5.)

which is a transcription factor involved in gonad and kidney development. Both syndromes are characterized by male pseudohermaphroditism, progressive glomerulopathy, and development of genitourinary tumors. DDS and FS have been distinguished by differences in nephropathy, with patients with DDS developing DMS in contrast to focal and segmental glomerulosclerosis (FSGS) that occurs in patients with FS. Patients with DDS have a high incidence of severe hypertension and rapid progression to ESRD by 3 years of age. In FS, male pseudohermaphrodites typically present in phenotypic females with amenorrhea or NS, or both. NS may be slowly progressive, usually over 10 years, and is typically steroid resistant. These patients develop ESRD in the second or third decade of life, with most cases occurring at puberty (see Fig. 19.3). Some cases manifest in much younger children.[23] Rarely, an XX karyotype with a less severe phenotype may not be identified clinically as Frasier syndrome and may manifest only with renal disease.

Nail-Patella Syndrome

Nail-patella syndrome (hereditary onycho-osteodysplasia; Fong syndrome) is an autosomal dominant disease, caused by mutations in the LIM homeodomain transcription factor *LMX1B,* involving abnormalities of the skeleton, nails, eyes, and kidneys (see Chapter 46). Affected patients have nail dysplasia, absence of or poorly developed patellas, dysplasia of the iliac horns and elbows, cataracts, glaucoma, and glomerulopathy with NS.

Pierson Syndrome

In 1963 Pierson and colleagues described cases of congenital NS with distinct eye abnormalities.[24] In this rare syndrome, patients present with hypoplasia of the ciliary body and iris, resulting in fixed narrowing of the pupil (microcoria) as well as massive proteinuria at birth and rapid progression to ESRD. Most patients die before 2 months of age. DMS exemplifies the renal pathology findings in the Pierson syndrome. The resultant mutation is in *LAMB2,* which codes for the laminin β2 chain.

GENETIC TESTING BY WHOLE EXOME SEQUENCING

Because of the high likelihood (~30%) of finding a causative monogenic mutation in SRNS with onset before 25 years of age,[5,14] and because of the many important implications for disease management, it is advisable to suggest genetic testing to all individuals with FSGS or with persistent proteinuria that manifests before the age 25 years. In many parts of the world, such testing, that is, by whole-exome sequencing (WES) is currently only available as part of research initiatives (www.genetests.org, www.renalgenes.org). In adult-onset FSGS, genetic testing is indicated if there is a positive family history. The likelihood of finding a causative (recessive) mutation is even higher in individuals with SRNS from consanguineous marriages. Recent advances in high-throughput sequencing, and the continuous reduction in cost for WES, have made mutation analysis less time and cost intensive.[25] WES allows sequencing of all approximately 330,000 exons in the human genome (i.e., the exome). WES to identify causative mutations is currently available by commercial genetic diagnostics or on a research basis (www.renalgenes.org). Exon-containing fragments of DNA are first enriched from the patient's DNA sample, using solid-phase/array-based hybridization of the patient's DNA fragments with bait probes that represent the sequences of all exons to capture the entire exome.[26] It is currently assumed that WES offers a theoretical likelihood of 86% of detecting the disease-causing mutation in a recessive disease.[27] Besides its use to detect mutations in an established list of known disease-causing genes, WES was also very successfully applied to detecting novel disease-causing genes (e.g., *ADCK4, EMP2, CRB2, FAT1, NUP93, KEOPS* complex, and *TNS2*).[25,28–32,42,43] After exome capture, all exon fragments are sequenced using a high-throughput next-generation sequencing platform.[33] The sequences are then compared with the human reference genome (www.genome.ucsc.edu) for genetic sequence variants that differ between the patient and a normal reference sequence. Any given two individuals differ by approximately 2000 genetic variants.[34] However, in a monogenic disease, only one or two variants in a single gene represent the causative mutation. Finding the relevant causative genetic mutation requires an elaborate a priori reduction process, by genetic mapping,[35] application of stringent genetic criteria (see Boxes 19.1 and 19.2), or applying algorithms on "deleteriousness" of genetic variants. Before mutation analysis is performed, genetic counseling is advisable.

SPECIFIC THERAPIES FOR HEREDITARY NEPHROTIC SYNDROME

The identification of causative monogenic mutations may have important therapeutic consequences in some cases. This is very important for patients who carry mutations in a gene of CoQ_{10} biosynthesis (*COQ2, COQ6, ADCK4,* or *PDSS2*).[28,36] In these patients, treatment with CoQ_{10} may be indicated. An illustrative example was recently published: a 5-year old girl presented with SRNS, and a causative homozygous mutation was detected in the *COQ6* gene.[36] She had previously responded partially to the treatment with cyclosporine A. The treatment with CoQ_{10} was commenced during the remission, and her proteinuria was minimal. After the inadvertent interruption of CoQ_{10} administration, the proteinuria relapsed into the nephrotic range, but after the reinstitution of therapy the proteinuria normalized.[36] Individuals with recessive mutations in *PLCE1, EMP2, TNS2, DLC1, CDK20, ITSN1,* or *ITSN2* may respond fully to the treatment with steroids or cyclosporine A.[12,29,42] The individuals with *CUBN* may benefit the treatment with vitamin B_{12},[37] and those with *ARHGDIA* mutations theoretically may be responsive to the eplerenone treatment.[38] Donor splice-site heterozygous mutations in intron 9 of the *WT1* gene have been reported to alter the alternative splicing leading to two WT1 isoforms, with (+) or without (−) three amino acids, lysine-threonine-serine (KTS), between zinc fingers 3 and 4. The detection of *WT1* mutations often has clinical consequences as, for instance, KTS+ mutations, depending on karyotype, may confer a risk for gonadoblastoma.[39] TRPC6 mutations may potentially be amenable to treatment with calcineurin inhibitors.[15,40] In childhood SRNS, that manifests beyond the first year of life, often one treatment attempt is made applying standard steroid therapy.[41] If a response is lacking, treatment attempts are made with calcineurin inhibitors, and more recently mycophenolate or rituximab. In summary, identifying monogenic causes of SRNS also may help define important genotype–phenotype correlations and may provide molecular genetic diagnosis to the families involved.

FUTURE DIRECTIONS

The recent identification of monogenic causes of NS that manifests before 25 years of age in the surprisingly high fraction of approximately 12% to 45% in individuals worldwide[5] has offered many advantages for future management of NS. With the available sequencing technology and the continuous reduction in sequencing cost, WES on a commercial or research basis should now be offered to every patient with persistent proteinuria occurring before 25 years of age, or in patients with FSGS manifesting after age 25 years and positive family history, if the patient consents for clinical genetic testing for the following reasons: (1) it will provide the patient and families with an unequivocal cause-based diagnosis, (2) it may uncover a form of NS that is amenable to treatment (e.g., coenzyme Q_{10}–related genes), (3) it may allow avoidance of a renal biopsy procedure, (4) it will further unravel the puzzle of pathogenic pathways of NS, and (5) it will permit personalized treatment options for NS, based on genetic causation in way of "precision medicine." Very recently, single-gene causes of partially steroid-sensitive NS (SSNS) also have been discovered, and the discovery of these genes may offer inroads into understanding the therapeutic actions of glucocorticoids in SSNS.[42]

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SELF-ASSESSMENT QUESTIONS

1. A 23-year-old man is admitted to the hemodialysis unit after inpatient hemodialysis initiation for end-stage renal disease (ESRD) secondary to focal segmental glomerulosclerosis (FSGS). In your initial evaluation, you obtain a detailed family history in which the patient discloses that his maternal grandfather, mother, and two brothers have all received dialysis. You suspect familial FSGS as the cause of renal disease in this family. Based on the pattern of kidney disease occurrence in his family, what mode of inheritance would you suspect in this patient?
   - **A.** Autosomal recessive
   - **B.** X-linked recessive
   - **C.** Autosomal dominant
   - **D.** X-linked dominant
2. You are called to consult on a patient with newly diagnosed FSGS. Her family history is significant for multiple family members with advanced chronic kidney disease (CKD) or ESRD requiring renal replacement therapy. Three family members are known to have had renal transplants without recurrence of disease. You construct a family pedigree that suggests an autosomal dominant inheritance pattern. Of the known genetic mutations to cause autosomal dominant FSGS, which gene may be affected in this patient?
   - **A.** CD2AP
   - **B.** MYO1E
   - **C.** CTN4
   - **D.** NPHS2 (podocin)
3. Genetic mutations affecting which of the following cell populations have been identified as a cause of familial FSGS?
   - **A.** Glomerular epithelial
   - **B.** Glomerular endothelial
   - **C.** Glomerular mesangial
   - **D.** Tubular epithelial
4. What is the approximate likelihood of finding a monogenic cause of steroid-resistant nephrotic syndrome that manifests by 25 years of age?
   - **A.** 10%
   - **B.** 30%
   - **C.** 50%
   - **D.** 80%
5. You are consulted on a 5-year-old girl with significant nephrotic range proteinuria. On genetic analysis, she is found to have a homozygous missense mutation in the COQ6 gene. Which of the following would be the most appropriate treatment that could help improve her condition?
   - **A.** Steroids
   - **B.** Coenzyme Q_{10}
   - **C.** Eplerenone
   - **D.** Calcineurin Inhibitors

20

Membranous Nephropathy

David J. Salant, Daniel C. Cattran

Definition

Membranous nephropathy (MN) is an immune complex glomerular disease in which immune deposits of immunoglobulin G (IgG) and complement components develop predominantly or exclusively beneath podocytes on the subepithelial surface of the glomerular capillary wall. Podocyte injury resulting from the immune deposits increases glomerular permeability to plasma proteins, which results in proteinuria and potentially in nephrotic syndrome.[1,2] *Primary* (formerly called *idiopathic*) MN is an organ-specific autoimmune disease. It accounts for about 75% to 80% of patients with MN and typically occurs in the absence of any identifiable initiating event. It is the most common cause of primary nephrotic syndrome in older (>60 years) white adults, but the age range is broad and patients may present for the first time as teenagers.[3] Various conditions have been identified in association with MN, some of which are likely to be causal, and are known as *secondary* MN (Table 20.1). The term *membranous* refers to thickening of the glomerular capillary wall on light microscopy of a renal biopsy, but the entity now referred to as *membranous nephropathy* is defined by immunofluorescence and electron microscopy (EM). These techniques reveal diffuse, finely granular immune deposits on immunofluorescence and electron-dense deposits in the subepithelial space that are now regarded as pathognomonic of MN. Consequently, MN is a pathologic diagnosis made in patients with proteinuria whose glomeruli exhibit these immune deposits without associated hypercellularity or inflammatory changes.

ETIOLOGY AND PATHOGENESIS

Experimental Membranous Nephropathy

Much of what we know about the pathogenesis of MN derives from observations in animal models.[4] Studies of the Heymann nephritis model of MN in rats in the late 1970s established that the subepithelial immune deposits form in situ when circulating antibodies bind to an intrinsic ("fixed") antigen in the glomerular capillary wall. The antigen was subsequently identified as *megalin,* a large (~600 kD) transmembrane receptor of the low-density lipoprotein receptor family expressed on the basal surface of rat podocytes. Binding of circulating antimegalin antibodies induces capping and shedding of the antigen-antibody complexes, where they bind to the underlying glomerular basement membrane (GBM), resist degradation, and persist for weeks or months as immune deposits characteristic of MN (Fig. 20.1A). In this model, proteinuria is caused by antibodies in the immune deposits that overcome local complement regulatory mechanisms and activate complement in situ. The primary mechanism involves sublethal podocyte injury induced by the complement membrane attack complex C5b-9, which triggers a cascade of structural and functional changes, including oxidative injury, calcium influx, activation of cytosolic phospholipase A_2, production of arachidonic acid metabolites and cytokines, endoplasmic reticulum stress, DNA damage, alterations in the ubiquitin-proteasome system, and disruption of the actin cytoskeleton[4] (Fig. 20.2). Podocyte foot process effacement is likely the result of the collapse of the actin cytoskeleton and loss of cell-GBM adhesion complexes, and the loss and displacement of slit diaphragms are associated with the onset of severe, nonselective proteinuria. Podocyte injury also leads to the production of new extracellular matrix (ECM) proteins that are laid down between and around the immune deposits, giving rise to the characteristic "spikes" and GBM thickening that are hallmarks of MN.

Another mechanism of subepithelial immune deposit formation involves planted antigens[2] (see Fig. 20.1B). This is best exemplified by animal models immunized with cationized bovine serum albumin (cBSA). The cBSA binds to negatively charged residues in the GBM, where it serves as a target for circulating anti-BSA antibodies. As in the Heymann nephritis model, podocyte injury and proteinuria result from local complement activation.

Human Membranous Nephropathy

Evidence has recently been obtained that both fixed and planted antigen mechanisms are involved in human MN (see Fig. 20.1). The first demonstration that circulating antibodies reactive with an intrinsic podocyte antigen may be involved in MN was provided by an unusual case of antenatal MN induced by the transplacental passage of alloantibodies to neutral endopeptidase (NEP), a known podocyte protein.[5] The mother of the affected child was found to be deficient in NEP and had been immunized during a previous pregnancy and, like subsequent cases, produced complement-fixing anti-NEP alloantibodies. Although antibodies to anti-NEP do not account for primary MN, alloantibodies probably explain the development of de novo MN after renal transplantation and MN in the setting of chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation (see Table 20.1). The predominant autoimmune system responsible for primary MN is that associated with autoantibodies directed at the M-type phospholipase A_2 receptor (PLA_2R) on podocytes.[6] Circulating anti-PLA_2R antibodies are detectable in the serum of 75% to 80% of patients with primary MN from all ethnic groups and are rarely found in secondary MN.[2,7] The antibodies are predominantly IgG4 and, as in the Heymann nephritis model, the antigen (PLA_2R) and antibodies (anti-PLA_2R) co-localize in the immune deposits in primary (but not in secondary) MN.[8,9] PLA_2R is a transmembrane protein of the mannose receptor family[10] (Fig. 20.3).[11-13] Although it has been shown to undergo constitutive endocytosis and is involved in the production of eicosanoids, reactive oxygen

TABLE 20.1 Classification of Conditions and Agents Associated With Membranous Nephropathy

Primary
Anti-PLA$_2$R associated (70%-80%)
Idiopathic (20%-30%)
Anti-THSD7A (up to 5%)

Secondary	**Common**	**Uncommon**
Autoimmune diseases	Class V lupus nephritis	Rheumatoid arthritis Autoimmune thyroid disease IgG4-related systemic disease Anti-GBM and ANCA-associated crescentic glomerulonephritis
Infections	Hepatitis B	Hepatitis C virus (HCV) Human immunodeficiency virus (HIV) Syphilis Schistosomiasis
Malignancy	Solid tumors (colon, stomach, lung, prostate)	Non-Hodgkin lymphoma Chronic lymphocytic leukemia (CLL) Melanoma
Drugs or toxins	Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 (COX-2) inhibitors	Mercury-containing compounds Gold salts D-Penicillamine, bucillamine
Miscellaneous		Sarcoidosis Anticationic bovine serum albumin

Alloimmune
Graft-versus-host disease after hematopoietic stem cell transplantation
De novo membranous nephropathy in renal allograft
Fetomaternal alloimmunization to neutral endopeptidase

ANCA, Antineutrophil cytoplasmic antibody; *GBM,* glomerular basement membrane; *IgG,* immunoglobulin G; *Anti-THSD7A,* anti-thrombospondin type 1 domain–containing 7A.
The list excludes conditions for which only a single case has been reported or the lesions were atypical of membranous nephropathy.

BOX 20.1 Clinical Features of Membranous Nephropathy

- Rare in children: Less than 5% of total cases of nephrotic syndrome
- Common in adults: 15% to 50% of total cases of nephrotic syndrome, depending on age; increasing frequency after 40
- Males > females in all adult groups
- Whites > Asians > African Americans > Hispanics
- Nephrotic syndrome in 60% to 70%
- Normal or mildly elevated blood pressure at presentation
- “Benign” urinary sediment
- Nonselective proteinuria
- Tendency to thromboembolic disease*
- Other features of secondary causes: Infection, drugs, neoplasia, systemic lupus erythematosus

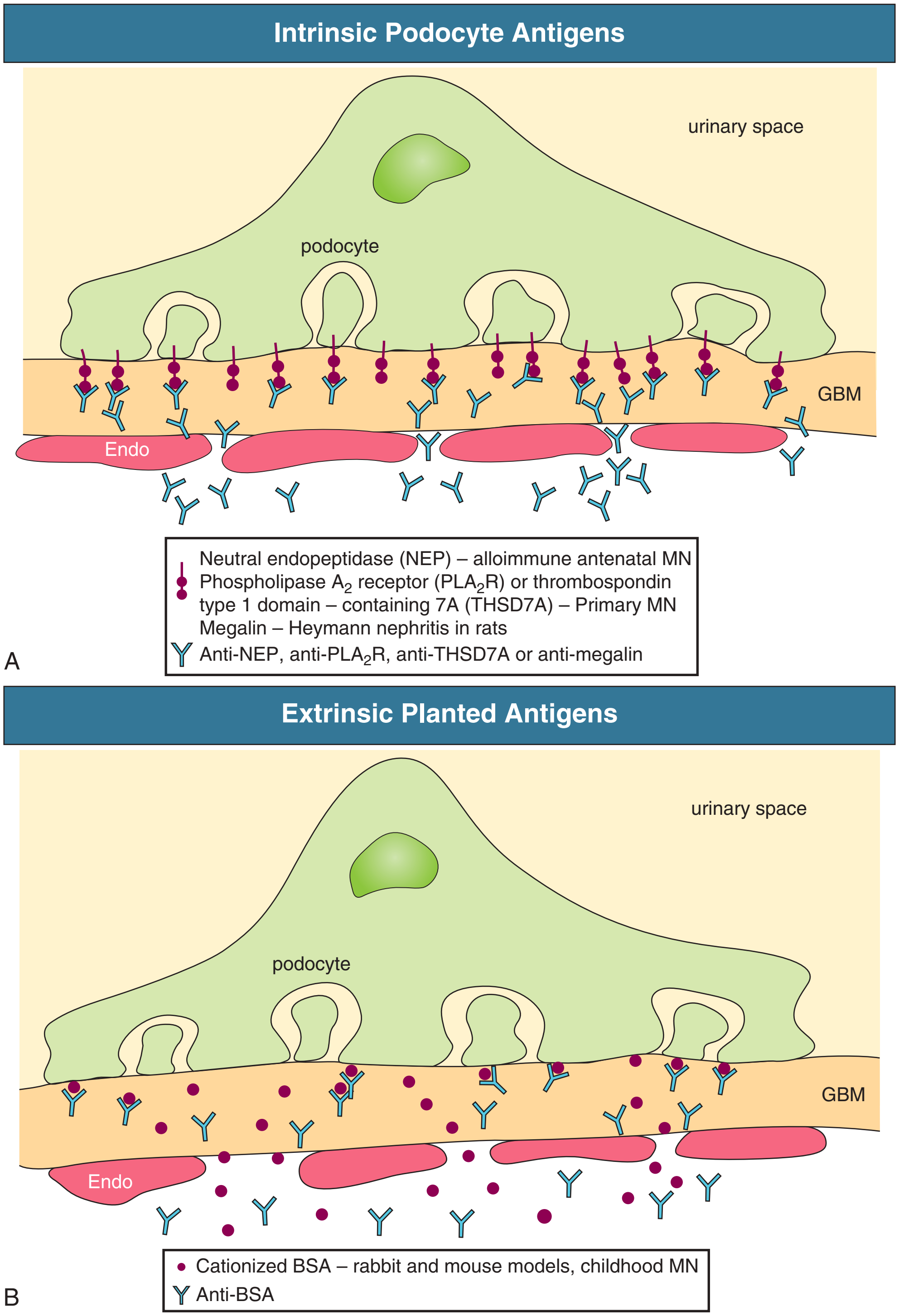
*Deep venous thrombosis, renal vein thrombosis, and pulmonary embolism.

species, DNA damage, and cellular senescence, its role in podocytes is unknown. Recently, antibodies to a second podocyte antigen, thrombospondin type 1 domain–containing 7A (THSD7A) were identified in patients with anti-PLA$_2$R-negative MN.[14] THSD7A is also expressed on podocytes and like PLA$_2$R redistributes to form the subepithelial immune deposits. It accounts for about 5% of cases of primary MN in Western countries, but appears to be more prevalent in Japanese patients with primary MN.[15] Reactivity to certain intracellular antigens, including aldose reductase, SOD2, and enolase, has been detected in primary MN and may contribute to the progression of podocyte injury. The best evidence of a planted antigen mechanism in MN is that described in children with MN who have been exposed to cBSA, presumably in bottled milk. In such cases, as in the animal models, the cBSA localizes in the GBM, where it forms complexes with circulating anti-BSA.[16] Planted antigens also may be responsible for immune deposition in class V (membranous) lupus nephritis and hepatitis B virus (HBV)–associated MN.

The resolution of MN depends on remission of the immune response, the extent of podocyte damage, and expansion of the GBM. In cases in which immunologic remission occurs before extensive podocyte loss and GBM remodeling, complete recovery is possible. On the other hand, proteinuria may persist for several weeks or months until the normal architecture is restored. Once there is extensive podocyte loss, proteinuria persists despite immunologic remission, and glomerular sclerosis, tubular atrophy, and interstitial fibrosis may ensue.

EPIDEMIOLOGY AND GENETICS

MN may occur at any age and in all ethnic groups, but primary MN is twice as common in men than in women and is rare in children. Primary MN has its peak incidence during the fourth and fifth decades of life (Box 20.1). In comparison, MN in childhood is more often secondary (e.g., caused by HBV). Primary MN is the most common cause of nephrotic syndrome in nondiabetic white adults, with an estimated annual incidence of 8 to 10 cases per 1 million population in Western countries. Reported variation in incidence may reflect specific country/physician indication for kidney biopsy but could also represent real differences related to socioeconomic status, ethnicity, or environment. Although association with certain human leukocyte antigen (HLA) class II immune response genes indicated a genetic predisposition, primary MN is not a familial disease, except in rare patients with more than one affected family member. The genetic predisposition became more evident after the discovery of PLA$_2$R as the major antigen, when studies from Korea and Taiwan documented a significant association with nonsynonymous single-nucleotide polymorphisms (SNPs)[17,18] in the first C-type lectin-like domain (CTLD) of PLA$_2$R (see Fig. 20.3), a region that is known to undergo conformational changes, as well as another in CTLD7. A subsequent genome-wide association study conducted by a European consortium revealed strong associations with a noncoding SNP in *PLA2R1* (rs4664308) and another in HLA-DQA1 (rs2187668), a member of HLA class II that includes isoforms that predispose carriers to autoimmunity.[19] Although each of these two associated SNPs was significant alone, the odds ratio of MN was almost 80 in individuals who were homozygous for both HLA-DQA1 and *PLA2R1* variants. Despite this, no unique coding variants have been found in *PLA2R1* that explain the association. Other genetic studies have suggested that *PLA2R1* variants may contribute to the severity or likelihood of MN progression. Alternatively, the interaction of *PLA2R1* with the autoimmune predisposition conferred by HLA class II may set the stage for an external trigger to initiate MN.[1,2] An example of such a trigger might be exposure to environmental pollutants.[20]



Intrinsic Podocyte Antigens

Extrinsic Planted Antigens

urinary space
podocyte
GBM
Endo
Neutral endopeptidase (NEP) – alloimmune antenatal MN
Phospholipase A_2 receptor (PLA_2R) or thrombospondin type 1 domain – containing 7A (THSD7A) – Primary MN
Megalin – Heymann nephritis in rats
Anti-NEP, anti-PLA_2R, anti-THSD7A or anti-megalin
A
urinary space
podocyte
GBM
Endo
● Cationized BSA – rabbit and mouse models, childhood MN
Anti-BSA
B

Fig. 20.1 Mechanisms of in situ immune complex formation in experimental and human membranous nephropathy (MN). (A) Circulating antibodies may cross the glomerular capillary wall and bind to podocyte *(Podo)* antigens exposed on the foot process, as in Heymann nephritis in rats (megalin), alloimmune MN (neutral endopeptidase), and primary MN (PLA_2R or THSD7A). *Endo,* Glomerular endothelial cell; *GBM,* glomerular basement membrane. (B) Certain extrinsic antigens such as cationized bovine serum albumin *(BSA)* may bind to sites in the GBM and serve as planted antigens and form deposits with circulating antibody.

CLINICAL AND SEROLOGIC MANIFESTATIONS

From 70% to 80% of all patients with MN present with the nephrotic syndrome. The remaining 20% to 30% present with asymptomatic subnephrotic proteinuria (<3.5 g/24 h). Proteinuria is nonselective. Microscopic hematuria is common (30% to 40%), but red blood cell (RBC) casts are rare and suggest a different glomerular pathologic process. In primary MN, serologic tests for anti-PLA_2R are positive in 75% to 80% of cases,[1,2] whereas serum complement levels are normal despite evidence of intraglomerular complement activation and serologic

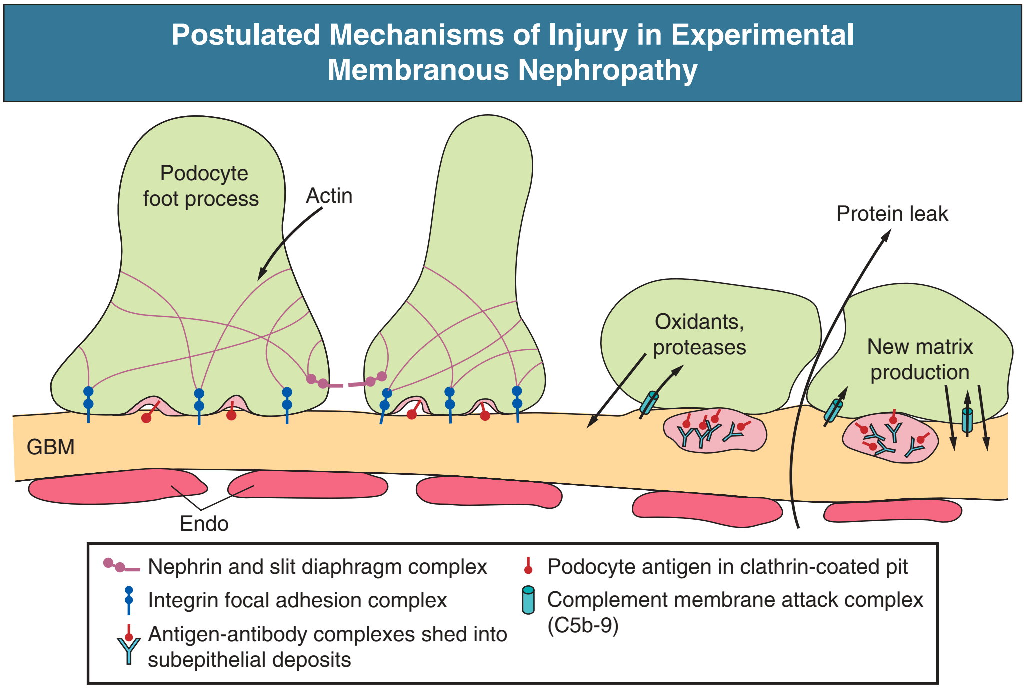

Postulated Mechanisms of Injury in Experimental Membranous Nephropathy
Podocyte foot process
Actin
Protein leak
Oxidants, proteases
New matrix production
GBM
Endo
Nephrin and slit diaphragm complex
Integrin focal adhesion complex
Antigen-antibody complexes shed into subepithelial deposits
Podocyte antigen in clathrin-coated pit
Complement membrane attack complex (C5b-9)

Fig. 20.2 **Postulated mechanisms of injury in experimental membranous nephropathy.** Antibodies against a podocyte antigen in clathrin-coated pits on the foot processes (left podocyte) form complexes that are shed to form deposits in the subepithelial space (right podocytes) and induce complement activation leading to formation of C5b-9. Insertion of C5b-9 is insufficient to cause lysis but stimulates the podocyte to release a host of inflammatory mediators. Disruption of the actin cytoskeleton causes altered cell-matrix adhesion and loss or displacement of slit diaphragms, leading to foot process effacement and loss of the filtration barrier to protein. New matrix production by the damaged podocytes expands the glomerular basement membrane *(GBM)* between and around the deposits. *Endo,* Glomerular endothelial cells.

markers (e.g., antinuclear antibodies, antineutrophil cytoplasmic antibody [ANCA], rheumatoid factor) are normal or absent. At diagnosis, only 10% to 20% of MN patients have hypertension. Renal function is usually normal at presentation, with only a small fraction (<10%) presenting with renal impairment (Table 20.2). These presenting features can be modulated by age or preexisting hypertension; tubulointerstitial and vascular changes on biopsy may be related to these factors rather than to the severity of the MN.[21] This is supported by recent evidence that age per se does not influence the rate of progression in MN but does influence the glomerular filtration rate (GFR) at presentation. Other complications related to nephrotic syndrome include dyslipidemia, a high prevalence of thromboembolic events and increases in cardiovascular events (see later discussion).

PATHOLOGY

The earliest pathologic feature of MN is the formation of subepithelial immune complexes of IgG and complement along the outer surface of the capillary wall in which glomeruli appear histologically normal and therefore may be mistaken for minimal change disease (MCD) if only light microscopy is performed. MN begins with the formation of immune complexes at the interface of the podocyte and GBM, with subsequent changes in the podocyte, deposition of new ECM material between and around the immune deposits, thickening of the GBM (membranous change), and, in some cases, focal glomerulosclerosis, tubular atrophy, and interstitial fibrosis.

Light Microscopy

In the earliest stages of MN, the glomeruli and interstitium appear normal on light microscopy, and the diagnosis is made by immunohistologic examination and EM (Fig. 20.4A). The next stage of MN involves a homogeneous thickening of the capillary wall, seen with light microscopy in sections stained with hematoxylin and eosin or with periodic acid–Schiff (PAS) reagent (see Fig. 20.4B). On silver methenamine staining, early projections of the GBM between deposits may be detected in a characteristic spike-like configuration (see Fig. 20.4C). Later, lucencies may develop in the GBM as immune deposits are resorbed, resulting in craters within the thickened GBM.

Leukocyte infiltration is absent in glomeruli in MN, probably because chemotactic products of complement activation follow filtration forces into the urinary space rather than diffusing backward into the capillary lumen, and the intervening GBM prevents immune adherence mechanisms from being operative. As a result, the pathologic lesion of MN is characterized only by changes in podocytes and basement membrane, without associated glomerular hypercellularity.

The podocyte response to this form of injury includes effacement of foot processes visible only by EM. In general, there are no visible mesangial or endothelial cell abnormalities. The presence of significant mesangial hypercellularity suggests immune deposit formation in the mesangium and is more consistent with a secondary MN, such as class V lupus nephritis (see Chapter 26). In some patients with heavy proteinuria and progressive disease, glomeruli exhibit reduced podocyte numbers and areas of focal sclerosis that resemble secondary focal segmental glomerulosclerosis (FSGS; see Chapter 18). These patients often have a more rapidly progressive course and a poor response to therapy. These sclerotic lesions may be a consequence of glomerular hypertrophy accompanied by an inability of terminally differentiated podocytes to proliferate leading to areas of denuded GBM, attachment to the Bowman capsule, and subsequent capillary collapse. As in all glomerular diseases, tubulointerstitial injury is common and correlates

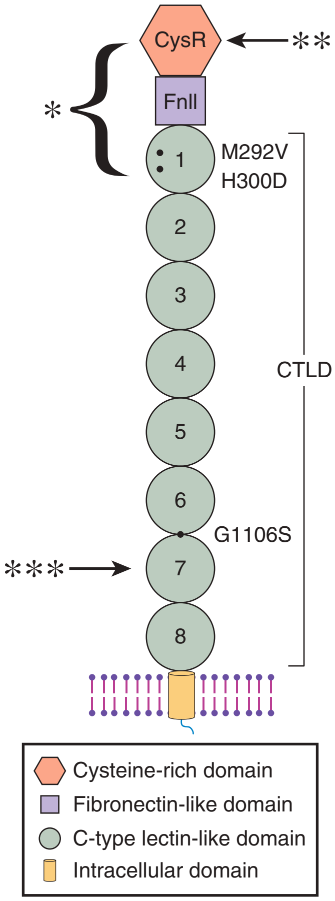


Fig. 20.3 **Structural domains of phospholipase A_2 receptor (PLA_2R).** The M-type phospholipase A_2 receptor is a transmembrane protein and receptor for secretory PLA_2 (CTLD5). The N-terminal region from the cysteine-rich domain through CTLD4 of other members of the mannose receptor family is known to exist in extended or folded configurations. PLA_2R is involved in the production of eicosanoids, reactive oxygen species, DNA damage, and cellular senescence. Its role in podocytes is unknown. The sites of polymorphisms associated with primary membranous nephropathy are shown as black dots and the location of epitopes identified by anti-PLA_2R are shown as asterisks.[14-16] *CysR,* Cysteine-rich (ricin B) domain; *FnII,* fibronectin II-like domain; *CTLD,* C-type lectin-like domains 1-8; *SNPs,* single-nucleotide polymorphisms.

with both renal function and the level of proteinuria. Some studies suggest the long-term outcome correlates in general with the severity of the tubulointerstitial damage (see Chapter 78).

Immunohistology

The pattern of granular glomerular capillary wall staining for IgG in MN is characteristic and easily recognizable by immunohistologic findings (Fig. 20.5A). Positive staining for IgG marks the finely granular subepithelial deposits, which are present on the outer surface of all capillary walls. The predominant IgG subclass in primary MN is IgG4. Positive staining for IgG1 or IgG3, IgA, IgM, or significant staining in the glomerular mesangium suggests lupus or other causes of secondary MN as an underlying mechanism.[22] κ and λ light-chain staining are typically equal, but rare cases of MN secondary to monoclonal IgG, including anti-PLA_2R have been reported.[23] Complement C3 is also present in most cases of active disease and usually reflects staining for C3c, a breakdown product of C3b that is rapidly cleared. Consequently, positive C3 staining probably reflects active, ongoing immune deposit formation. When sought, staining for C5b-9 is generally present as well, consistent with the proposed pathogenetic role of C5b-9 in this disease.[4] Strong C1q staining is not typically found in primary MN (<20% of cases) and is more common in lupus-associated MN.[24] Positive staining for C4d in the absence of C1q also has been described in primary MN.[25] Another feature that helps distinguish primary and secondary MN is the presence of PLA_2R staining in the immune deposits in a pattern that co-localizes with IgG in anti-PLA_2R–associated MN but not in secondary MN (see Fig. 20.5B).[6,8,9] Thus several histopathologic features help distinguish primary and secondary forms of MN (Table 20.3).

TABLE 20.2 Diagnosis and Management of Patients With Membranous Nephropathy

Patient Groups	Test
All patients	Blood pressure Renal function (serum creatinine and creatinine clearance) Urinalysis Urine protein excretion (24-hour urine or urine protein-creatinine ratio) Serum albumin Serum cholesterol, including LDL/HDL Renal biopsy Anti-PLA_2R
Associated disease	Hepatitis B (HBs antigen) Hepatitis C (HCV antibody) Antinuclear antibody (ANA), anti–double-stranded DNA (hallmark of systemic lupus erythematosus) Complement C3, C4 (usually normal in idiopathic MN)
Selected Patients	
With suspected thromboembolic events, flank pain, hematuria, acute renal failure	Renal venous Doppler ultrasound Contrast CT, MRI
With sudden decrease in renal function, development of active urine sediment	Anti-GBM antibody Antineutrophil cytoplasmic antibody (ANCA) Assess for interstitial nephritis
Suggestive symptoms or age >50 years	Diagnostic testing for cancer (see text)

Anti-PLA_2R, Anti–phospholipase A_2 receptor antibody; *CT,* computed tomography; *GBM,* glomerular basement membrane; *LDL/HDL,* low-density/high-density lipoprotein; *MRI,* magnetic resonance imaging.

Electron Microscopy

The finding of subepithelial electron-dense deposits by EM parallels IgG staining. In primary MN, immune deposit formation occurs in a subepithelial distribution; subendothelial deposits are not seen, and mesangial deposits are rare (see Table 20.3). These deposits in early stages of the disease process are homogeneous and may even be confluent in some areas, with overlying podocyte foot process effacement and little change in the underlying GBM (stage I). As the disease persists, basement membrane material is laid down between the deposits and corresponds to the spikes seen on light microscopy with use of a silver methenamine stain and are easily visible by EM (stage II; Fig. 20.6A). Later, the spikes extend and deposits may become surrounded by new

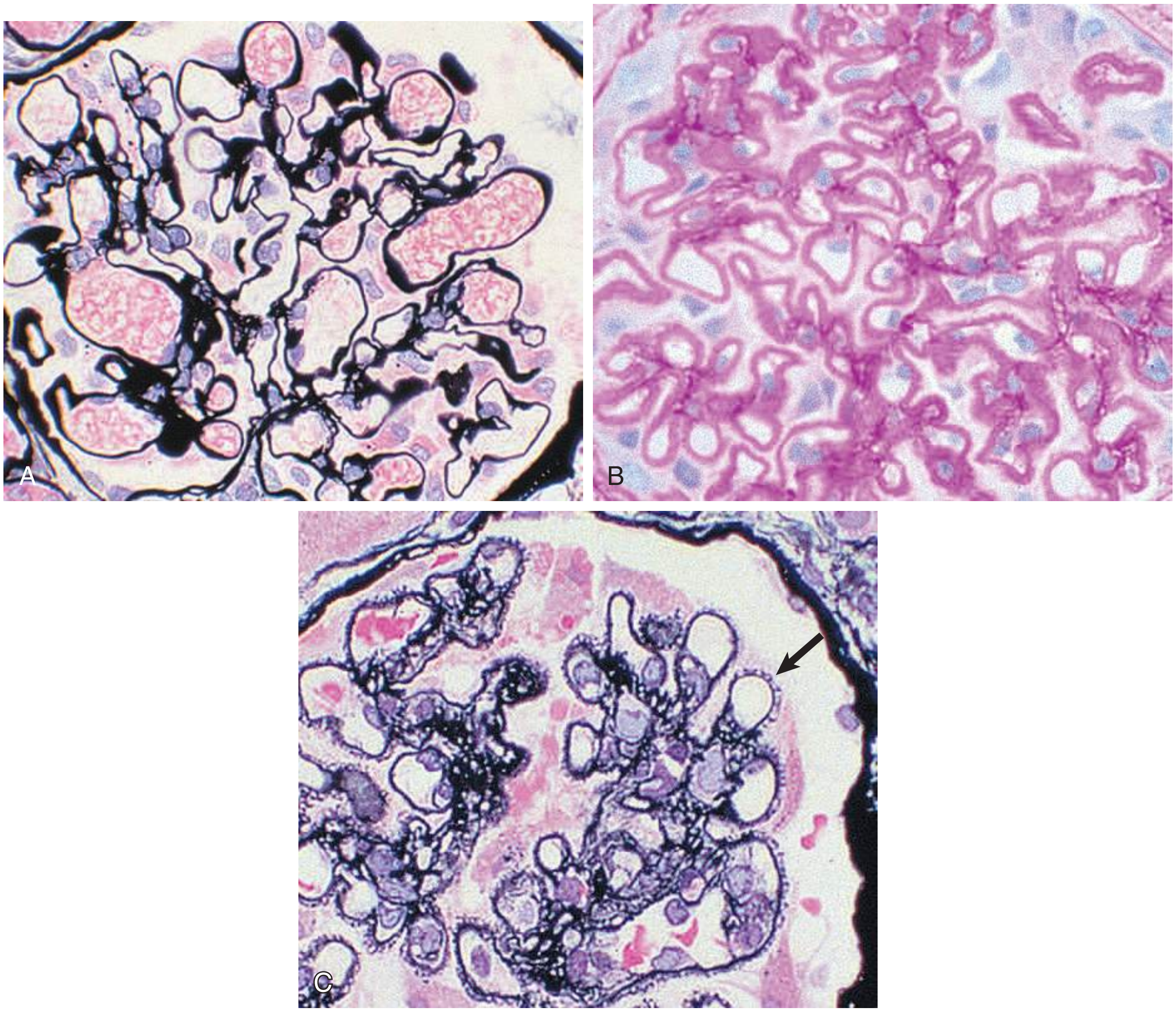


Fig. 20.4 Light microscopy in membranous nephropathy (MN). (A) Early MN. Glomerulus from a patient with severe nephrotic syndrome exhibiting normal architecture and peripheral capillary basement membranes of normal thickness. (B) Morphologically advanced MN. Uniform increase in thickness of glomerular capillary walls throughout the glomerulus with no increase in glomerular cellularity. (C) More morphologically advanced MN in the same patient as in (B) Discrete spikes of matrix emanating from outer surface of the basement membrane *(arrow),* indicative of advanced MN. (**A** and **C,** Silver methenamine stain; magnification ×400; **B,** periodic acid–Schiff reaction; ×400.) (Courtesy C. E. Alpers.)

TABLE 20.3 Histopathologic Features That Help Distinguish Primary From Secondary Membranous Nephropathy

Primary	Secondary
Immunofluorescence Microscopy	
IgG4 > IgG1, IgG3	IgG1, IgG3 > IgG4
IgA, IgM absent	IgA, IgM may be present
Mesangial Ig staining absent	Mesangial Ig staining may be present
C1q negative or weak	C1q positive
PLA_2R positive and co-localizes with IgG	PLA_2R negative
Electron Microscopy	
Subepithelial deposits only ± mesangial deposits rarely	Subepithelial deposits ± mesangial and subendothelial deposits

Ig, Immunoglobulin; *PLA_2R,* phospholipase A_2 receptor.

basement membrane–like material (stage III; see Fig. 20.6B). In stage IV disease, the basement membrane is overtly thickened, the deposits incorporated in it become more lucent, and the spikes are less apparent (stage IV; see Fig. 20.6C). Although clearly reflecting the duration of disease, these GBM changes do not correlate well with clinical manifestations or outcome. The overlying podocyte foot processes are effaced with condensation of the actin cytoskeleton; the filtration slits between the foot processes may be occluded; and in those still open, the slit diaphragms may be displaced or disrupted. Microvillous changes of the podocyte membrane are common, as are protein reabsorption droplets within podocytes and proximal tubular cells. The presence of tubuloreticular inclusions in the endothelial cells is strongly suggestive of lupus-associated MN, although these may rarely be found in primary MN as well.[26,27]

Diagnosis and Differential Diagnosis

When the initial presentation includes nephrotic syndrome, the differential diagnosis includes MCD, FSGS, the membranoproliferative

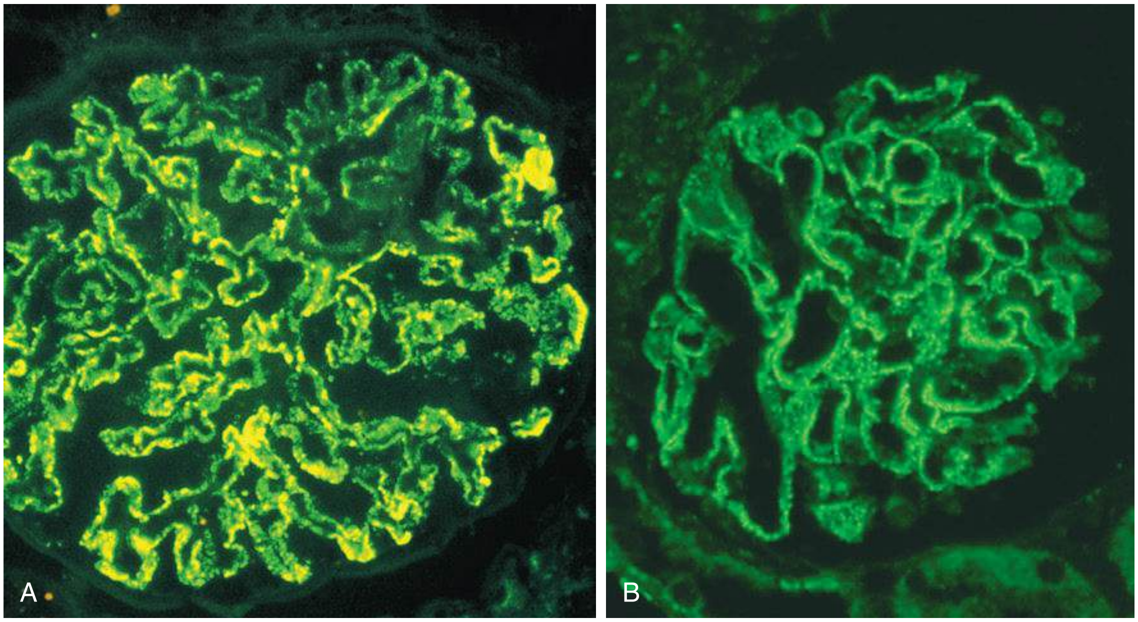


Fig. 20.5 **Immunofluorescence in membranous nephropathy (MN).** (A) *Left panel:* Glomerulus with diffuse, finely granular deposits of immunoglobulin G (IgG) along outer surface of all capillary walls. In primary MN, the antibodies eluted from the glomeruli are reactive with PLA_2R. (Courtesy C. E. Alpers.) (B) *Right panel:* Glomerulus stained for PLA_2R with diffuse, finely granular deposits of the antigen along outer surface of all capillary walls in a similar distribution as IgG. (Original magnification ×400.)

glomerulonephritis spectrum of diseases (including C3 glomerulopathies and immune complex glomerulonephritis [GN]; see Chapters 21 and 22), amyloidosis, light-chain deposition disease, lupus nephritis, and diabetic nephropathy. In the 20% to 25% of patients whose initial presentation is asymptomatic non-nephrotic proteinuria, the differential is even more extensive. Although clinical clues in proteinuric patients may increase the likelihood of one specific histologic pattern over another, confirmation that MN is the underlying cause of nephrotic syndrome generally requires a kidney biopsy. However, the diagnosis can be confidently made with a positive serologic test for anti-PLA_2R or anti-THSD7A when a biopsy cannot be performed. On the other hand a negative test for anti-PLA_2R anti-THSD7A does not exclude primary MN, because a few patients may have positive glomerular staining for PLA_2R or THSD7A despite negative serology.[1,11] In addition, some patients have all the features of primary MN but lack evidence of PLA_2R- or THSD7A-associated MN.

Secondary MN represents 20% to 30% of all cases (see Table 20.1); the most common causes are systemic lupus, hepatitis B, malignant neoplasms, and drugs. In addition to a careful history and physical examination, appropriate laboratory evaluation for potential secondary causes should include a complement profile, antinuclear antibodies, hepatitis serology, chest radiography, stool testing for occult blood, mammography in women, and prostate-specific antigen testing with digital rectal examination in men. In women age 20 to 50, a high index of suspicion is warranted for underlying lupus. This diagnosis can be particularly difficult to make because most of these patients have no systemic symptoms, and serologic markers of systemic lupus erythematosus are often absent. Membranous lupus accounts for 8% to 27% of cases of lupus nephritis (see Chapter 26).

In adults, regardless of age, malignancy is an important secondary cause of MN (see Table 20.1). The colon, kidney, and lung are the most common primary sites, and in some patients, the tumor may not be evident at presentation. Although the diagnosis of PLA_2R-associated MN tends to exclude the concurrent existence of an associated malignancy,[28] given the therapeutic implications regarding immunosuppression versus treatment for cancer, each case should still be carefully assessed and evaluations beyond routine age-appropriate health maintenance tests considered if patients have risk factors for cancer. All PLA_2R-negative cases merit a more thorough search for a malignant tumor, as do patients with THSD7A-associated MN.[29]

Hepatitis B virus–associated MN is also a common secondary cause in countries where HBV is endemic. It can affect both adults and children who are chronic carriers of HBV (positive HBsAg, HBcAg, and usually HBeAg). This can occur with or without a history of overt liver disease. In children, HBV-associated MN most often manifests as nephrotic syndrome and usually follows a benign course.[3] In adults, progressive renal impairment is a more common outcome but may be prevented by treatment with antiviral therapy and tacrolimus.[30]

MN secondary to drugs usually resolves after discontinuation of the offending agent. The time to resolution, however, varies significantly, from as early as 1 week for the drugs more commonly implicated (and used) today (e.g., for nonsteroidal antiinflammatory drugs [NSAIDs] and proton pump inhibitors [PPIs]), as compared with several years for the more classic but rarely used drugs such as gold and D-penicillamine. Many other renal disorders have been seen in association with or superimposed on MN, including IgA nephropathy, FSGS, anti-GBM disease, ANCA vasculitis, acute interstitial nephritis, and diabetic nephropathy.

Clinical Course, Outcomes, and Complications

The clinical course of MN varies widely. Spontaneous remissions in proteinuria have been reported in up to 30% of patients. As the severity of proteinuria at presentation increases, the frequency of spontaneous remission appears to decrease. Female gender and lower grade (non-nephrotic) proteinuria at presentation are the only two features associated with a higher likelihood of spontaneous remission.[31] This is likely to produce a bias in renal survival because most studies reporting 10-year outcomes in untreated patients have included those with subnephrotic

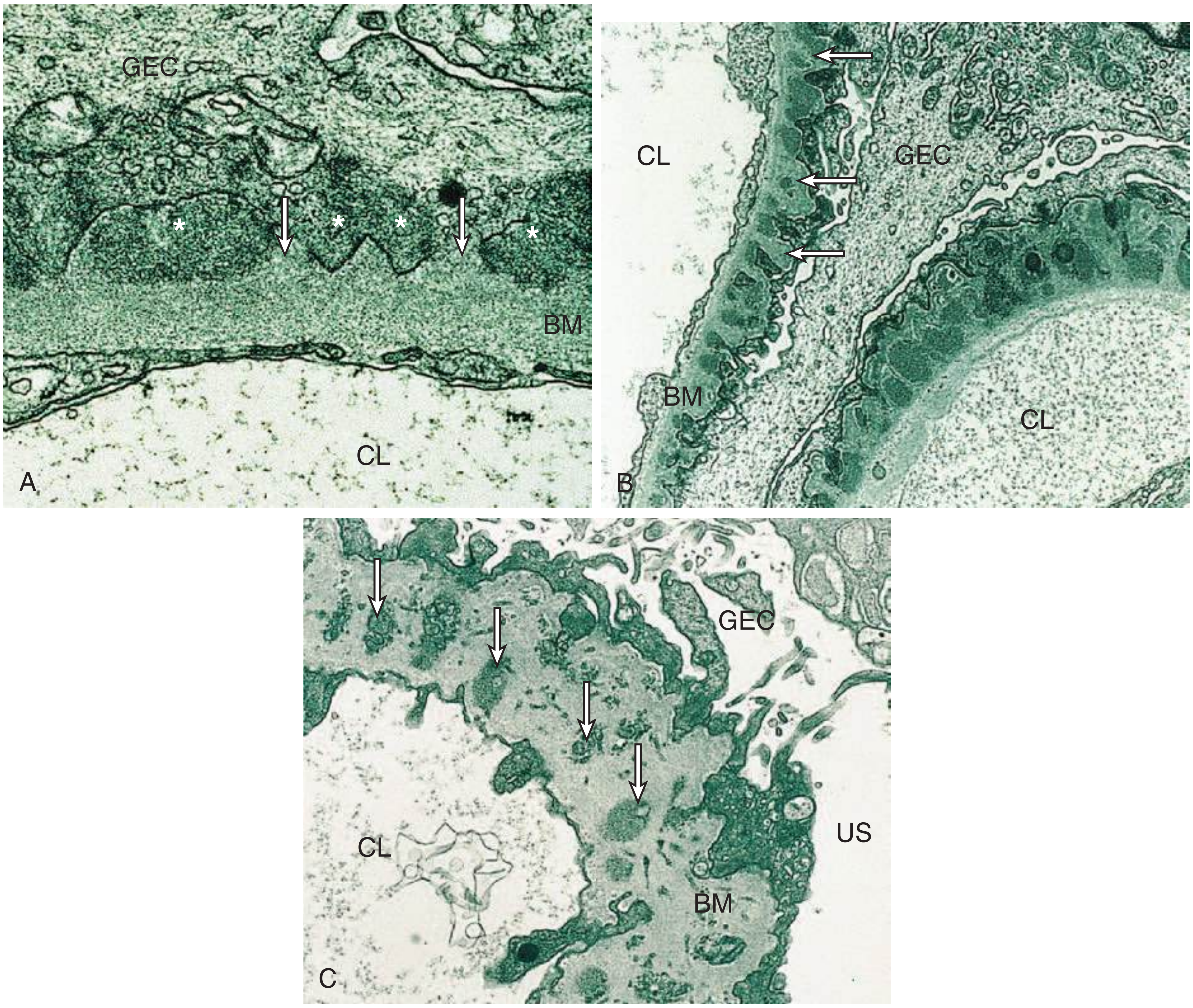


Fig. 20.6 Electron microscopy in membranous nephropathy (MN). (A) Early (stage II) MN. Glomerular capillary wall with discrete, electron-dense deposits on the subepithelial surface of the basement membrane *(BM)* corresponding to granular deposits of immunoglobulin G (IgG) detected by immunofluorescence microscopy (corresponding to light micrograph in (B). There are diffuse, granular immune complex deposits *(white asterisks)* along outer surface of the capillary wall, with effacement of overlying podocyte foot processes. Small extensions of BM between deposits *(arrows)* are also evident and represent the projections that are seen as spikes by light microscopy with silver methenamine staining. *CL,* Capillary lumen; *GEC,* glomerular epithelial cell. (B) More advanced (stage III) MN. Two glomerular capillary loops show involvement of the BM by the immune complex deposition *(arrows).* There is prominent membrane synthesis surrounding and incorporating these deposits into the BM (corresponding to spikes seen on silver-stained histologic preparations). Overlying cells continue to demonstrate widespread effacement of foot processes. (C) Morphologically advanced (stage IV) MN. Capillary BM is diffusely thickened; scattered electron-dense immune deposits *(arrows)* are present throughout its thickness, in addition to scattered subepithelial deposits. Overlying GECs continue to demonstrate effacement of foot processes. *US,* Urinary space. (Original magnifications ×18,000.) (Courtesy C. E. Alpers.)

proteinuria (<3.5 g/24 h). For example, one study reported a 72% renal survival at 8 years for 100 untreated patients, but 37% of the patients were non-nephrotic at presentation and more than 50% had less than 5 g/day.[32] In addition, deaths were excluded from the kidney survival analysis. Even so, there was a 25% end-stage renal disease (ESRD) rate by 8 years and almost 50% by 15 years. Thus, patients presenting with less than 3.5 g/day of proteinuria, no RBC casts, no hypertension, normal renal function, and no systemic features suggestive of a secondary cause have a relatively benign prognosis. However, these patients must be monitored, because up to 50% are likely to develop nephrotic-range proteinuria at some time in the disease course, most within the first 2 years after presentation.

In summary, although most patients with MN do reasonably well long term, MN is still the second or third leading cause of ESRD in patients with primary GN. The factor still missing from most MN survival data is the much higher-than-expected mortality from cardiovascular disease or thromboembolic events seen in patients who remain nephrotic. When another renal condition is superimposed on MN, there is often an associated acceleration in the rate of renal function loss. The most common conditions to consider in this setting are drug-induced interstitial nephritis; superimposed crescentic GN, including anti-GBM disease; and renal vein thrombosis.

Patients with primary MN who develop ESRD are generally suitable candidates for kidney transplantation, although the disease may recur

TABLE 20.4 Univariate Factors Associated With Worse Renal Survival in Membranous Nephropathy

Factors	Predictor	PPV (%)
Clinical Features		
Age	Older > younger	43
Gender	Male > female	30
HLA type	HLA/B18/DR 3/Bffl present	71
Hypertension	Present	39
Serum Levels		
Albumin	<1.5 g/dL	56
Creatinine	Above normal	61
Urine Protein		
Nephrotic syndrome	Present	32
Proteinuria	>8 g for >6 months	66
IgG excretion	>250 mg/day	80
β_2-Microglobulin excretion	>54 µg/mmol creatinine <54	79
C5b-9 excretion	>7 mg/mg creatinine	67
Biopsy Changes		
Glomerular focal sclerosis	Present	34
Tubulointerstitial disease	Present	48

(*PPV,* Positive predictive values modified from reference 37.) Univariate factors associated with increased likelihood of progression and their positive predictive value.

TABLE 20.5 Risk Categories of Renal Disease Progression in Membranous Nephropathy

Low Risk	Medium Risk	High Risk
Normal serum creatinine and creatinine clearance plus proteinuria <4 g/day over 6 mo of observation	Normal or near-normal creatinine clearance and persistent proteinuria 4-8 g/day over 6 mo despite maximum conservative treatment	Deteriorating renal function and/or persistent proteinuria >8 g/day for 3 (up to 6) mo of observation

in up to 50% (see Chapter 108). Recurrence may be asymptomatic and found only on protocol biopsy, but those with recurrence of nephrotic syndrome have a high rate of graft loss. A high titer positive serologic test for anti-PLA$_2$R at transplantation may forecast early recurrence.[33-35]

Predictors of Poor Outcome

Given the wide variation in the natural history of MN, markers that predict individual outcome would be valuable. Testing for circulating anti-PLA$_2$R autoantibody has the potential to detect increases in MN immunologic activity before changes in classic laboratory parameters become apparent.[1,36] Table 20.4 lists the more traditional factors associated with progression and the strength of those associations. Male sex and increasing age are associated with a higher risk for renal failure, but both have limitations as prognostic factors. Age seems to be related to the underlying pathologic process at presentation rather than the severity of disease, because age does not influence rate of deterioration in function, and the gender of the patient seems more closely related to the severity of proteinuria at presentation rather than representing an independent risk factor for progression. The severity of chronic changes seen on the biopsy specimen (i.e., degree of glomerulosclerosis, tubulointerstitial fibrosis, and vascular disease) has been associated with a poor prognosis but more closely reflects initial GFR than the subsequent rate of renal functional deterioration.[21] Other pathologic features, including the percentage of glomeruli with glomerulosclerosis and the configuration of the immune deposits (synchronic/single stage or heterogeneous/multistage) on EM also have been suggested as predictors of outcome and response to treatment. However, these features have not been validated in prospective studies. The degree of renal impairment at presentation also has been found to correlate with long-term renal survival, but a better and more sensitive predictor of long-term prognosis is the ongoing rate of renal function loss, as measured by the decline in creatinine clearance over time.

One of the best models to calculate risk for MN takes into consideration the initial creatinine clearance, the slope of the creatinine clearance during a fixed period, and the lowest level of proteinuria during that observation period[37] (see Table 20.3). This risk score has a reported sensitivity of 60% to 89%, specificity of 86% to 92%, and overall accuracy of 79% to 87% in validation studies. The model predicts that patients with a normal creatinine clearance at presentation that remains stable for 6 months, and with persistent proteinuria of less than 4 g/24 h, have less than a 5% chance of progression, and only conservative treatment is recommended. In contrast, patients with proteinuria of 4 to 8 g/24 h during the same time frame have a 55% probability for development of chronic renal impairment; and those with persistent proteinuria greater than 8 g/24 h have a 66% to 80% probability of progression to chronic kidney disease within 10 years (Table 20.5). Recent data also suggest that a greater than 50% reduction in the baseline proteinuria estimate at 1 year is an independent predictor of spontaneous remission.[38] Other biomarkers, including urinary α_1-microglobulin, β_2-microglobulin, IgM, and IgG have also been strongly associated with MN progression. These markers measured together at a single time point have a higher positive predictive value than proteinuria alone, but none has yet been validated in an independent dataset.

Several studies have examined the relationship of anti-PLA$_2$R antibodies and clinical course. In general, the presence and titer of anti-PLA$_2$R antibody help define the diagnosis of primary MN, predict who might have spontaneous remission, monitor the disease activity and response to therapy, identify those at risk for progression, and, most significantly, decide when to minimize or stop treatment.[1]

Relapse After Complete Remission or Partial Remission

Relapse from a complete remission occurs in approximately 25% to 40% of MN cases, but the timing is unpredictable. Relapses have been reported up to 20 years after the primary remission. However, the majority of patients will relapse only with subnephrotic-range proteinuria and will maintain stable long-term kidney function with conservative management alone.[39] In contrast, the relapse rate is as high as 50% in those achieving only a partial remission. Achievement of either a complete or a partial remission, however, significantly slows progression and increases renal survival. Review of 348 nephrotic patients with MN documented a 10-year renal survival in patients with a complete remission of 100%; with partial remission, 90%; and with no remission, only 45%.[40] A recent update suggested durability of remission, whether complete or partial, drug-induced or spontaneous, is closely related to the long-term outcome.[41] This offers hope that complete and partial remission may become acceptable end-points for clinical trials rather than reduction in GFR, which commonly takes years to evolve in MN.[42]

TREATMENT

Nonimmunosuppressive Therapy

Conservative management of MN is directed at control of edema, hypertension, hyperlipidemia, and proteinuria and is similar to that used for nephrotic syndrome of any etiology (see Chapter 15). Blood pressure control is important for both renal and cardiovascular protection. For patients with proteinuria of more than 1 g/day, the target for blood pressure is 125/75 mm Hg unless contraindicated for clinical reasons. Numerous studies have shown that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are cardioprotective and can reduce proteinuria and slow progression of renal disease in both diabetic and nondiabetic patients with chronic nephropathy (see Chapter 79). A recent meta-analysis of the largest renal protection trials using ACE inhibitors showed that the degree of protection is closely correlated to the degree of proteinuria reduction. None of these studies has focused on the specific effect of renin-angiotensin system (RAS) blockade in MN. In secondary analyses, the number of patients with MN has been small, and although the use of ACE inhibitors has been associated with significant improvement in some series, their antiproteinuric effect was modest (<30% reduction in proteinuria) in others. When effective, the benefit of RAS blockade occurs early, usually within the first 3 months of initiation of treatment. Even patients at low risk for progression (proteinuria <4 g/24 h) should be treated with ACE inhibitors or ARBs because this may reduce proteinuria and offer additional renal protection, with minimal risk for significant adverse effect. Patients must also follow a low-salt diet (1.5 to 2 g sodium/day) to achieve the maximum benefit from RAS blockade.

Proteinuria is also an independent risk factor for cardiovascular morbidity and mortality. When proteinuria is in the nephrotic range, there is a clear increase in cardiovascular risk, with a threefold to fivefold increase in both coronary events and death rates in this population.[43] Patients with significant proteinuria almost always have elevated serum cholesterol and triglyceride levels. Although not proven, we recommend the use of statins to reduce low-density lipoprotein cholesterol to 100 mg/dl (2 mmol/l) or lower, especially if treatment has not resulted in attaining subnephrotic range proteinuria (see Chapters 79 and 81).

It is recommended that both RAS blockade and lipid control be initiated early in patients with MN, given that reaching a goal of complete remission or even partial remission in patients at higher risk for progression (with persistent proteinuria >5 g/24 h) with conservative treatment alone is unlikely. Dietary protein intake may be restricted to 0.8 g/kg/day of high-quality protein with additional dietary protein (gram per gram) to correct for urinary losses. Dietary protein restriction has been associated with reduced proteinuria (15% to 25%) and a slowing in renal disease progression, but has never been shown to induce a complete remission or add to effects obtained with RAS blockade. Protein restriction must be carefully monitored in nephrotic patients to avoid malnutrition.

Retrospective reviews have shown that prophylactic anticoagulation is beneficial in reducing fatal thromboembolic episodes in nephrotic patients with MN, without a concomitant increase in the risk for bleeding.[44] No randomized controlled trial (RCT) has ever been done, however, and thus there is no current consensus about prophylactic anticoagulation and no laboratory test that can predict with any accuracy such an event. A thromboembolic event is more likely in certain patients, including those with severe and persistent nephrotic syndrome (proteinuria >10 g/day and/or serum albumin <25 g/l). Two additional recent clinical observations indicate that most thromboembolic events occur within the first 2 years of presentation and that there is an increasing likelihood of an event associated with progressively lower levels of serum albumin once below 30 g/l. Although there is still a tendency for nephrologists to wait until a primary thromboembolic event has occurred before using anticoagulants, recent algorithms suggest that the benefits of prophylactic anticoagulant therapy appear to outweigh the risks in patients with serum albumin below 2 or 2.5 g/l and low to intermediate risk for bleeding.[45]

Other agents that have been tried with modest effects in small numbers of patients with MN include probucol, a lipid peroxidation scavenger, and high-dose intravenous immune globulin, an agent with multiple effects on antibody-mediated tissue injury.[46]

Immunosuppressive Therapy

Several regimens using a variety of immunosuppressive agents can successfully reduce proteinuria in patients with MN. Many questions remain unresolved, however, including duration of conservative therapy while awaiting a spontaneous remission, when to initiate immunosuppressive therapy, most effective and safest of the available agents, and duration of treatment before treatment is considered futile.[47] Many of these issues, based on clinically available evidence, are discussed in the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for glomerulonephritis.[27]

The current evidence suggests that specific immunosuppressive drug therapy should not be considered unless the patient has had persistent nephrotic-range proteinuria (>4 g/day) and the proteinuria has not declined more than 50% from baseline, over a minimum observation period of 6 months, despite maximum antihypertensive and antiproteinuric therapy. Other suggested criteria for early intervention are the presence of severe disabling or life-threatening symptoms related to the nephrotic syndrome or a rise in serum creatinine greater than 30% within 12 months. The latter needs to be documented as related to disease progression and not a complication such as a renal vein thrombosis, transformation to crescentic MN variant, or interstitial nephritis from diuretics. Recent data also suggest that persistent low titers of the PLA_2R antibody are associated with a higher likelihood of spontaneous remission and that very high levels of the anti-PLA_2R might be an indication for early intervention.[8,36]

Corticosteroids

In the three RCTs of corticosteroids in primary MN treatment, the overall consensus has been no significant long-term beneficial effect on proteinuria, rate of disease progression, or renal survival.[48,49] The use of oral corticosteroids as a single agent for the treatment of MN is therefore not recommended. The one exception may be the East Asian (Japanese) population, in whom long-term observational studies have indicated improvement in both proteinuria and renal function preservation with use of corticosteroids as monotherapy.[50]

Cytotoxic Agents Combined With Corticosteroids

In patients at moderate risk for progression, a significant benefit has been described with the combination of corticosteroid and a cytotoxic agent beginning with methylprednisolone pulses 1 g intravenously for 3 days at the start of months 1, 3 and 5 followed by oral methylprednisolone 0.4 mg/kg/day for 27 days, and each cycle followed by 1 month of treatment with a cytotoxic agent (cyclophosphamide or chlorambucil).[51] Complete or partial remission of nephrotic syndrome was seen in almost 80% of treated patients, a threefold to fourfold increase compared with the control group. Both progression rate and renal survival were significantly improved. Both treatment regimens were remarkably safe, although relapses were seen within 2 years in 30% of the treatment group. Similar results were obtained in an RCT ($n = 93$) using this same regimen to treat patients of Asian (East Indian) ethnicity with MN.[52] Because the results of a cyclophosphamide-based regimen were similar to one based on chlorambucil,[52] cyclophosphamide is most often used because of a better safety profile.

The most recent RCT in MN studied a select population of 108 patients with documented deteriorating renal function (>20% decline in GFR within 3 to 24 months of study entry).[53] The combination of corticosteroids and a cytotoxic drug (chlorambucil) showed better protection against progressive kidney disease than placebo or cyclosporine. A difficult study to complete, trial entry took 10 years, and of the 108 patients entered, only 42% had 1 year of data, and less than 20% had 3 years of data. There were 117 severe adverse events reported, usually hematologic issues in the chlorambucil group, renal function deterioration in the cyclosporine group, and infections in both groups. Statistically, there was a small benefit in terms of preventing further progression in the chlorambucil/corticosteroid group (60% progressed) versus no difference between the cyclosporine compared with the placebo group (80% progressed), a 20% differential. However, the very high dropout rate and inability to manage these therapies safely in patients with MN with significantly declining renal function should give pause to applying any of these options under these conditions.[53]

One smaller RCT ($n = 26$) using intravenous cyclophosphamide in patients at high risk for progression (mean creatinine 2.3 to 2.7 mg/day; proteinuria 11 g/day) noted no statistical differences in proteinuria, remission rate, or rate of decline of renal function between the corticosteroid-alone and the combined-treatment groups.[54] However, this RCT used monthly intravenous doses of cyclophosphamide rather than the oral regimen used in the Italian and Indian studies and in the 2013 UK trial.

In older, smaller studies, these cytotoxic agents, even with appropriate adjustments in dose, have produced variable effects on outcome and significant adverse events in a high percentage of patients. The most recent longer term studies in high-risk patients prospectively studied 65 patients with MN and serum creatinine concentration above 1.5 mg/dl treated with oral cyclophosphamide for 12 months plus corticosteroids (same as previous regimen).[55] Renal survival was 86% after 5 years and 74% after 7 years. Partial remission occurred in 86% of the patients. The relapse rate was similar to earlier cytotoxic-corticosteroid regimens, 30% at 5 years. Treatment-related complications were significant and occurred in two thirds of patients, mainly bone marrow suppression and infections. Most adverse events could be managed by dose reduction, although some required permanent discontinuation of treatment.

A meta-analysis showed that the use of alkylating agents was associated with higher remission rates (partial or complete remission), but no statistical benefit of cytotoxic drug therapy was demonstrated compared with placebo in rates of ESRD or death.[56] The difficulty with this type of analysis is that the end-point of renal survival is far beyond the termination point of most clinical trials. The latest UK study, for example, had few patients still in follow-up after 3 years in any of the three treatment groups, so it was not possible to demonstrate any effect on long-term preservation of renal function.

In summary, cyclophosphamide used in combination with corticosteroids appears to be effective in the treatment of patients with nephrotic-range proteinuria resulting from primary MN, especially if renal function is well preserved at initiation of therapy. This combination may work even in those with impaired renal function, but the supporting evidence is much less compelling, adverse effects are higher, and the likelihood of benefit is reduced, especially in patients with advanced renal failure (GFR <30 ml/min).[55] The favorable effects are maintained beyond the 1-year treatment period, but relapse rates approach 35% by 2 years. The adverse effects of long-term cyclophosphamide therapy are the major drawbacks to the universal application of this treatment. These include increased susceptibility to infections, anemia, thrombocytopenia, nausea, vomiting, sterility, and, over time, malignant disease. Evidence from the membranous nephropathy literature suggests that the incidence of cancer is increased at a much lower level of exposure than previously considered; an increased number of malignant neoplasms with total cyclophosphamide exposure as low as 10–20 g (~100 mg/day for 6 months).[57]

Calcineurin Inhibitors

Early uncontrolled studies using the calcineurin inhibitor (CNI) cyclosporine suggested an initial benefit but a high relapse rate. Cyclosporine may reduce proteinuria not only through its immunosuppressive effects but also by direct effects on the podocyte. In a single-blinded RCT, 51 patients with corticosteroid-resistant MN were treated for 6 months with cyclosporine 2 to 5 mg/kg plus low-dose prednisone and compared with placebo plus prednisone.[58] Complete remission and partial remission were seen in 75% of cyclosporine-treated patients versus 22% of the placebo controls. Cyclosporine was well tolerated, with no adverse events requiring discontinuation of treatment. However, 38% relapsed within 6 months of discontinuation of treatment.

Only one RCT has used cyclosporine in patients with high-grade proteinuria and progressive renal failure.[59] Both proteinuria and rate of renal function loss were reduced with cyclosporine compared with placebo and when the treatment group was compared with their status 6 months before starting cyclosporine. This improvement in proteinuria was sustained for up to 2 years after cyclosporine was discontinued. The entry criteria included documented GFR decline and high-grade proteinuria, but in contrast to the UK study, the cyclosporine was introduced at a lower dose and slowly increased to minimize toxicity (mean treatment dose 3.5 mg/kg/day). Treatment with longer term cyclosporine (i.e., 12 months) has resulted in a higher rate of complete remission and partial remission (84%). In addition, persistence of remission was maintained with doses of cyclosporine as low as 1 to 2 mg/kg, although relapses were still common if the cyclosporine level fell below 100 ng/ml. Time to remission with use of cyclosporine varies from a few weeks to several months.[59a] This suggests that unless there is a significant reduction in proteinuria (>25%) within 3 to 4 months, a change in therapy should be considered.

Significant adverse effects seen with cyclosporine include hypertension, gingival hyperplasia, gastrointestinal complaints, muscle cramps, and, most important, nephrotoxicity. The latter depends on both dose and duration of treatment.

In a 12-month RCT ($n = 48$), monotherapy with tacrolimus, an alternative CNI, was compared with a control group (conservative therapy only).[60] Proteinuria remission was 76% with tacrolimus versus 35% in the control group, and progression rate also was substantially slowed by the CNI. The relapse rate after stopping of the drug, however, approached 50% by the end of 2 years of follow-up.

In summary, RCTs have shown that both cyclosporine and tacrolimus are effective in reducing proteinuria in MN. Although relapses are common after short exposure (6 to 12 months), a longer exposure time and lower maintenance doses of CNI can be used to maintain partial remission. No studies using CNIs have been of sufficient duration to confirm that maintenance of remission in proteinuria prolongs renal survival. Side effects are substantial, with the major concern being nephrotoxicity. This is particularly common if the medication is not introduced at a low dose and slowly increased until an effective drug level is reached. Clinical experience indicates increased potential for nephrotoxicity with the CNIs if the level of renal function is low (GFR <40% of normal), if there is a high degree of interstitial or vascular pathology accompanying the membranous lesion, or if the patient's renal function is rapidly deteriorating.[27,53]

Mycophenolate Mofetil

Studies using mycophenolate mofetil (MMF) in patients with MN report conflicting results. However, even in the most optimistic study, although initial response was high (used in combination with prednisone), the relapse rate within months approached 50%. The most pessimistic study (the only RCT), compared with conservative management only, showed no difference in remission rates in patients with MN.[61,62] Follow-up was limited and numbers in the latter study were small, but the reason for the marked differences between these two trials is not clear. In a small retrospective study in corticosteroid-resistant Asian patients with MN, a higher response with MMF was observed, with the partial remission rate approaching 50%, possibly related to the ethnic characteristics of the population studied. The role of MMF as monotherapy or as an adjunct in the treatment of MN remains unclear.

Rituximab

In several pilot studies, rituximab, despite substantial variations in the dose and timing of the drug, consistently reduced proteinuria by 60% to 70%.[63,64] The response rate to rituximab in patients who previously failed immunosuppressive therapy was similar to patients receiving the drug as first-line therapy. A delayed response in proteinuria reduction was seen, similar to that with cytotoxic therapy, with remissions continuing to occur up to 12 months after the last rituximab infusion. The anti-PLA$_2$R antibody was measured in the Mayo Clinic cohorts, and a decline in titer preceded proteinuria reductions by as long as 3 months and was associated with patients subsequently achieving a partial or complete remission compared with those with no change in titer.[65] Although the first RCT comparing rituximab plus conservative therapy to conservative therapy alone did not achieve a significant primary end-point of remission at 6 months (35% vs. 22%), anti-PLA2R levels were significantly reduced by rituximab and remission rates after a mean of 17 months of observation, increased to 65% in those treated with rituximab compared with 34% in those treated conservatively ($P < .01$).[66] These results are consistent with those of prior studies showing that immunologic remission precedes clinical remission by several months in patients treated with rituximab.[65] Although the data from these studies are quite compelling, additional RCTs are required before widespread use of this agent is advocated, despite the obvious advantages of an almost guaranteed adherence and low adverse event rate, but counterbalanced by high cost and uncertain long-term toxicity. To that end, RCTs comparing rituximab to cyclosporine or cytotoxic/corticosteroid regimens are underway and will help define the relative efficacy, safety, and relapse rate of rituximab compared with those of standard therapies.

Eculizumab

Eculizumab is a humanized anti-C5 monoclonal antibody designed to prevent the cleavage of C5 into its proinflammatory by-products. An RCT in 200 patients with MN that compared eculizumab with placebo during a total of 16 weeks showed no significant effect on proteinuria or renal function, but effective complement inhibition was not achieved.

Adrenocorticotropic Hormone

Two small studies have reported the use of an intramuscular long-acting synthetic form of adrenocorticotropic hormone (ACTH) in MN.[65] The exact mechanism of action of this agent in MN is unknown but likely unrelated to corticosteroid effects because corticosteroids alone are not beneficial in MN. A dose escalation study showed prolonged remission in the majority of patients with MN treated with the synthetic form of ACTH, 1 to 2 mg weekly intramuscularly for 1 year. In a small RCT ($n = 32$) with a similar dose regimen, ACTH was compared with a standard cytotoxic plus corticosteroids regimen. The remission rate was the same in the two groups, 80% to 90%, but the relapse rate in the ACTH group was lower, 14% versus 30%, after a follow-up of 1 year. Side effects of ACTH were few and included fluid retention, sleep disturbances, and bronze skin discoloration. Potassium supplementation was required in the majority of patients in one trial.[67]

A more recent nonrandomized study using the synthetic agent found a substantially lower response rate and an incidence of adverse events approaching 95%, prompting the authors to suggest this agent not be used in MN.[68] In contrast, a recent dose escalation study using the natural ACTH gel found a significant reduction in proteinuria proportionate to drug exposure in the majority of patients with MN with an acceptable adverse effects profile.[69]

TREATMENT SUMMARY

Control of proteinuria, specifically achieving either complete or partial remission of nephrotic syndrome, is associated with prolonged renal survival and a slower rate of renal disease progression in patients with MN. Supportive or conservative care should be provided to all patients first, including diuretics, antihypertensive agents such as ACE inhibitors and ARBs (potentially renal protective), and lipid-lowering agents, with lifestyle modifications such as salt restriction, weight normalization, and smoking cessation (see Chapter 79). In patients with MN who require disease-specific therapy, the choice of agents remains controversial. Fig. 20.7 outlines a suggested management algorithm based on the level and persistence of proteinuria.

Cytotoxic/corticosteroid combinations, CNIs, and, most recently, rituximab have proved effective in reducing proteinuria in moderate-risk or high-risk MN patients. The physician, in concert with the patient, must consider all risks as well as benefits in deciding which therapy should be used first. These approaches are not mutually exclusive and can be used in sequence if the first one chosen fails to induce a remission or if adverse effects are untenable. Ideally, the approach should leave 2 to 3 months between treatment regimens to help immune system recovery. Alternatively, a second course of the same immunosuppressive regimen could be used, but at the potential cost of cumulative toxicity,

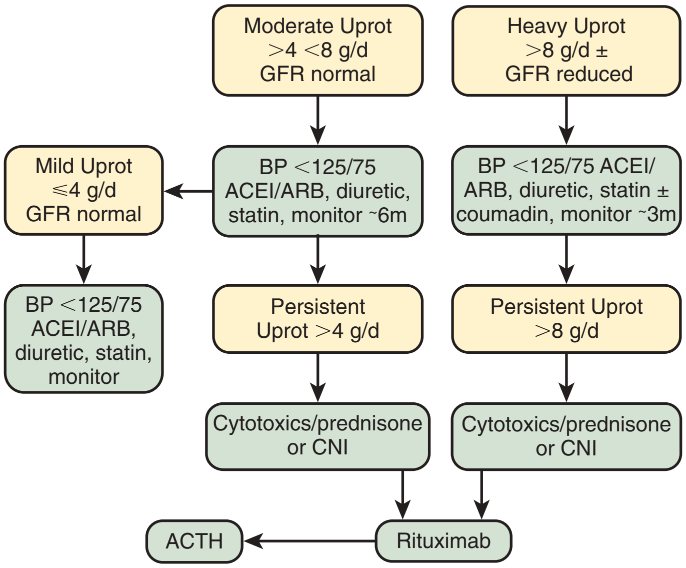


Fig. 20.7 Algorithm for treatment of the patient with membranous nephropathy (MN). Details of possible therapies are discussed in the text. *ACEi,* Angiotensin-converting enzyme inhibitor; *ACTH,* adrenocorticotropic hormone; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CNI,* calcineurin inhibitor; *GFR,* glomerular filtration rate. Uprot, proteinuria.

or another treatment regimen may be indicated if the patient's risk profile has changed. Although the risks for malignancy from alkylating agents are reduced by limiting treatment to 6 months (especially with the alternating regimen), tobacco smokers are at increased risk for bladder and lung cancer and might be candidates for an alternative treatment regimen. In addition, men wanting to procreate are advised to bank sperm before treatment with alkylating agents.

Preliminary evidence on the use of long-acting ACTH suggests it may be effective and safer than current regimens; however, the current cost is prohibitive, and efficacy needs to be assessed in an RCT before it is recommended as standard therapy. Patients with severe renal impairment (GFR <30 ml/min), especially if the MN course has been slowly progressive and histopathology indicates significant interstitial fibrosis and glomerular obsolescence, are less likely to benefit from immunosuppressive therapy, and the risks of treatment may favor conservative therapy as the best option for such patients.

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21

Membranoproliferative Glomerulonephritis and Cryoglobulinemic Glomerulonephritis

Sanjeev Sethi, An S. De Vriese, Fernando C. Fervenza

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Definition

Membranoproliferative glomerulonephritis (MPGN) is a pathologic pattern of glomerular injury resulting from subendothelial and mesangial deposition of immune complexes and/or complement factors and their products, along with proliferative changes in the glomeruli. This pattern does not represent a disease entity per se, but can occur as a result of different pathogenic processes. Other names for MPGN include lobular glomerulonephritis and mesangiocapillary glomerulonephritis.

Epidemiology

MPGN is decreasing in frequency in developed countries (possibly due to better control of infectious diseases) but remains common in patients presenting with nephrotic syndrome in low- and middle-income countries of South America, Asia, and Africa. The incidence of MPGN in most developed countries is fewer than 1 to 2 cases per million population per year.[1] Only about 4% to 5% of kidney biopsy samples showing an MPGN pattern are due to C3 glomerulonephritis (see Chapter 22).

Former Classification

Traditionally, MPGN was classified based on the ultrastructural characteristics as MPGN type I, MPGN type II, and MPGN type III. MPGN type I was defined by the presence of mesangial and subendothelial deposits. MPGN type II, also referred to as dense deposit disease (DDD), was characterized by mesangial and intramembranous highly electron-dense deposits. MPGN type III was defined by the presence of subendothelial, intramembranous, and subepithelial electron-dense deposits. However, results of immunofluorescence (IF) microscopy demonstrated that some cases had glomerular deposition of immunoglobulins and complement components, whereas in others, only complement deposition was present. This insight engendered a new classification. However, older publications regarding epidemiology, therapy, and transplantation may be difficult or impossible to interpret because (with the exception of DDD), immune-complex and complement-mediated MPGN were included together (see later discussion).

Newer Classification Based on Etiology and Pathogenesis

The Mayo Clinic classification of MPGN[2,3] divides MPGN based on two broad pathogenetic pathways: immune complex or monoclonal immunoglobulin deposition in the glomeruli with or without complement deposition and complement deposition subsequent to dysregulation of the complement system.

The MPGN pattern of injury secondary to deposition of immune complexes in the glomeruli can occur when there are persistent circulating antigen-antibody immune complexes resulting from chronic infections, autoimmune diseases, or paraproteinemias. On light microscopy, a proliferative glomerulonephritis is seen in the acute phase with initial influx of neutrophils followed by mononuclear inflammatory cells. In the reparative phase, the injured mesangial cells and endothelium produce new basement membrane and there is expansion of the mesangial matrix. As a result of remodeling, the glomerular basement membrane (GBM) thickens and glomeruli acquire a lobular appearance typical of MPGN pattern. The immune-complex and monoclonal immunoglobulin–mediated MPGN are characterized by the presence of immunoglobulins by IF; in immune complex–mediated MPGN the deposits are polyclonal, whereas in monoclonal immunoglobulin–mediated MPGN the immunoglobulin is monotypic. C3 is also usually present, indicating activation of the complement pathway.

Complement-mediated MPGN is less common than immune complex–mediated MPGN and results from dysregulation of the complement alternative pathway (see Chapter 22).

A third pathogenic pathway with an MPGN pattern can be seen in the absence of immune complex or complement deposition in the setting of chronic endothelial injury or chronic thrombotic microangiopathy. Uncommon causes such as cryofibrinogen glomerulopathy and lipoprotein glomerulopathy that result in endothelial injury and deposition of proteins along the capillary walls also can result in an MPGN pattern of injury (Table 21.1).

Clinical Presentation and Pathology

Infection-Associated MPGN

Chronic viral infections such as hepatitis C (HCV) and B (HBV) are important causes of immune complex–mediated MPGN (cryoglobulinemic glomerulonephritis, see later discussion and Chapter 55).[4,5] The exact mechanism of HCV-related glomerular disease is unknown. Toll-like receptors, particularly TLR3, might play a role in HCV-related MPGN.[6] HBV most frequently causes a membranous nephropathy pattern of injury, but more rarely can be associated with MPGN. The pathology of HBV-related MPGN is likely related to the trapping of circulating immune complexes in the mesangium and subendothelial regions.[7] It is also possible that mesangial cells are directly infected by HBV virions. Rarely, MPGN may be seen with acute viral infections such as with Puumala hantavirus.[8]

Chronic bacterial infections can cause MPGN as a result of continuous low-grade antigenemia.[9,10] Potential causative agents include *Staphylococcus, Mycobacterium tuberculosis,* streptococci, *Propionibacterium acnes, Mycoplasma pneumoniae, Coxiella burnetii, Nocardia, Brucella,* and *Meningococcus.*[11,12] “Shunt nephritis,” as may be seen with

TABLE 21.1 **Causes of a Membranoproliferative Pattern of Glomerular Injury**

Immune complex–mediated	Deposition of immune complexes as a result of an infection	Viral: Hepatitis B and C Bacterial: Endocarditis, infected ventriculoatrial shunt, visceral abscesses, leprosy, meningococcal meningitis Protozoa/other infections: Malaria, schistosomiasis, mycoplasma, leishmaniasis
	Deposition of immune complexes as a result of an autoimmune disease	Systemic lupus erythematosus Sjögren syndrome Rheumatoid arthritis
	Deposition of monoclonal immunoglobulin as a result of a monoclonal gammopathy due to a plasma cell or B-cell disorder	
Complement-mediated (C3 glomerulonephritis and dense deposit disease)	Mutations in complement-regulating proteins: CFH, CFI, CFHR5 Antibodies to complement regulating proteins: C3 nephritic factor, antibodies against CFH, CFI, or CFB Mutations in complement factors: C3, CFB	
Non-immunoglobulin/ complement–mediated	Healing phase of HUS/TTP Anti-phospholipid (anti-cardiolipin) antibodies syndrome POEMS syndrome Radiation nephritis Nephropathy associated with bone marrow transplantation Drug-associated thrombotic microangiopathies Sickle cell anemia and polycythemia Dysfibrinogenemia and other prothrombotic states Transplant glomerulopathy	
Idiopathic	None of the conditions above are present	

Modified from Fervenza FC, Sethi S, Glassock RJ. Idiopathic membranoproliferative glomerulonephritis: does it exist? Nephrol Dial Transplant 2012;27(12):4288-4294, with permission.

ventriculoatrial or ventriculocaval shunts for hydrocephalus or as a result of catheter infections (e.g., parenteral nutrition), is caused most commonly by coagulase-negative staphylococci.

Fungal and parasitic infections are less commonly associated with an MPGN pattern of injury.[13] Leishmaniasis also has been associated with MPGN.[14]

In the setting of viral infections, IF typically shows granular deposition of immunoglobulin M (IgM), C3, and both kappa and lambda light chains (Fig. 21.1). IgG may or may not be present, and C1q is typically negative. On the other hand, the presence of IgG staining stronger than IgM and C3 is more often seen in bacterial infections, although in some cases with chronic infections the immunoglobulin staining may be weak compared with the C3 staining. Electron microscopy (EM) shows mesangial and subendothelial deposits. The capillary walls are thickened with entrapment of cellular elements, subendothelial electron-dense deposits, matrix-like material and new GBM formation manifested by the presence of double contours on light microscopy.

Autoimmune-Associated MPGN

An MPGN pattern of injury is commonly seen in patients with autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), primary Sjögren syndrome, undifferentiated connective tissue disease, primary sclerosing cholangitis, and Graves disease.[15,16] The majority of patients with Sjögren syndrome and glomerulonephritis (80%) have type II monoclonal cryoglobulinemia and low complement C4 levels.[17] Sjögren syndrome is considered one of the most common causes of non–HCV-related cryoglobulinemia.[18]

On IF, a full house pattern with positive staining for IgG, IgA, IgM, C1q, C3, and kappa and lambda light chains is frequently seen, particularly in the setting of SLE. IgM may be the dominant immunoglobulin in MPGN associated with RA and primary Sjögren syndrome. EM shows mesangial and subendothelial capillary wall electron-dense deposits. Subepithelial deposits also may be present. In such cases, a membranous component of the disease should be considered. Tubuloreticular inclusions are often present in the endothelial cells.

Monoclonal Immunoglobulin–Associated MPGN

Monoclonal gammopathies encompass a heterogenous spectrum of disorders characterized by clonal proliferation of immunoglobulin-producing B lymphocytes or plasma cells. Generally, a monoclonal immunoglobulin can be detected in the blood or urine (M-protein),[19] although in some cases routine serum electrophoresis and immunofixation fail to reveal a monoclonal protein. The physicochemical properties of the monoclonal immunoglobulin often result in renal disease, sometimes in the absence of overt malignancies such as lymphoma, multiple myeloma, or Waldenström macroglobulinemia. In those cases the term *monoclonal gammopathy of renal significance* (MGRS) is used.[20] The glomerular diseases included in this group are proliferative glomerulonephritis with monoclonal immunoglobulin deposits, amyloidosis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, and monoclonal immunoglobulin deposition disease (see Chapter 27).[21-23] Although each of these entities may have a varied morphologic appearance, the common pattern of glomerular injury is MPGN. In the next paragraph, we will discuss proliferative glomerulonephritis resulting from glomerular deposition of monoclonal immunoglobulin.

On kidney biopsy (Fig. 21.2), glomerular deposition of the monoclonal immunoglobulin results in an MPGN pattern of injury in most cases. Less commonly, other patterns of proliferative glomerulonephritis can be seen, including mesangial proliferative, diffuse proliferative, crescentic, and necrotizing, and sclerosing glomerulonephritis.[24,25] IF studies are crucial for the diagnosis and show mesangial and capillary wall monoclonal immunoglobulin deposits. The monoclonal immunoglobulin most

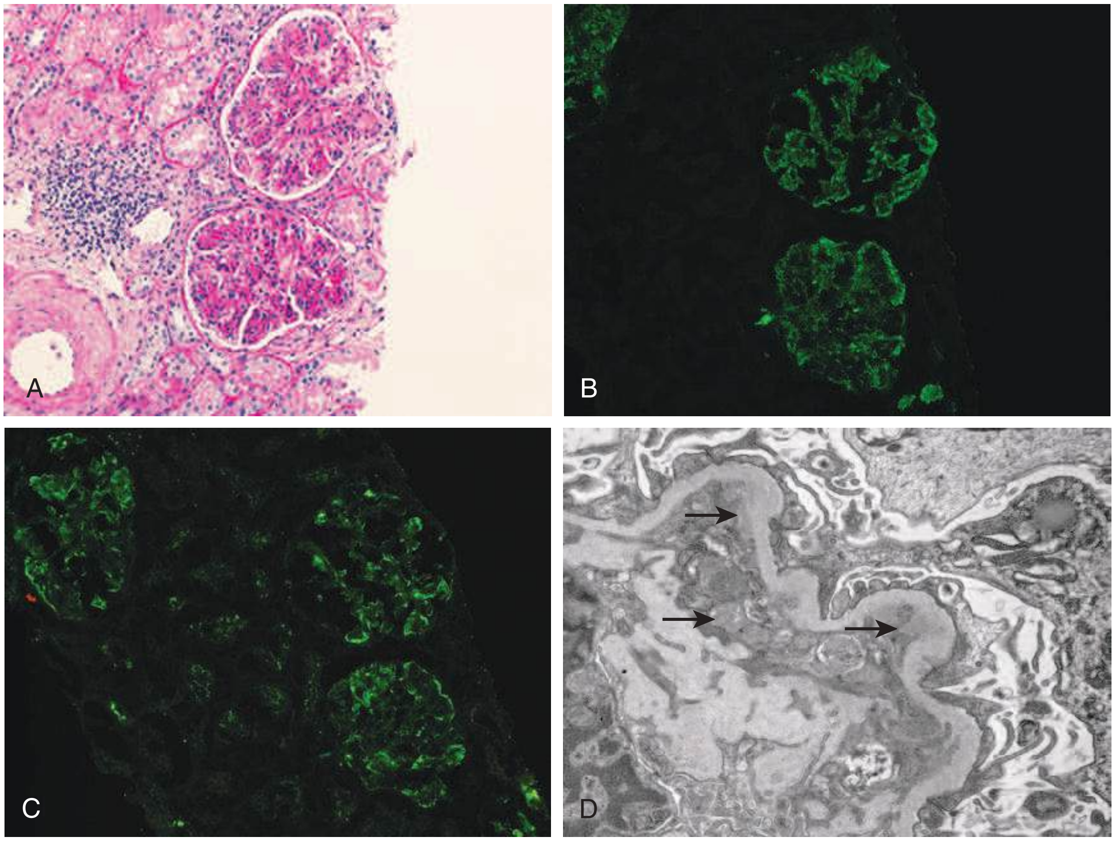

Fig. 21.1 Membranoproliferative glomerulonephritis associated with hepatitis C. (A) Light microscopy showing two glomeruli with an MPGN pattern of injury (periodic acid–Schiff stain ×20). (B and C) Immunofluorescence microscopy showing bright granular staining for (B) IgM, and (C) C3. There was equal staining for kappa and lambda light chains (not shown). (D) Electron microscopy showing subendothelial electron-dense deposits and double contour formation. *Black arrows* point to subendothelial deposits. (**D,** ×13,000).

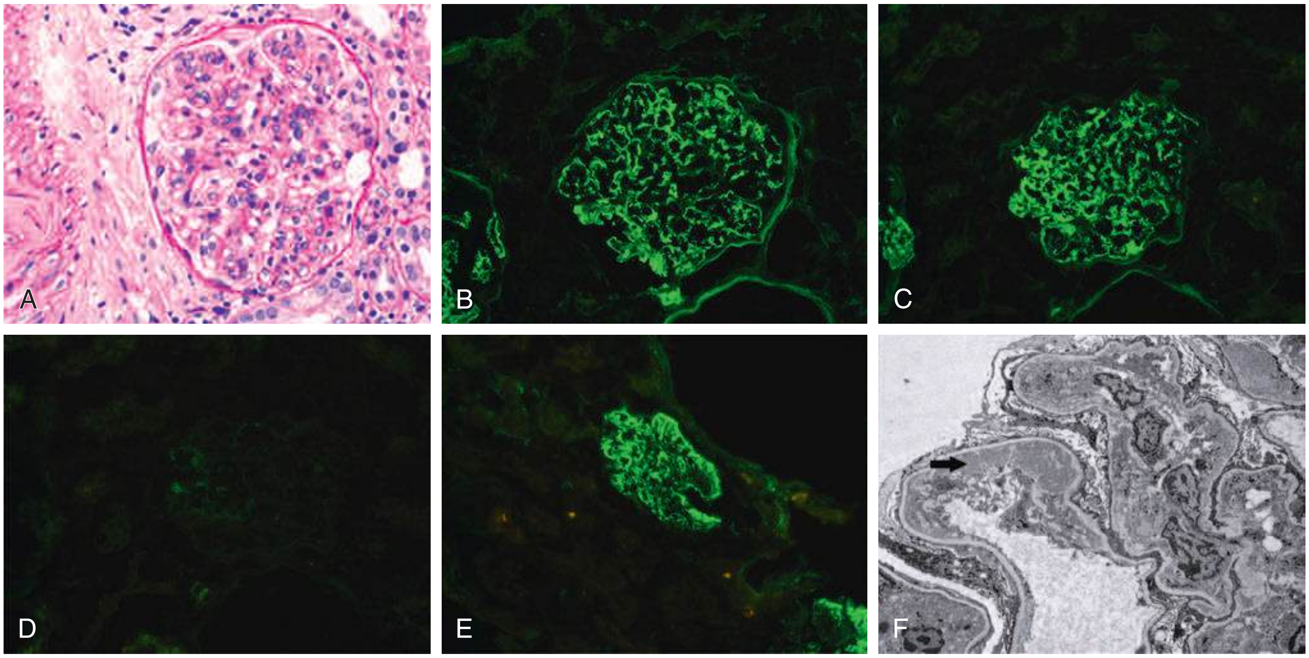

Fig. 21.2 Proliferative glomerulonephritis with monoclonal immunoglobulin deposits. (A) Light microscopy showing an MPGN pattern of injury (periodic acid–Schiff stain, ×40). (B to E) Immunofluorescence microscopy showing bright granular staining for (B) IgG, (C) kappa light chains, (E) IgG3 subtype, and (D) negative staining for lambda light chains. (F) Electron microscopy showing subendothelial electron-dense deposits and double contour formation. *Black arrows* point to subendothelial deposits (**F,** ×4000).

often contains heavy chain IgG, less commonly IgM or rarely IgA, with kappa or lambda light chain restriction. Less commonly, only heavy or light chains may be present. EM shows mesangial and subendothelial electron-dense deposits, and rarely subepithelial and intramembranous deposits. Glomerular capillary wall remodeling with double contour formation is often present.

In cases in which the heavy chain consists of IgG, the IgG3 subclass is the most common subclass. Interestingly, this class of deposits is most likely to have undetectable circulating monoclonal immunoglobulin by routine serum and urine electrophoresis studies.[26]

In a recent study of monoclonal immunoglobulin–associated MPGN, almost all patients had a monoclonal or biclonal band on serum immunofixation studies. Furthermore, bone marrow studies revealed 16 cases of MGRS, of which 2 converted to multiple myeloma, 2 cases of chronic lymphocytic leukemia (CLL), 1 case of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, 3 cases of low grade B-cell lymphoma not further classifiable, and 6 cases of multiple myeloma.[22] Thus all patients with MPGN associated with monoclonal immunoglobulin should be evaluated for an underlying plasma cell or B-cell proliferative disorder.

MPGN With Masked Immune Deposits

MPGN with isolated C3 deposits rarely occurs in the setting of monoclonal gammopathy.[27] Hypocomplementemia is common. IF on formalin-fixed, paraffin-embedded tissue after protease digestion unmasks monoclonal immunoglobulin glomerular deposits. The immunoglobulin on the glomerular deposits matches the monoclonal protein on serum immunofixation. It is important that these cases are not misdiagnosed as C3 glomerulopathy, because most are associated with a low-grade lymphoma or plasma cell dyscrasia. A C4d stain can be helpful in detecting masked immune deposits.[28,29]

Complement-Mediated MPGN

MPGN is also the most common pattern MPGN seen in C3 glomerulopathy, a lesion that is characterized by dominant C3 staining with minimal or no immunoglobulin staining on IF (see Chapter 22).

MPGN Without Immunoglobulins or Complement

Glomeruli may demonstrate membranoproliferative-like changes in the absence of immunoglobulin or complement deposits in chronic thrombotic microangiopathy (see Chapter 29).

Uncommon Causes of MPGN

Cryofibrinogen-related membranoproliferative glomerulonephritis. Cryofibrinogenemia is a rare disease resulting in an MPGN pattern of injury (Fig. 21.3). Cryofibrinogen is a cryoprecipitate that develops after refrigeration of plasma but not serum (when both serum and plasma form a precipitate on refrigeration, the responsible proteins are called cryoglobulins). Cryofibrinogen may be asymptomatic, but can be associated with thromboembolic disease, particularly affecting the skin.

C4 glomerulopathy. C4 glomerulopathy is characterized by glomerular deposits of predominantly C4 with little or no immunoglobulin or C3 deposition. This glomerulopathy encompasses C4 DDD and C4 glomerulonephritis[30] and may be caused by an overactive lectin pathway of complement. Renal biopsy shows a membranoproliferative pattern of injury with extremely thick glomerular capillary walls.

Collagen type III glomerulopathy. Collagen type III glomerulopathy is a rare disorder characterized by massive accumulation of atypical type III collagen fibrils in the mesangium and subendothelial space (see Chapter 28).

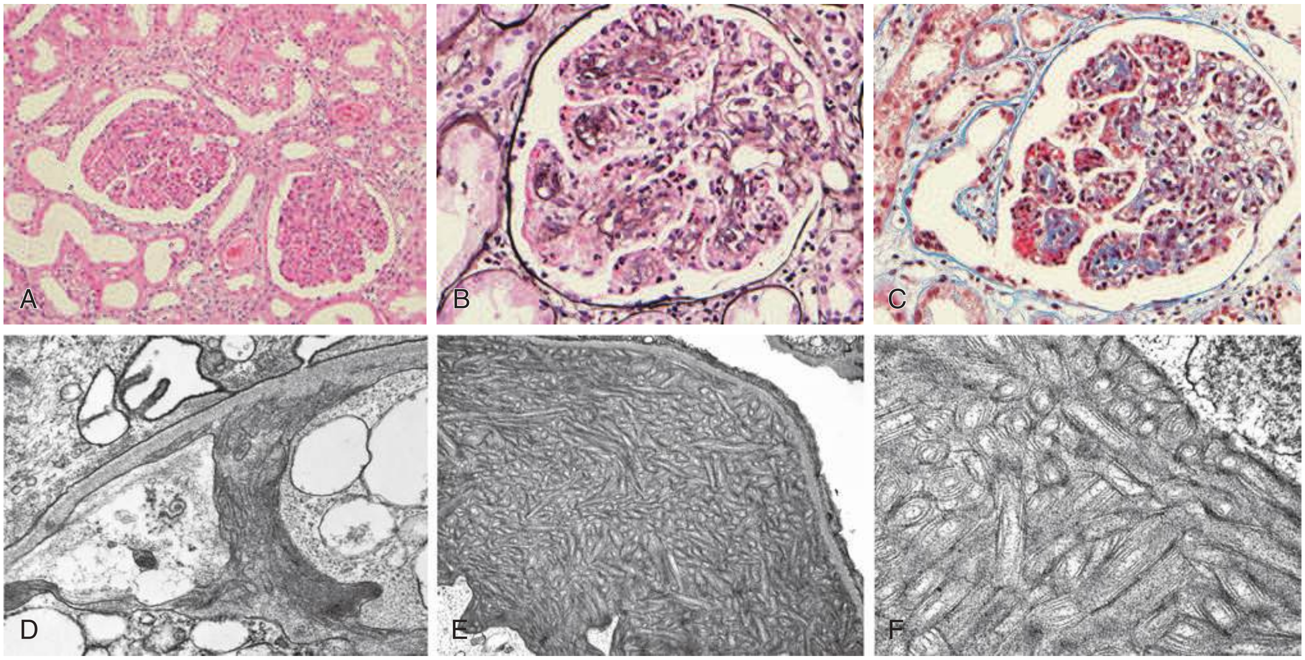

Fig. 21.3 Cryofibrinogen glomerulopathy with a membranoproliferative pattern of injury. (A to C) Light microscopy showing an MPGN pattern of injury. Scattered fuschinophilic material can be seen with some capillary loops in (C) (**A,** Hematoxylin and eosin, ×20; **B,** silver methenamine silver ×40; Masson trichrome stain, ×40). Immunofluorescence microscopy was negative for immune deposits. Electron microscopy showing (**D**) randomly arranged and loosely arranged subendothelial fibrillary deposits with tubular substructures and (**E** and **F**) aggregates of intraluminal tubular deposits with large central bore with double and triple layering (**D,** ×30,000; **E,** ×9300; **F,** ×3000).

Evaluation

The evaluation for MPGN should be guided by the suspected cause, based on clinical presentation and biopsy findings. A standard workup for MPGN should include complement evaluation. Low C3 and C4 is more typical of classic pathway activation, as in immune complex–mediated glomerulonephritis. A low C3 with a normal C4 suggests abnormalities of the alternative complement pathway. These findings along with the biopsy results, particularly IF and EM can further guide detailed evaluation.

Infections

Workup in the evaluation of infection-related MPGN depends on the suspected pathogen (see Chapter 55). In the case of hepatitis-related MPGN, tests should include viral serology examination and quantification of viral load by polymerase chain reaction. The workup for parasitic infection–related MPGN should include blood tests for malaria, urine and stool tests for schistosomiasis, and serologic tests for schistosomiasis and leishmaniasis. Blood cultures, cultures of indwelling catheter tips, imaging studies for deep-seated abscesses, and transthoracic echocardiograms for valvular vegetations should be performed in the case of suspected fungal and bacterial infections. Parasitic and fungal infections are investigated only in the appropriate clinical situation (history of recent travel to endemic regions, prolonged fever of unknown origin, atypical pulmonary infiltrates).

Autoimmune Diseases

The diagnostic tests for autoimmune diseases should follow the established criteria, such as that of the American College of Rheumatology.

Monoclonal Gammopathy

The workup should include serum protein electrophoresis, urine protein electrophoresis, serum and urine immunofixation, and serum free light chain assays. Bone marrow evaluation should be performed to confirm an underlying plasma cell dyscrasia and/or lymphoproliferative disorder.

Treatment

Therapy should be directed to treatment of the underlying condition, for example, chronic infection, autoimmune disease, and malignancy such as myeloma, lymphoma, or CLL.

Treatment of monoclonal immunoglobulin–associated MPGN is complex. Conservative as well as immunosuppressive therapy with the use of corticosteroids (alone or in combination with an alkylating agent), thalidomide, bortezomib, and mycophenolate mofetil (MMF) have been used in a small number of patients with variable outcomes. Preliminary results in seven patients treated with rituximab have been encouraging: five of seven had a complete remission of the nephrotic syndrome and two of seven had a partial response,[31] but our own unpublished observations have not been so encouraging. Treatment also may differ based on the type of the immunoglobulin. In patients with IgM monoclonal proteins, we suggest a regimen used to treat Waldenström macroglobulinemia for initial therapy: rituximab 4 doses of 375 mg/m^2, with or without corticosteroids. For patients with non-IgM monoclonal proteins, a regimen of bortezomib plus dexamethasone or bortezomib, cyclophosphamide, and dexamethasone similar to that used in myeloma could be considered because these regimens are well tolerated and safe for use in renal failure, with minimal dose adjustments needed. We typically treat patients for at least 6 months and then reassess. Some patients also may respond to a 3- to 6-month combined course of prednisone and cyclophosphamide with disappearance of the monoclonal gammopathy. Daratumumab is an IgG1-kappa human monoclonal antibody that binds to the CD38 transmembrane glycoprotein on the surface of tumor cells and induces apoptosis. The molecule showed promise in the treatment of refractory multiple myeloma and is being evaluated in patients with proliferative glomerulonephritis and monoclonal immune deposits. Success has been reported with the use of autologous stem cell transplantation with monoclonal gammopathy of renal significance and light chain proximal tubulopathy, but apart from unpublished anecdotal cases no information is available on its use regarding monoclonal immunoglobulin–associated MPGN.[32] Prospective, controlled studies in larger cohorts of patients with MPGN and monoclonal gammopathy are needed to ascertain optimal therapy.

Similarly, there is no strong evidence to guide treatment in patients with “idiopathic” MPGN.[33] Corticosteroids have been widely used as monotherapy and/or in combination with other immunosuppressives. In a randomized trial, 80 children with nephrotic range proteinuria and preserved renal function were randomly assigned to either prednisone or lactose 40 mg/m^2 every other day for a mean duration of 41 months.[34] Prednisone therapy had a significantly lower rate of treatment failure (40% vs. 55%), but was associated with significant toxicity, particularly hypertension, and it is uncertain whether the findings (published in 1992) are applicable to contemporary practice. No randomized studies with corticosteroids have been performed in adults with idiopathic MPGN.

Cytotoxic agents have been tried, with unimpressive results and significant side effects. Calcineurin inhibitors also have been used in uncontrolled studies, suggesting a modest decline of proteinuria in patients with MPGN not otherwise characterized. Data on the use of MMF in patients with MPGN is limited.[35-37]

A small observational study compared five adults treated with MMF and oral prednisolone to six patients on no immunosuppressive agents.[35] At 18 months, proteinuria fell and glomerular filtration rate (GFR) was preserved or improved in the MMF group, compared with no change in proteinuria and a 40% decline in GFR in patients who were not treated. Whether the benefit was derived from MMF or prednisone cannot be ascertained from the study.

Our own experience with rituximab is limited to four patients with idiopathic MPGN.[38] Rituximab 1000 mg intravenously on days 1 and 15 led to a 65% reduction in proteinuria and preserved the GFR over 1 year.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines published in 2012 recognized difficulties in interpreting previous information, because in many instances historical controls were used, studies antedated the use angiotensin II blockade, statistical significance was marginal, or the power to detect substantial differences was small. More importantly, in these studies, the underlying pathogenic processes that lead to MPGN were not taken into account. Thus the KDIGO guidelines only “Suggest that adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome AND progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate-day or daily corticosteroids with initial therapy limited to less than 6 months.”[33]

We have taken a pragmatic approach based on our clinical experience, as follows:

- Patients with normal kidney function, no active urinary sediment, and non-nephrotic range proteinuria can be treated conservatively as outlined in Chapter 79, because the long-term outcome is relatively benign in this setting. Frequent follow-up is required initially to detect early deterioration in kidney function. If there is no disease progression, follow-up every 6 months should suffice.
- Patients with nephrotic syndrome and preserved renal function could be treated with a regimen similar to that used in focal segmental glomerulosclerosis, such as prednisone 1 mg/kg/day (maximum dose 60 to 80 mg/day) for 12 to 16 weeks (see Chapter 18). If the patient

responds, prednisone is gradually tapered to alternate-day therapy over 6 to 8 months. If there is less than a 30% reduction in proteinuria after 12 to 16 weeks, we recommend tapering and discontinuation of prednisone. Calcineurin inhibitors may be considered in patients who do not respond to or tolerate glucocorticoids.

- Patients who present with impaired kidney function, with or without nephrotic syndrome and without crescents, also can be considered for treatment with corticosteroids, as mentioned previously. If there is no response, cyclophosphamide 2 mg/kg/day, (reduced to 1.5 mg/kg/day in patients with a serum creatinine greater than 2.5 mg/dL or age greater than 60 years) for 3 to 6 months could be added, realizing that the efficacy of cyclophosphamide in these patients has not been demonstrated.
- Patients presenting with rapidly progressive disease and crescents on biopsy can be treated as in other forms of crescentic glomerulonephritis with pulse methylprednisolone followed by oral corticosteroids and cyclophosphamide (see Chapter 25).
- Patients who present with advanced renal insufficiency and severe tubulointerstitial fibrosis of renal biopsy are unlikely to benefit from immunosuppressive therapy.

Transplantation

Recurrent MPGN after kidney transplantation is discussed in Chapter 108.

CRYOGLOBULINEMIC GLOMERULONEPHRITIS

Definition

Cryoglobulins are immunoglobulins that precipitate at cold temperatures and dissolve when rewarmed. Cryoglobulins can be present in the setting of infections, autoimmune diseases, and monoclonal gammopathy. Thus all of the three above-mentioned causes can present with an MPGN pattern of injury with intraluminal deposits (immune microthrombi) suggestive of cryoglobulins.

Cryoglobulins are often divided into three types (Table 21.2). Type I cryoglobulinemia is characterized by the presence of a single monoclonal immunoglobulin, most often resulting from an underlying B-cell hematologic malignancy, typically Waldenström macroglobulinemia or multiple myeloma. In the absence of criteria for malignancy, the diagnosis of MGRS should be established. The cryoglobulins are usually IgM or IgG, but IgA and monoclonal free light chains also may occur.

In type II mixed cryoglobulinemia, there is a mixture of monoclonal IgM with rheumatoid factor activity directed against a polyclonal IgG. It is most commonly due to chronic infections, generally HCV infection, but also HBV and HIV infections. It also can occur in the context of autoimmune diseases, particularly Sjögren syndrome, in which it is mostly type II cryoglobulins. In patients with HCV infection, cryoglobulinemia may be the first manifestation of liver disease.[5,39]

In type III mixed cryoglobulinemia, the IgG and IgM are polyclonal. Type III cryoglobulinemia is most commonly seen in HCV infection, as well as in chronic inflammatory and autoimmune disease (e.g., SLE and Sjögren syndrome), and in lymphoproliferative malignancies. Thus there is a significant overlap between the underlying causes of type II and III cryoglobulins.

Clinical Presentation

The syndrome of cryoglobulinemia is caused by deposition of antigen-antibody complexes in capillaries and small arterioles and occasionally in small arteries. Most cases are associated with HCV. In the majority of patients with HCV infection, the immune complexes consist of HCV, anti-HCV IgG, and monoclonal IgM anti-IgG (with rheumatoid factor activity) (type II mixed cryoglobulinemia). Clinical presentation of mixed cryoglobulinemia includes weakness, palpable nonpruritic purpura (Fig. 21.4), symmetric arthralgias (arthritis is rare), peripheral neuropathy and, renal involvement.[40] The purpura is usually painless and mainly localized to the extremities and buttocks similar to patients with IgA vasculitis (see Chapter 23). Other manifestations include digital necrosis (Fig. 21.5), congestive heart failure, pulmonary infiltrates, and mesenteric ischemia. The clinical syndrome and dominant symptoms may evolve over time. On the other hand, patients with type I cryoglobulinemia are usually asymptomatic. Renal disease will be manifested in approximately 20% to 60% of the patients. The clinical presentation varies from microscopic hematuria with low-grade proteinuria to a full-blown nephrotic or nephritic syndrome or both. Hypertension is common and can be severe. Renal disease is a major determinant of long-term prognosis and substantially increases mortality.

Evaluation

Laboratory data suggestive of a cryoglobulin are low C4 levels (and normal or mildly decreased C3 levels) and a positive rheumatoid factor. It is crucial that blood is drawn into collection tubes that have been prewarmed to 37° C without anticoagulants, because anticoagulants can produce false-positive results due to cryofibrinogen or heparin-precipitable complexes. However, in as many as 40% of patients with type II and in occasional patients with type III mixed cryoglobulinemia, circulating cryoglobulins may not be detected. In some cases, renal disease presents in the absence of detectable cryoglobulins or other manifestations of mixed cryoglobulinemia such as purpura or arthritis. There is a poor correlation between the clinical manifestations and the cryocrit.

On renal biopsy an MPGN lesion is seen in more than 80% of the cases (Fig. 21.6). Light microscopy findings that point toward a cryoglobulinemic MPGN include a greater number of macrophages than seen in other forms of proliferative glomerulonephritis, as well as the presence of intraluminal thrombi composed of precipitated cryoglobulins. On IF, there is diffuse IgM deposition in capillary loops, and EM may show subendothelial deposits that often have a characteristic "fingerprint" pattern of cryoprecipitates. MPGN with features of cryoglobulins should lead to evaluation for infections (in particular HCV infection), autoimmune diseases (in particular Sjögren syndrome), and monoclonal gammopathies. Features that suggest glomerulonephritis due to monoclonal immunoglobulin–associated cryoglobulins (type I

TABLE 21.2 Cryoglobulin Classification and Associated Diseases

	Cryoglobulin Type	Immunoglobulin Class	Associated Diseases
I.	Monoclonal immunoglobulins	M>G>A>BJP	Myeloma, CLL, Waldenström macroglobulinemia
II.	Mixed cryoglobulins with monoclonal immunoglobulins	M/G≫G/G	Infection (hepatis C), Sjögren syndrome, CLL, lymphoma
III.	Mixed polyclonal immunoglobulins	M/G	Infection (hepatitis B/C), SLE, RA, vasculitis, neoplasia

CLL, Chronic lymphocytic leukemia; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus; *BJP,* Bence Jones protein (light chains).

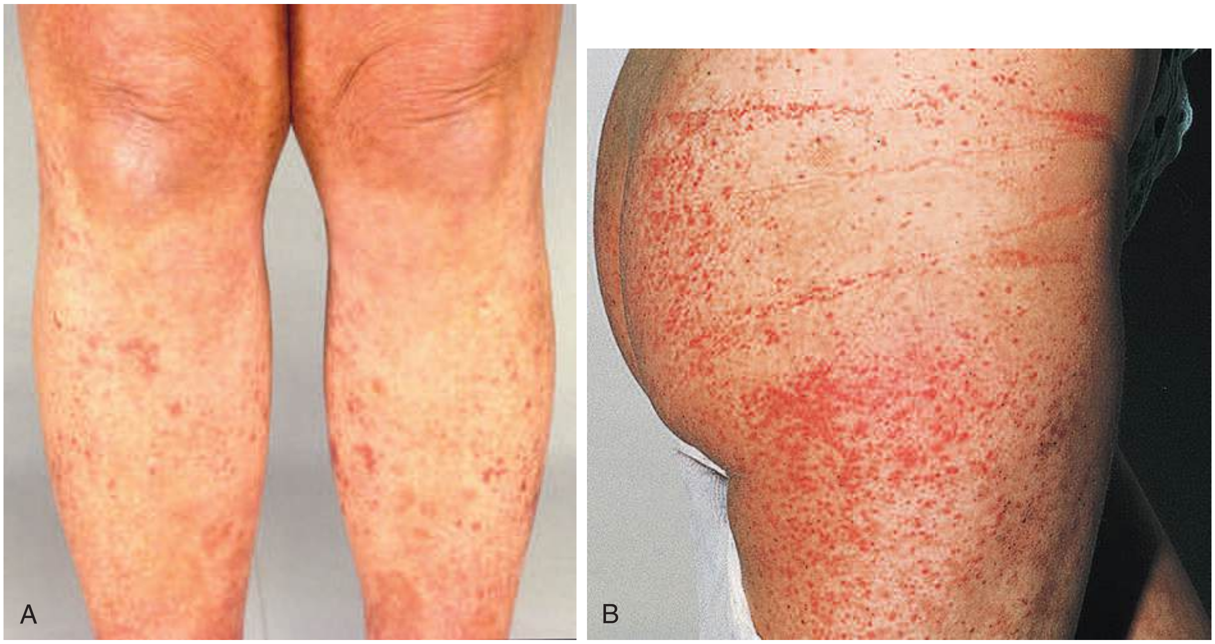

Fig. 21.4 Purpura in patient with hepatitis C virus–associated cryoglobulinemia. **(A)** Palpable nonpruritic purpura affecting the lower extremities in a patient with hepatitis C virus infection and cryoglobulinemia. Raised purpuric lesions are present on the legs. Differential diagnosis for patients with dermatorenal syndromes includes Henoch-Schönlein purpura (IgA vasculitis) and antineutrophil cytoplasmic antibody–associated vasculitis. **(B)** Purpuric lesions are present on the patient's buttocks and thigh. Note the purpuric lesions along the superior and inferior elastic border of the undergarment line.

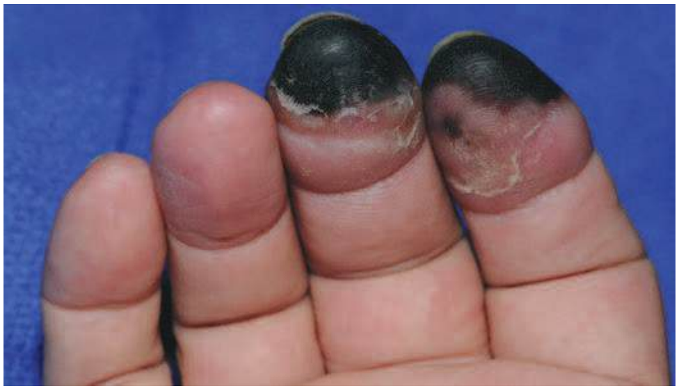

Fig. 21.5 Necrosis of the fingertips in a patient with cryoglobulinemia.

cryoglobulins) include intraluminal periodic acid–Schiff (PAS) positive (hyaline-like) deposits on light microscopy, intraluminal monoclonal immunoglobulin on IF microscopy, and substructures (microtubules, fibrillary, finger prints) on EM.

Treatment

Patients with a rapidly progressive, organ-threatening, or life-threatening cryoglobulinemic syndrome such as rapidly progressive glomerulonephritis, severe digital ischemia, gastrointestinal vasculitis, rapidly progressive neuropathy, central nervous system vasculitis, and heart failure should be treated with immunosuppressive therapy, regardless of the cause of the mixed cryoglobulinemia.[41] This typically involves a short course of corticosteroids combined with either rituximab, or if this is unavailable, cyclophosphamide.

Patients with life-threatening disease (e.g., acute respiratory failure with pulmonary hemorrhage) or cryoglobulinemia-associated hyperviscosity syndrome should also receive plasmapheresis in addition to immunosuppressive therapy. After disease stabilization, therapy should be directed at the underlying disease. Patients with HCV infection (without decompensated cirrhosis) and mixed cryoglobulinemia should receive antiviral therapy as per current guidelines.[42]

However, patients with severe vasculitic manifestations as described previously and not yet treated with antiviral therapy should receive immunosuppression first, with antiviral therapy delayed for 1 to 4 months in agreement with the European League Against Rheumatism (EULAR) and the Group for the Study of Cryoglobulinemias (GISC) guidelines.[43,44] The rationale is based on the fact that immunosuppression can rapidly improve inflammation and resolve target-organ damage. However, this approach may change with the introduction of newer interferon-free antiviral regimens. The specific antiviral drugs and therapy schemes depend on the HCV genotype, renal function, prior treatment response, type of antiviral agent used, tolerance to treatment, and clinical and laboratory response to treatment.

Patients with a lymphoproliferative disorder should receive disease-specific therapy. Exceptions include mixed cryoglobulinemia secondary to HIV or HBV infections; in such patients, antiviral therapy should be initiated before or concomitantly with immunosuppressive therapy, particularly rituximab.

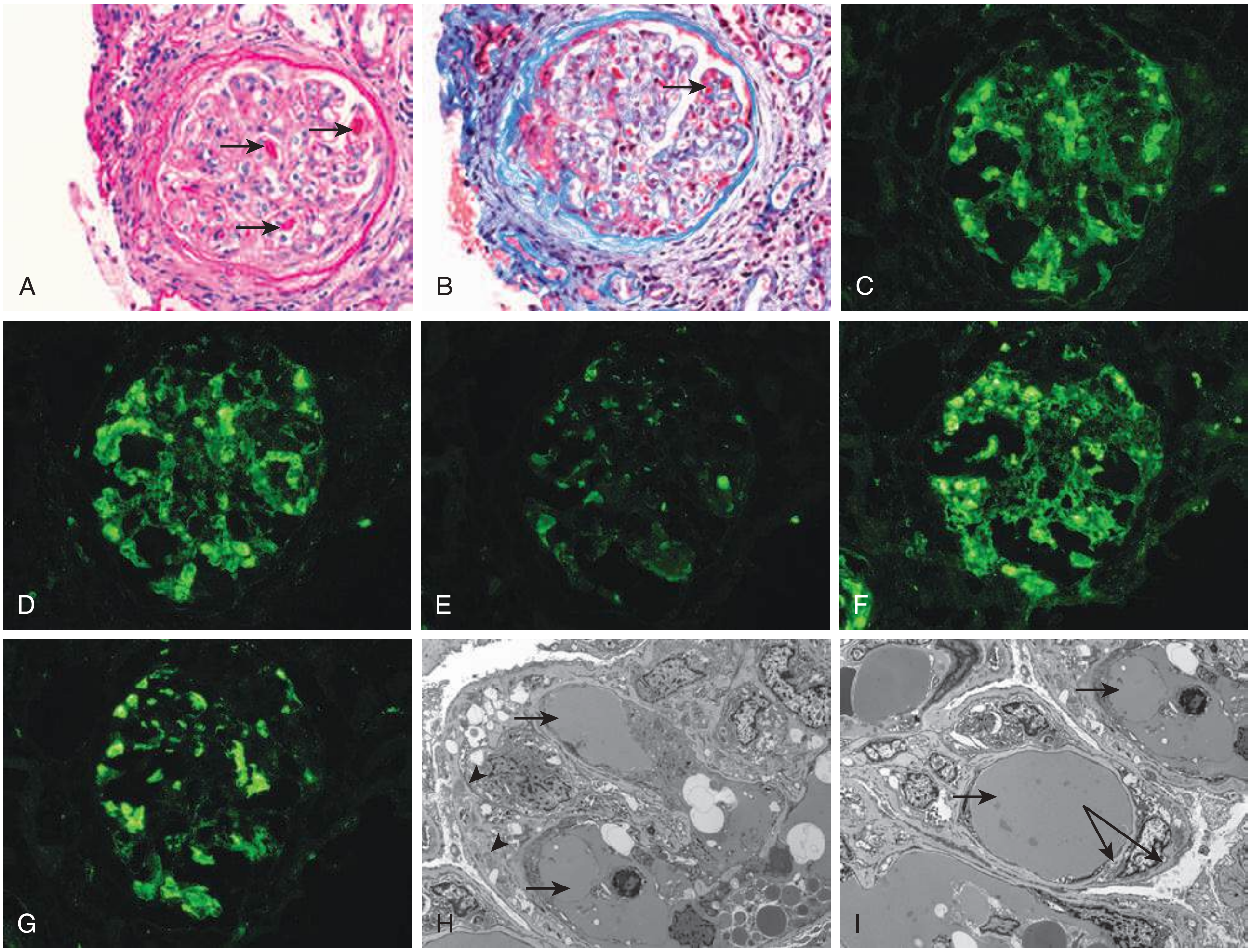

Fig. 21.6 Membranoproliferative glomerulonephritis and cryoglobulins associated with Sjögren syndrome. (A and B) Light microscopy showing an MPGN pattern of injury. (**A,** Periodic acid–Schiff stain ×40; **B,** Masson trichrome stain, ×40.) Immunofluorescence microscopy showing bright granular staining for **(C)** IgG, **(D)** IgM, **(E)** C3, **(F)** kappa chains, and **(G)** lambda light chains. (**H** to **I**) Electron microscopy showing numerous intraluminal deposits (arrowheads in H); subendothelial deposits and double contours (double arrow in H) are also present. *Black arrows* point to intraluminal deposits representing cryoglobulins (**H** and **I,** ×2900).

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SELF-ASSESSMENT QUESTIONS

1. A 50-year-old woman is referred for sudden onset of edema and hypertension. Past medical history is unremarkable. Apart from a blood pressure of 155/95 mm Hg and 2+ edema, the physical examination is unremarkable. Serum creatinine is 1.8 mg/dl and proteinuria is 3.2 g/24 h. Urinalysis shows 50 to 100 red blood cells per high-power field, of which more than 25% are dysmorphic. C3/C4 complement levels, antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), and anti–glomerular basement membrane (GBM) are all normal or negative. A renal biopsy is performed. Light microscopy shows a membranoproliferative glomerulonephritis (MPGN) pattern of injury on immunofluorescence (IF) immunoglobulin G (IgG) (+++), IgM (+), IgA (–) C3 (+++), C1q (–), kappa (+++), lambda (–) chains, and electron microscopy (EM) duplication of the GBM with subendothelial deposits.
   The most likely diagnosis is:
   A. MPGN secondary to a monoclonal gammopathy
   B. MPGN secondary to underlying infection
   C. MPGN secondary to abnormalities in the alternative pathway of complement
   D. MPGN type I (idiopathic)
2. A 65-year-old man undergoes orthotopic liver transplantation for liver failure secondary to hepatitis C virus (HCV) infection. The immediate post-transplantation course is uneventful. However, 1 year later he presents with recurrence of HCV infection, blood pressure of 150/90 mm Hg, proteinuria of 3 g/24 h, a rising serum creatinine up to 1.8 mg/dl, and a serum albumin of 3.9 g/dl. Urinalysis shows 40 to 50 red blood cells per high-power field, of which more than 25% are dysmorphic. C3 complement is 101 mg/dl (normal 75-115 mg/dl), C4 complement is 2 mg/dl (normal 10-40 mg/dl), and rheumatoid factor is positive.
   In this patient, a renal biopsy is most likely to show:
   A. Focal segmental glomerulosclerosis
   B. Minimal change disease
   C. Membranous nephropathy
   D. Cryoglobulinemic glomerulonephritis
3. Which of the following causes of glomerulonephritis is typically associated with low serum complement C4?
   A. Mixed cryoglobulinemia
   B. Henoch-Schönlein purpura nephritis
   C. Anti-GBM disease
   D. Post-streptococcal glomerulonephritis
4. A 52-year-old woman with a long history of rheumatoid arthritis and Sjögren syndrome is evaluated for new onset of a skin rash on the lower extremities and impaired kidney function. Blood pressure is 150/90 mm Hg. Serum creatinine is 1.8 mg/dl. Urinalysis shows more than 50% red blood cells per high-power field, of which more than 25% are dysmorphic. Proteinuria is 2.8 g/24 h. C3 complement is 82 mg/dl (normal 75-115 mg/dl), C4 complement is less than 5 mg/dl (normal 10-40 mg/dl). ANCA, ANA, anti-DS-DNA and anti-GBM serologic results are negative.
   In this patient a renal biopsy is most likely to show:
   A. MPGN with IgA (+++), C3 (++), IgG (+), kappa (+), lambda (++)
   B. MPGN with linear IgG
   C. MPGN with C3 (+++), IgG (neg), IgM (neg), IgA (neg)
   D. MPGN with IgG (++), IgM (+++), IgA (+) C3 (++), kappa (++), lambda (++)

22

Glomerulonephritis Associated With Complement Disorders

H. Terence Cook, Matthew C. Pickering

Glomerular diseases associated with abnormalities of the complement system include thrombotic microangiopathy (see Chapter 29) and glomerulonephritides. Activation of complement in most cases of glomerulonephritis is secondary to other processes in the glomerulus such as deposition of immune complexes. However, in a small number of cases, abnormalities of the complement system itself, both genetic and acquired, are the cause of glomerulonephritis and it is those that are discussed in this chapter. Abnormalities of the classic pathway of complement have been associated with glomerulonephritis. Most importantly there is an association between deficiencies of early components of the classic pathway of complement, autoimmunity, and glomerulonephritis.[1] This is most clearly seen in the very rare individuals with C1q deficiency, almost all of whom have a lupus-like illness. This is thought to be due to the failure of clearance of immunogenic apoptotic bodies and other cellular debris in the absence of normal classic pathway complement activation.

The largest group of patients with complement abnormalities and glomerulonephritis is that in which there is an abnormality of control of the alternative pathway of complement activation with glomerular deposition of C3 in the absence of immunoglobulin—now termed C3 glomerulopathy (Box 22.1).

C3 GLOMERULOPATHY

C3 glomerulopathy is a recently introduced term[2] that encompasses glomerular disease characterized by the accumulation of complement component C3 in glomeruli because of abnormal control of complement activation, deposition, or degradation, particularly abnormal control of the alternative pathway of complement activation (Fig. 22.1). Characteristically, glomeruli show strong immunohistologic staining for C3 without significant staining for immunoglobulins or for components of the classic pathway of complement activation, C1q and C4. C3 glomerulopathy, thus defined, is distinct from atypical hemolytic uremic syndrome (aHUS), which also may be associated with alternative pathway activation, because in aHUS complement activation is on the renal endothelium and is not associated with well-defined deposits on electron microscopy (EM; see Chapter 29). C3 glomerulopathy may show a variety of appearances on light microscopy, including mesangial proliferation, a membranoproliferative pattern (see Chapter 21), endocapillary proliferation, and crescent formation. Importantly, it is now recognized that many cases previously classified morphologically as membranoproliferative glomerulonephritis (MPGN) are cases of C3 glomerulopathy. This includes cases that had been classified as MPGN types I, II, or III. Indeed, it appears that most cases that have previously been called MPGN type III (see Chapter 21) are examples of C3 glomerulopathy. However, monoclonal gammopathy–associated MPGN also may be misclassified as C3 glomerulopathy, if the glomerular immunoglobulin deposits are masked and only become detectable after protease digestion of the histologic section (see Chapter 21).

On EM, C3 glomerulopathy also may have a variety of appearances. Common is dense deposit disease (DDD), which is characterized by replacement of the glomerular basement membrane (GBM) by dense bands on EM (Fig. 22.2). In some cases the light microscopic appearance in DDD resembles that of MPGN, explaining the older term MPGN type II (see also Chapter 21). However, as will be discussed later in more detail, most cases of DDD do not have MPGN morphology on light microscopy.

Cases of C3 glomerulopathy that do not have typical highly dense deposits of DDD show a range of appearances on EM with deposits that may be mesangial, subendothelial, or subepithelial and may be more or less well defined. The relevance of the site of the deposits has not been defined, although it is likely, by analogy with diseases such as lupus nephritis, that capillary wall deposits are associated with more glomerular inflammation and higher levels of proteinuria. These cases of non-DDD C3 glomerulopathy have been given the collective name of C3 glomerulonephritis (C3GN).[3,4]

Etiology and Pathogenesis

The pathogenesis of C3 glomerulopathy involves dysregulation of the alternative pathway of complement (see Fig. 21.1). In health the alternative pathway is constantly being activated, but at a very low rate. This means there is a constant generation of small amounts of activated C3, and this low-grade activation allows the pathway to be rapidly switched on when needed. In the presence of pathogens, rapid amplification of C3b is achieved through a positive feedback loop (termed the C3b amplification loop) that can generate millions of C3b molecules within minutes. Because this amplification can progress so rapidly, very efficient systems are needed to prevent inappropriate activation of the pathway. The most important regulator of the alternative pathway is factor H (CFH). CFH does this in three ways: (1) it blocks the formation of alternative pathway C3 convertases by binding to C3b and thereby inhibiting interaction between C3b and factor B, (2) it promotes the spontaneous dissociation of these convertases, and (3) it works together with another plasma protein, factor I, to cleave C3b to iC3b. Mice that have been genetically engineered to lack factor H have undetectable circulating C3 because their C3 is constantly consumed by the uncontrolled alternative pathway.[5]

CFH is an abundant single chain glycoprotein predominantly made in the liver. It is composed of protein subunits, termed short consensus repeat (SCR) domains. The activity of CFH can be modulated by a group of closely related proteins called factor H–related (CFHR) proteins.[6] There are five in CFHR proteins in humans (CFHR1-5) encoded by individual genes adjacent to the *CFH* gene. The CFHR proteins, like CFH, are composed of SCR domains and share considerable sequence similarity with CFH. This has led to genomic rearrangements within the *CFH-CFHR* locus, which include both polymorphisms and mutations. The most common polymorphism is a combined deletion of the *CFHR1* and *CFHR3* genes. This is present in homozygosity in 5% to 20% of healthy individuals depending on ethnic origin. It is now clear that some CFHR proteins are able to compete with the binding of CFH to C3b.[7] This is important because, unlike CFH, the CFHR proteins are unable to inhibit complement activation. Furthermore, the CFHR-C3b interaction prevents CFH from negatively regulating C3b production. Consequently, the CFHR-C3b interaction promotes C3b amplification, a process termed CFH deregulation (Fig. 22.3). In many cases of C3 glomerulopathy the pathogenesis is a failure of CFH to control the activation of the alternative pathway in the circulation, and this is associated with low levels of circulating C3 because of uncontrolled consumption. Up to 80% of patients with DDD and up to half of patients with C3GN have low levels of serum C3.[3] Many of these patients have a C3 nephritic factor (C3Nef). C3Nefs are autoantibodies that stabilize the alternative pathway C3 convertase by preventing CFH from carrying out its normal functions. It therefore seems likely that C3Nef plays an important etiologic role in these patients. C3Nef can be identified in 40% to 60% of cases of C3GN and 80% to 90% of cases of DDD.[3,8] However, our understanding of the role of C3Nef is complicated by the fact that C3Nefs also may be found in patients with other forms of glomerulonephritis and even in healthy patients. In other cases, genetic mutations lead to failure of alternative pathway control. These cases include patients with complete CFH deficiency secondary to gene deletion,[9,10] mutations in CFH that interfere with its binding to C3b,[11,12] and mutations in C3 that change its structure so that it cannot be inhibited by CFH.[13] In some patients, failure of

BOX 22.1 Definitions

C3 glomerulopathy—A *disease process* secondary to abnormal control of complement activation, deposition, or degradation characterized by predominant glomerular C3 fragment deposition with electron-dense deposits on electron microscopy.

Dense deposit disease—A form of C3 glomerulopathy with a characteristic electron microscopy appearance of intensely osmiophilic transformation of the glomerular basement membrane.

C3 glomerulonephritis—C3 glomerulopathy without the characteristic appearances of dense deposit disease.

Glomerulonephritis with dominant C3—A morphologic term for cases of glomerulonephritis with dominant staining for C3c. Dominant is defined as C3c intensity ≥2 orders of magnitude more than any other immune reactant on a scale of 0 to 3 (including 0, trace, 1+, 2+, 3+). Many, but not all, of these will represent cases of C3 glomerulopathy.

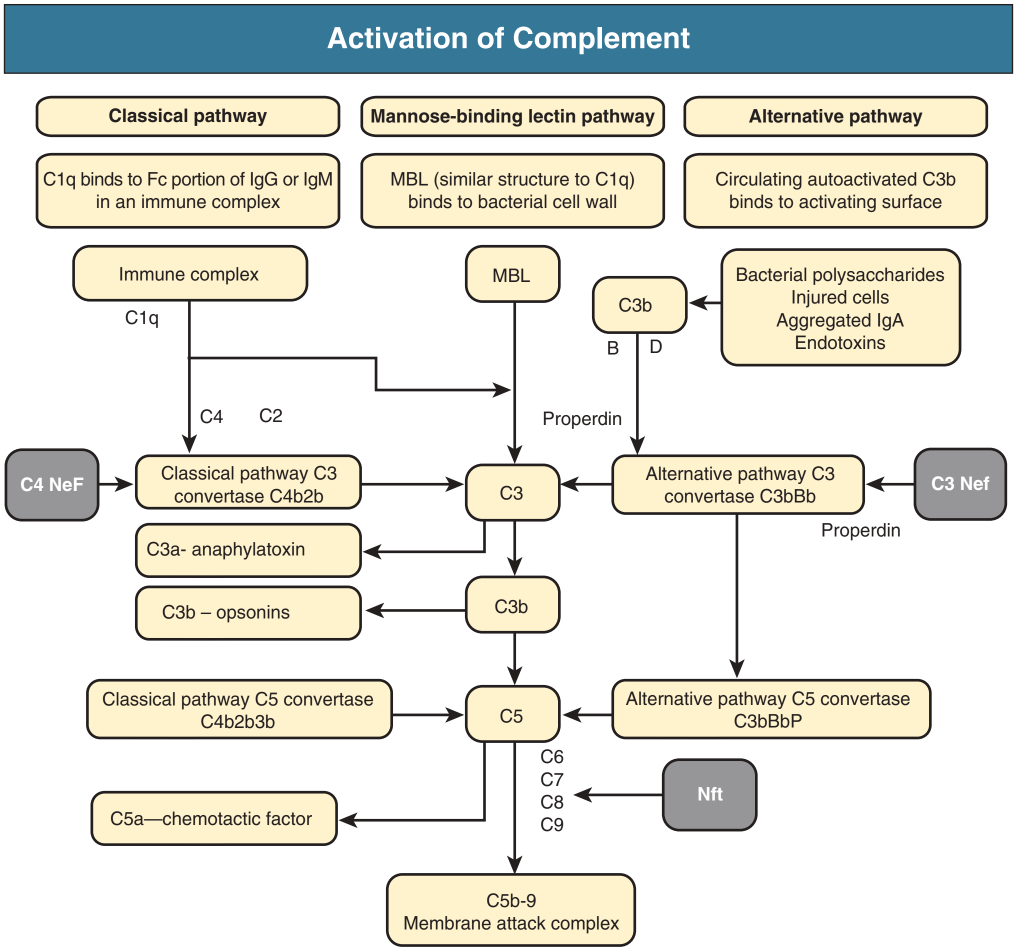
Activation of Complement
Classical pathway
Mannose-binding lectin pathway
Alternative pathway
C1q binds to Fc portion of IgG or IgM in an immune complex
MBL (similar structure to C1q) binds to bacterial cell wall
Circulating autoactivated C3b binds to activating surface
Immune complex
C1q
MBL
C3b
B
D
Bacterial polysaccharides
Injured cells
Aggregated IgA
Endotoxins
C4
C2
Properdin
C4 NeF
Classical pathway C3 convertase C4b2b
C3
Alternative pathway C3 convertase C3bBb
C3 Nef
Properdin
C3a- anaphylatoxin
C3b – opsonins
C3b
Classical pathway C5 convertase C4b2b3b
C5
Alternative pathway C5 convertase C3bBbP
C6
C7
C8
C9
Nft
C5a—chemotactic factor
C5b-9
Membrane attack complex

Fig. 22.1 Mechanisms of activation of the complement pathways. These activators include nephritic factors (NeF, Nef). *MBL,* Mannose-binding lectin; *Nft,* Nephritic factor of the terminal pathway.

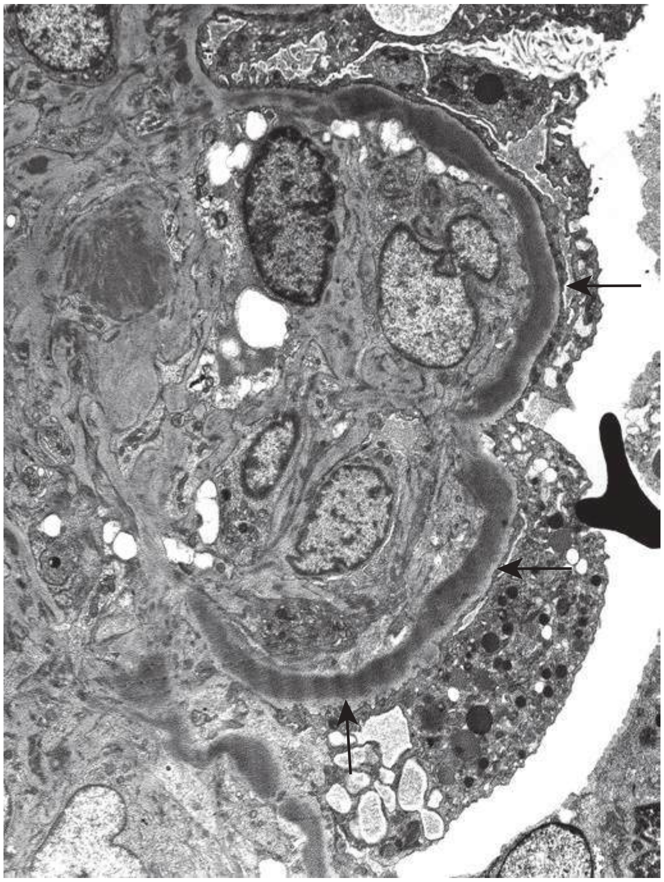

Fig. 22.2 Dense deposit disease (DDD). Electron micrograph of a glomerulus showing typical appearances of DDD with very osmiophilic transformation of the basement membrane *(arrows)*.

alternative pathway control is associated with autoantibodies directed against factor H that target its regulatory domain.

In those cases of C3 glomerulopathy that are not associated with excessive activation of C3 in the circulation, it can be assumed that there is a failure to control the alternative pathway locally within the glomerulus. This might be due to a failure to control activation or inappropriate handling of the fragments of C3 generated by alternative pathway activation. In most cases the pathogenesis is still not clear, but there is an example of a familial form of C3 glomerulopathy (now called CFHR5 nephropathy) without systemic C3 activation. This is a common cause of kidney disease in Cyprus, where the mutation is a duplication of the first 2 exons of the *CFHR5* gene.[14] This leads to an abnormal protein that forms multimers that are able to deregulate the activity of CFH on surfaces.[7] Therefore it appears the abnormal protein interferes with the action of CFH locally within the glomerulus and enhances alternative pathway activation.

Apart from the mutations described previously, several other mutations and polymorphisms in complement genes have been associated with C3 glomerulopathy, but their role is at present uncertain. It is also notable that there appears to be an association between monoclonal gammopathy and C3 glomerulopathy (see Chapter 21).[15-17] In some cases the monoclonal immunoglobulin may act as a C3Nef.

Epidemiology

DDD has been reported to have a prevalence of 2 to 3 per million population and to be primarily a disease of children and young adults. However, in a 2009 series from New York 39% of the adult patients were over 60 years of age.[18] DDD affects males and females equally in many cohorts, although some studies have shown a female predominance. In one large series from France[3] the ratio of C3GN to DDD was approximately 2 : 1 and patients with C3GN were significantly older, with a mean age at diagnosis of 30 years. In the United Kingdom and Ireland we found a C3GN/DDD ratio of approximately 3 : 1 and estimated the incidence of C3 glomerulopathy at 1 to 2 per million population per year.[19] It is likely that the apparent incidence of C3GN will increase as the entity becomes better recognized by nephrologists and pathologists. There is no reliable information on geographic variation in incidence, with the notable exception of C3GN resulting from a specific mutation in *CFHR5*, apparently originating in Cyprus several hundred years ago.[14]

Clinical Manifestations

Dense Deposit Disease

At presentation almost all patients have proteinuria, usually with hematuria. Nephrotic range proteinuria is present in two thirds of patients[18,20] and frank nephrotic syndrome in 12% to 65% in different series. In a series of 98 patients from North America[21] about one fifth of patients did not suspect a problem and kidney disease was detected as part of a routine examination. Many patients have initial signs and symptoms of acute nephritic syndrome. In some cases there may be episodes of acute kidney injury that show complete clinical resolution.[22] Decreased kidney function is common at presentation and is more common in adults. Hypertension is commonly found either at presentation or in follow-up. In about half of patients, clinical onset of DDD is preceded by acute infection with elevated antistreptolysin O (ASO) titers in 20% to 40%.

Patients with DDD may develop ocular drusen (Fig. 22.4), lipoproteinaceous deposits of complement-containing debris within the Bruch membrane beneath the retinal pigment epithelium. This pathology is similar to that in age-related macular degeneration (AMD), but, in contrast to AMD, drusen in DDD may be found as early as the second decade of life. There is no correlation between the severity of the disease in the kidney and that in the eye. A small minority of patients with DDD have acquired partial lipodystrophy (APL), a condition with symmetric loss of adipose tissue from the face, arms, and upper portions of the trunk (see Fig. 22.4).

The overall long-term outcome in DDD is poor. In a series of 98 patients from North America, 50% of the patients progressed to end-stage renal disease (ESRD) within 10 years of diagnosis, with young females having the greatest risk for kidney failure.[21]

C3 Glomerulonephritis

C3GN has only recently been recognized, and thus clinical manifestations are less well defined. In a French series, 27% of patients with C3GN had nephrotic syndrome at presentation.[3] Approximately two thirds of patients had microhematuria at presentation, and about one third had elevated blood pressure. In that series the rate of progression to ESRD was similar to that in the patients with DDD.

In CFHR5 nephropathy in Cyprus the major clinical feature in young patients is hematuria. Microhematuria was present in 90%, and 20% of patients reported episodes of macrohematuria often associated with upper respiratory tract infection.[23] Proteinuria became more common with increasing age and was seen in 80% of males and 20% of females over the age of 50. Impaired kidney function was more common with increasing age, particularly in men, and of 18 patients who reached ESRD 78% were male. The cause for the striking gender difference in outcome is unclear.

Laboratory Findings

Low levels of serum C3 are found in approximately 80% of patients with DDD and up to 50% of patients with C3GN. In C3GN secondary

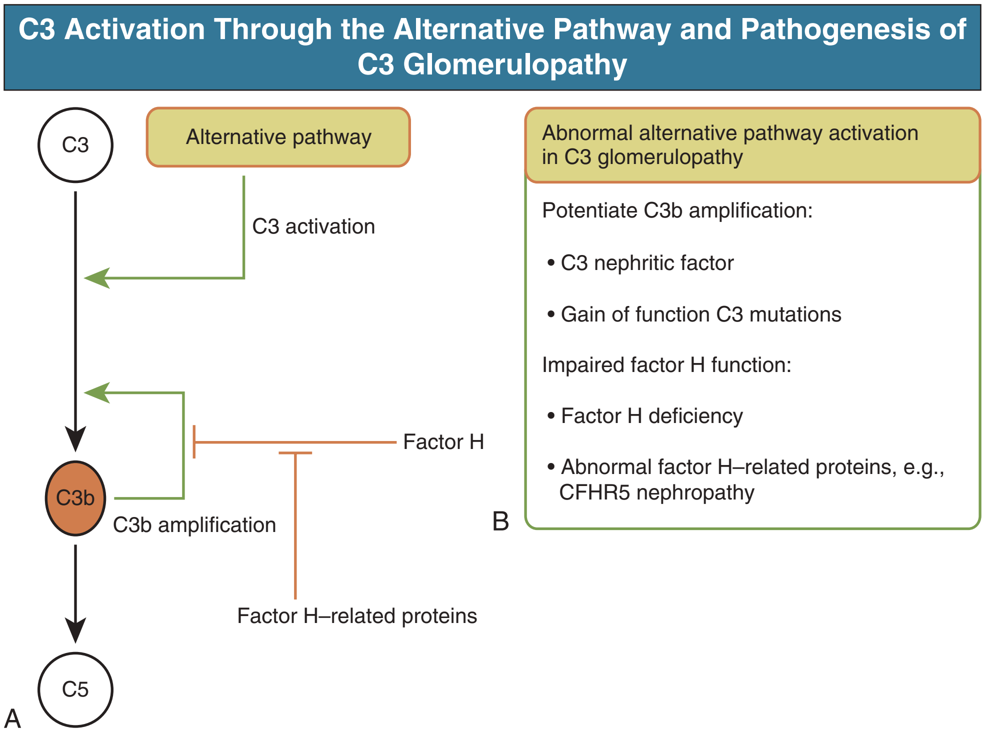
C3 Activation Through the Alternative Pathway and Pathogenesis of C3 Glomerulopathy
C3
Alternative pathway
C3 activation
Factor H
C3b
C3b amplification
Factor H–related proteins
C5
A
Abnormal alternative pathway activation in C3 glomerulopathy
Potentiate C3b amplification:
• C3 nephritic factor
• Gain of function C3 mutations
Impaired factor H function:
• Factor H deficiency
• Abnormal factor H–related proteins, e.g., CFHR5 nephropathy
B

Fig. 22.3 **C3 activation through the alternative pathway and pathogenesis of C3 glomerulopathy.** (A) Activation of C3 results in the formation of C3b and then C5 activation. C3b production is amplified through a positive feedback loop. Factor H inhibits this amplification (depicted). Some factor H–related proteins (e.g., complement factor H–related protein 5 [CFHR5]) interact with C3b and, unlike factor H, allow C3b amplification to proceed. In this way they antagonize the actions of factor H, in a process termed factor H deregulation. (B) C3 glomerulopathy is associated with abnormal (increased) activation of the alternative pathway. These include situations in which there is enhanced C3b amplification despite normal factor H function, for example, in the presence of C3 nephritic factor, and where there is a defect in the ability of factor H to negatively regulate the alternative pathway. Examples include cases of factor H deficiency (extremely rare); and abnormal factor H–related proteins associated with familial C3 glomerulonephritis (e.g., CFHR5 nephropathy).

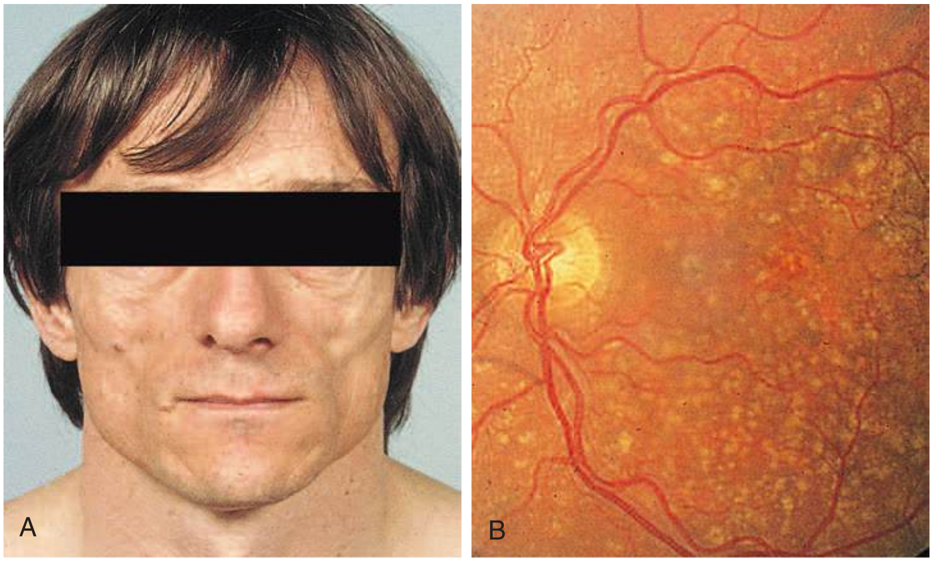

Fig. 22.4 **Dense deposit disease.** (A) Partial lipodystrophy. Note the absence of subcutaneous fat from the face. (B) Drusen bodies in the retina. (Courtesy Dr. C. D. Short, Manchester, UK.)

BOX 22.2 Serologic and Genetic Evaluation of C3 Glomerulopathy

Tests Recommended in All Patients With C3 Glomerulopathy

- Measurement of serum levels of C3 and C4
- Measurement of C3 nephritic factor
- CH50—classic pathway hemolytic assay, and AH50—alternative pathway hemolytic assay
- Measurement of factor H and factor I
- Serum paraprotein detection
- Testing for the genetic mutation of CFHR5 nephropathy
- Anti–factor H autoantibodies

Tests That Should Be Considered on a Case-by-Case Basis

- Measurement of serum factor B and C5
- Measurement of markers of C3 and C5 activation (e.g., C3d, Bb, soluble C5b9)
- Detection of autoantibodies to factor B
- Mutation testing of complement regulatory genes (e.g., CFH, CFI, CD46), activation protein genes *(C3, CFB),* and assessment of copy number variation across the *CFH-CFHR* locus

to CFHR5 nephropathy, serum C3 levels are typically normal. Serum levels of the early components of the classic pathway (C1q and C4) are usually normal. Most patients with DDD are positive for serum C3NeF and in more than 50% of patients C3NeF persists throughout the clinical course.[24] However, C3NeF is not a specific serologic marker because it also occurs with MPGN type I, lupus nephritis, and poststreptococcal glomerulonephritis. C3Nef can be identified in 40% to 60% of cases of C3GN.[3,8] It is important to note that methods for measuring C3Nef are not standardized.

Box 22.2 shows a list of investigations that may be helpful in C3 glomerulopathy.[25,26] It is recommended that investigations in the second category are discussed with experts and performed in laboratories with experience in complement assays. Complement laboratories across the world are listed on the International Complement Society (www.complement.org) and European Complement Network (www.ecomplement.org) websites. Depending on the clinical scenario, it may be possible to prioritize some of these assays. For example, in patients with C3 glomerulopathy and low serum C3 levels in the absence of C3NeF, it is important to test for anti-CFH autoantibodies. In familial cases of C3 glomerulopathy a search for genetic mutations may be important for elucidating pathogenesis and genetic counseling.

Pathology

The defining feature of C3 glomerulopathy is the presence of C3 (usually detected with an antibody to C3c) in glomeruli on immunohistologic examination (Fig. 22.5). In most cases the C3 staining is seen on capillary walls and in the mesangium, but in some cases the staining may be mainly mesangial. In some cases, particularly in DDD, C3 also may be found on the Bowman capsule or on tubular basement membranes.

The light microscopic appearances are quite variable. In both DDD and C3GN, membranoproliferative changes are common with increased glomerular lobulation, increase in mesangial matrix and cells, and capillary wall thickening with double contour formation (Fig. 22.6). In some cases there may be a predominantly mesangial proliferative pattern. Some cases show endocapillary hypercellularity, in part as a result of influx of macrophages or neutrophils. Sometimes this endocapillary hypercellularity may affect almost all the glomeruli, giving an appearance of diffuse endocapillary proliferative glomerulonephritis similar to that typically seen with postinfectious glomerulonephritis (PIGN). Crescent formation may be sufficiently prominent to merit the designation of crescentic glomerulonephritis (>50% crescents). In a series of 69 cases of DDD[27] the incidence of different histologic patterns was membranoproliferative (25%), mesangial proliferative (45%), crescentic (18%), and acute proliferative and exudative (12%). In a French series of patients with C3GN,[3] 71% showed an MPGN pattern on light microscopy.

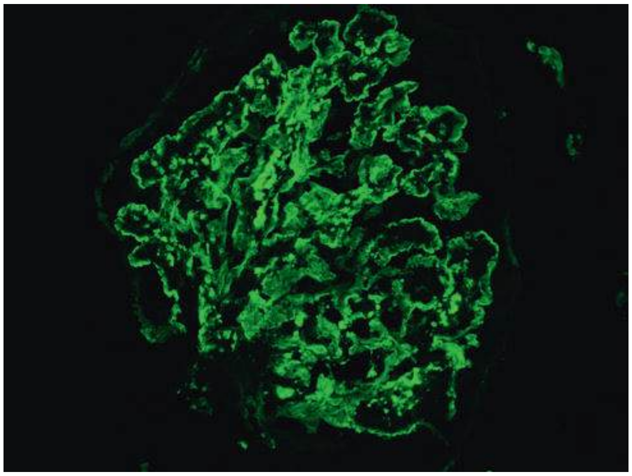

Fig. 22.5 Dense deposit disease (DDD). Immunofluorescence for C3c in a case of DDD. There is widespread staining of capillary walls and focal granular mesangial staining.

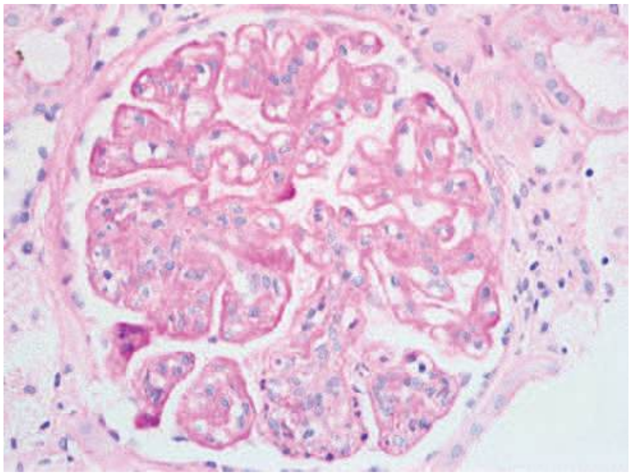

Fig. 22.6 C3 glomerulonephritis. Light microscopy in a case of C3 glomerulonephritis. The glomerulus shows a membranoproliferative pattern of injury, with increased mesangium, capillary wall thickening, and segmental endocapillary hypercellularity. (Periodic acid–Schiff staining.)

The EM appearances of C3 glomerulopathy are also very variable, but in many cases the diagnosis of C3 glomerulopathy can be suspected from the EM changes. By definition, DDD shows the presence of typical osmiophilic dense transformation of the GBM (see Fig. 22.2), with similar features often seen in the Bowman capsule and tubular basement membranes. However, these changes may be segmental within glomeruli, in some cases making it difficult to define DDD with certainty. In DDD there are typically large electron densities in the mesangium.

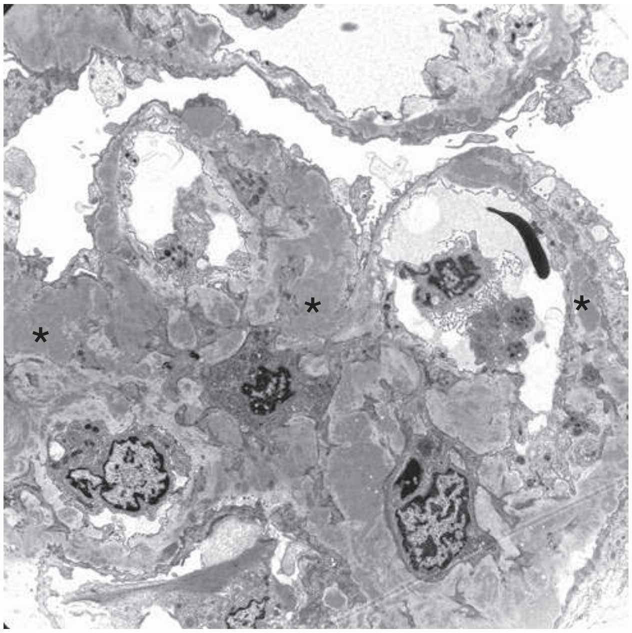

Fig. 22.7 **C3 glomerulonephritis.** Electron micrograph of a glomerulus in a case of C3 glomerulonephritis. There is a complex pattern of thickening of the glomerular basement membrane with intramembranous electron-dense material. *Similar deposits are also seen in the mesangium.

In some cases of C3GN, there is electron-dense material that expands the GBM similar to the changes in DDD but without such marked electron density; the distinction between these cases and DDD may not be clear-cut and depends on a subjective interpretation by the pathologist.[28] Other cases have more distinct subendothelial and mesangial electron-dense deposits reminiscent of those seen in immune complex glomerulonephritis. Some cases show a very complex pattern of intramembranous deposits that was previously designated as a form of MPGN type 3 (Fig. 22.7).

In both DDD and C3GN subepithelial hump-shaped deposits are frequently seen. These are identical to those characteristically seen in PIGN. Their significance is not clear, although it may be that they are more common in infectious exacerbations of the disease.

There are few data on the relationships between histology, clinical presentation, clinical course, and underlying genetic abnormalities. In several series of DDD the presence of crescents was associated with a more rapid decline in renal function.

Differential Diagnosis

The diagnosis of C3 glomerulopathy is relatively straightforward if there is isolated C3 deposition with typical deposits on EM. However, some patients have otherwise typical appearances of DDD or C3GN but also have small amounts of immunoglobulin in glomeruli, which presents a diagnostic challenge. Evidence suggests that, on immunofluorescence, the criterion with the best balance of sensitivity and specificity is the presence of dominant C3 staining with the intensity of C3, staining at least two orders of magnitude greater than any other immunoreactant (i.e., immunoglobulin G [IgG], IgM, IgA, and C1q).[26,29] This is referred to as glomerulonephritis with dominant C3 (see Box 22.1). In some cases, the initial kidney biopsy may not show C3-dominant GN, but it may appear in subsequent biopsies,[29-31] suggesting that repeat biopsy may be useful in cases with an atypical clinical course.

Another problem is the distinction of C3 glomerulopathy from PIGN. PIGN may show markedly reduced serum C3, and glomeruli may stain for C3 without immunoglobulin. In some cases the distinction from C3 glomerulonephritis may be possible only by following the patient to see if resolution of the disease occurs.[26] It has been suggested that PIGN could be considered a self-limiting form of C3 glomerulopathy. Some patients who have been labeled as having atypical PIGN have C3 glomerulopathy.[32] Cryoglobulinemia also should be considered in the differential diagnosis as cases may present with prominent C3 with only sparse IgG staining.

Treatment

The optimal treatment for C3 glomerulopathy remains undefined. Most information relates to DDD, because C3GN was not previously recognized as a specific diagnostic category. However, in many studies DDD was grouped with forms of MPGN, which makes it difficult to make specific statements about DDD. Treatments that have been tried include renin angiotensin system blockade, corticosteroids and other immunosuppressants, anticoagulants, and plasma exchange.[33] A recent Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference[26] recommended that all patients should receive optimal blood pressure control and patients with moderate disease—defined as urine protein greater than 500 mg/24 h despite supportive therapy, moderate inflammation on renal biopsy, or recent rise in creatinine—should receive prednisone or mycophenolate mofetil (MMF). A recent case series suggested that MMF is effective in C3 glomerulonephritis.[34] In severe disease with proteinuria more than 2 g/24 h, severe disease on biopsy, or progressive creatinine increase, the KDIGO conference suggested the use of methylprednisolone pulse dosing as well as other anticellular immune suppressants.[26]

In many cases of C3 glomerulopathy the deposition of C3 in glomeruli leads to subsequent activation of C5, and there is considerable interest in the possibility of using the anti-C5 antibody eculizumab for treatment. There are a number of case reports and one small open label, nonblinded clinical trial of eculizumab for C3 glomerulopathy.[35] Some but not all patients have shown clinical improvement, and in some there was reduction of glomerular inflammation on repeat biopsy. In the patients who underwent repeat biopsy, IgG-κ was found, consistent with binding of the monoclonal eculizumab to C5 in glomeruli.[36] However, the exact role of eculizumab remains to be defined and the KDIGO conference concluded “Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease.”[26] Rational treatment of C3 glomerulopathy would involve inhibition of C3 activation, and a number of drugs are in preclinical development that may achieve that and allow more targeted therapy in future.

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23

Immunoglobulin A Nephropathy and IgA Vasculitis (Henoch-Schönlein Purpura)

John Feehally, Jürgen Floege

IgA NEPHROPATHY

Definition

IgA nephropathy (IgAN) is a mesangial proliferative glomerulonephritis characterized by diffuse mesangial deposition of IgA. IgAN was first recognized in 1968 by Jean Berger when immunofluorescence techniques were introduced for the study of renal biopsy specimens. IgAN is unique among glomerular diseases in being defined by the presence of an immune reactant rather than by any other morphologic feature on renal biopsy, and the light microscopy changes are variable. IgAN is the most prevalent pattern of glomerular disease seen in most Western and Asian countries where renal biopsy is widely practiced. It is likely that IgAN is not a single entity but rather a common response to various injurious mechanisms.

Etiology and Pathogenesis

Although there has been much recent progress in understanding the pathogenesis of IgAN, it is not certain that all subjects with IgAN share a single common process leading to mesangial IgA deposition. Fig. 23.1 summarizes some key elements involved in the pathogenesis of IgAN.[1]

IgA Immune System

The regular recurrence of IgAN after renal transplantation in patients with prior underlying IgAN strongly implies an abnormality in the host IgA immune system (see Chapter 108).

IgA is the most abundant immunoglobulin in the body and is chiefly concerned with mucosal defense.[2] It has two subclasses, IgA1 and IgA2. Mucosal antigen challenge provokes *polymeric* IgA (pIgA) production by plasma cells of the mucosa-associated lymphoid tissue; the pIgA is then transported across epithelium into mucosal fluids, where it is released after coupling to secretory component as *secretory* IgA (sIgA). The function of circulating IgA is less clear; it is bone marrow derived and mostly *monomeric* IgA1 (mIgA1). Circulating IgA1 is cleared by the liver through hepatocyte asialoglycoprotein receptors and Kupffer cell Fcα receptors.

The mesangial IgA in IgAN is predominantly pIgA1. The clinical association with mucosal infections or superantigens from *Staphylococcus aureus* originally suggested that the mesangial pIgA1 comes from the mucosal immune system.

Available data on mucosal immune responses in IgAN are not easily synthesized into a single model of pathogenesis. On the one hand, pIgA1 production is downregulated in the mucosa and upregulated in the bone marrow. Moreover, the pIgA response to systemic immunization with common antigens is increased, whereas the response to mucosal immunization is impaired. These findings suggest that impaired mucosal IgA responses allowing enhanced antigen challenge to the marrow could be the primary abnormality in IgAN, although this remains unproven. However, there is also evidence for mucosal hyperresponsiveness to a variety of food antigens in patients with IgAN.[1,2] The mesangial IgA therefore may represent a common response to a variety of foreign antigens and various mucosal abnormalities, each of which facilitates a systemic response to mucosal antigens.

Another unproven hypothesis is that some mucosal IgA-producing plasma cells translocate to the bone marrow in IgAN; this also could explain the variation in glycosylation of serum IgA in IgAN (see later discussion). Tonsillar pIgA1 production is also increased, although IgAN can occur after tonsillectomy, and the tonsil is a very minor source of IgA production compared with the mucosa or marrow. There are reports of sIgA in the mesangium, but this finding is not easily explained by current pathogenic concepts of IgAN. Hepatic clearance of IgA is reduced, possibly because of the altered molecular characteristics of IgA in IgAN (see later discussion).

Serum IgA levels are increased in one third of patients with IgAN. There are elevations in both mIgA and pIgA. However, high serum IgA itself is not sufficient to cause IgAN and serum IgA levels are not useful for diagnosing IgAN. High circulating levels of monoclonal IgA in myeloma or polyclonal IgA in AIDS only infrequently provoke mesangial IgA deposition.

Circulating macromolecular IgA is characteristic of IgAN. Some represent IgA immune complexes, and there are circulating IgA rheumatoid factors (IgA against constant domain of IgG) in 30% of patients with IgAN. Studies in vitro indicate that IgA production by mononuclear cells is exaggerated in IgAN, and that these cells show abnormal patterns of cytokine production. However, the direct relevance of these observations to events in vivo is uncertain.

IgA Glycosylation

A striking feature of IgAN is altered glycosylation of the hinge region of IgA1. IgA1 carries distinctive *O*-linked sugars at its hinge region; IgA2 has no hinge and carries no such sugars. There is good evidence that circulating IgA1 in IgAN has abnormal *O*-linked hinge-region sugars with reduced galactosylation; this is usually named galactose-deficient IgA1 (gd-IgA1) and is found in up to 90% of individuals with IgAN.[1] Some data indicate defective function of the relevant glycosyltransferases that *O*-glycosylate IgA1, possibly with a genetic basis. Other findings suggest that the primary abnormality may be that IgA of the mucosal type, which has glycosylation patterns different from that of serum IgA1, reaches the circulation, for example, by translocation of mucosal lymphocytes to the bone marrow. The latter is consistent with experiments in which immortalized lymphocytes from patients with

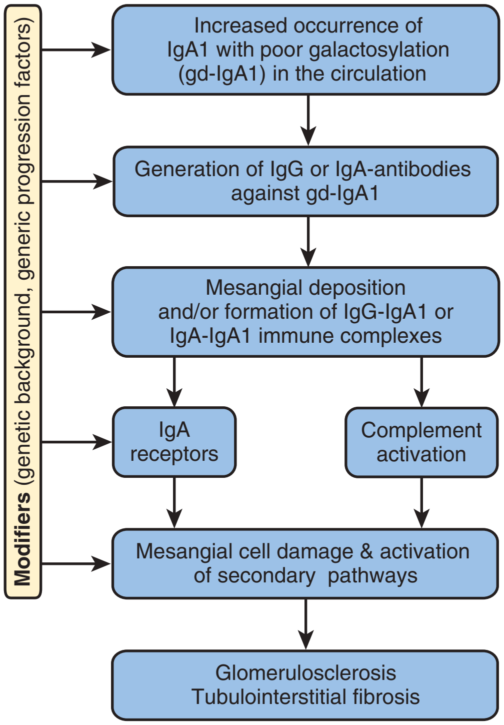
Modifiers (genetic background, generic progression factors)
Increased occurrence of IgA1 with poor galactosylation (gd-IgA1) in the circulation
Generation of IgG or IgA-antibodies against gd-IgA1
Mesangial deposition and/or formation of IgG-IgA1 or IgA-IgA1 immune complexes
IgA receptors
Complement activation
Mesangial cell damage & activation of secondary pathways
Glomerulosclerosis
Tubulointerstitial fibrosis

Fig. 23.1 **Pathogenesis of IgA nephropathy.** Proposed mechanisms leading to mesangial deposition of abnormally glycosylated IgA1 and mesangial injury. (Modified from reference 1.)

IgAN continue to produce dimeric and polymeric IgA with altered galactosylation in vitro.[3]

Mesangial IgA1 in IgAN also has increased gd-IgA1.[4,5] The gd-IgA1 can act as an autoantigen leading to IgG or IgA anti–gd-IgA1 autoantibodies and formation of circulating immune complexes.[6] Mesangial IgA1 may be the result of deposition of these circulating IgA1 immune complexes or of altered IgA1 interactions with matrix proteins and mesangial cell or monocyte Fc receptors. There also may be impaired clearance of gd-IgA1 through inhibition of its interactions with hepatic and circulating myeloid cell IgA receptors.

Increased serum gd-IgA1 is found in the unaffected relatives of subjects with IgAN, suggesting that gd-IgA1 is necessary but not sufficient for the development of IgAN, which requires a “second hit,” for example, an event that provokes the formation of autoantibodies against gd-IgA1 and thus provokes tissue injury.

Role of Infection

The clinical association of visible hematuria with upper respiratory tract infection in IgAN indicates the mucosa may be a site of entry for foreign antigens or alternatively may be a site for nonspecific activation of the innate immune system that enhances renal injury. There have been occasional reports of IgAN in association with infection, both bacterial (e.g., *Campylobacter, Yersinia, Mycoplasma, Haemophilus*) and viral (e.g., cytomegalovirus, adenovirus, coxsackievirus, Epstein-Barr virus). A severe form of IgAN, which may be crescentic, has been reported in association with staphylococcal infection (see Chapter 55). However, no organism has been consistently implicated by the finding of microbial antigen in glomerular deposits in typical cases of IgAN.

Glomerular Injury After IgA Deposition

Polymeric IgA deposition in the mesangium is typically followed by mesangial proliferative glomerulonephritis (GN). In animal models, co-deposition of IgG and complement is necessary for inflammation, but this is not mandatory in human disease. Complement deposits are usually C3 and properdin without C1q and C4. There may be complement activation via the mannose-binding lectin pathway. The extent to which IgA engages inflammatory cells in the circulation, especially in the kidney, will determine the intensity of inflammation. Fc receptors for IgA (Fcα receptors) on myeloid and mesangial cells may play a key role.[7]

The mechanisms of mesangial proliferative GN have been studied in detail in animal models, particularly anti–Thy 1 nephritis in the rat. These studies have shown the key role of cytokines and growth factors in mesangial cell proliferation, particularly the B and D isoforms of platelet-derived growth factor[8] (PDGF) and in the subsequent matrix production and sclerosis, particularly transforming growth factor-β (TGF-β). Studies of renal biopsy specimens in human IgAN also support a role for PDGF and TGF-β. These mechanisms are not unique to IgAN but are likely involved in all forms of mesangial proliferative GN, including those without IgA deposition.

Subsequent progressive renal injury involving glomerulosclerosis and tubulointerstitial fibrosis is likely the result of generic mechanisms of damage, rather than specific to IgAN.

Animal Models of IgA Nephropathy

Animal IgA does not have the same characteristics as human IgA1, and some animals also have IgA clearance mechanisms distinct from those in humans. Therefore animal models, even if they provoke mesangial IgA deposits, are not particularly informative about the mechanisms that underlie human mesangial pIgA1 deposition, although they have provided many insights into events after IgA deposits have developed.

Genetic Basis of IgA Nephropathy

Urine abnormalities increase in frequency among the relatives of patients with IgAN, although only in a few pedigrees is IgAN found in multiple generations. More than 90% of all cases of IgAN appear to be sporadic.

Large worldwide genome-wide association studies have identified genetic modulators that seem to affect the prevalence of sporadic IgAN and modulate its course.[9-11] Variations in major histocompatibility gene loci (HLA-DR, -DQ, -DP and HLA-B) have consistently been identified. Other gene loci are less consistent and include inflammatory mediators (tumor necrosis factor and α-defensin), gene loci affecting complement factor H, innate immunity, IgA-regulating cytokines, and mucosal integrity.[11]

Other Modulators of the Course of IgA Nephropathy

Many cases of IgAN probably never come to medical attention, and when the diagnosis is obtained by renal biopsy, only a minority will develop end-stage renal disease (ESRD). Thus, in addition to genetic factors, there must be potent further modulators of the course of IgAN, such as essential hypertension, obesity, or smoking (see Fig. 23.1; see also Natural History).

Epidemiology

IgA nephropathy is the most prevalent pattern of glomerular disease in most countries where renal biopsy is widely used as an investigative tool. Its estimated frequency is at least 2.5 cases per year per 100,000 adults.[12] However, the striking geographical variation has been associated with the presence of particular gene alleles that protect from IgAN[9] (Fig. 23.2). This racial predisposition is maintained in other locations; in the United States, for example, IgAN is less common in Blacks than in Whites of European origin. Perceived prevalence of IgAN also may be influenced by attitudes to the investigation of microhematuria. A country with an active program of routine urine testing will inevitably

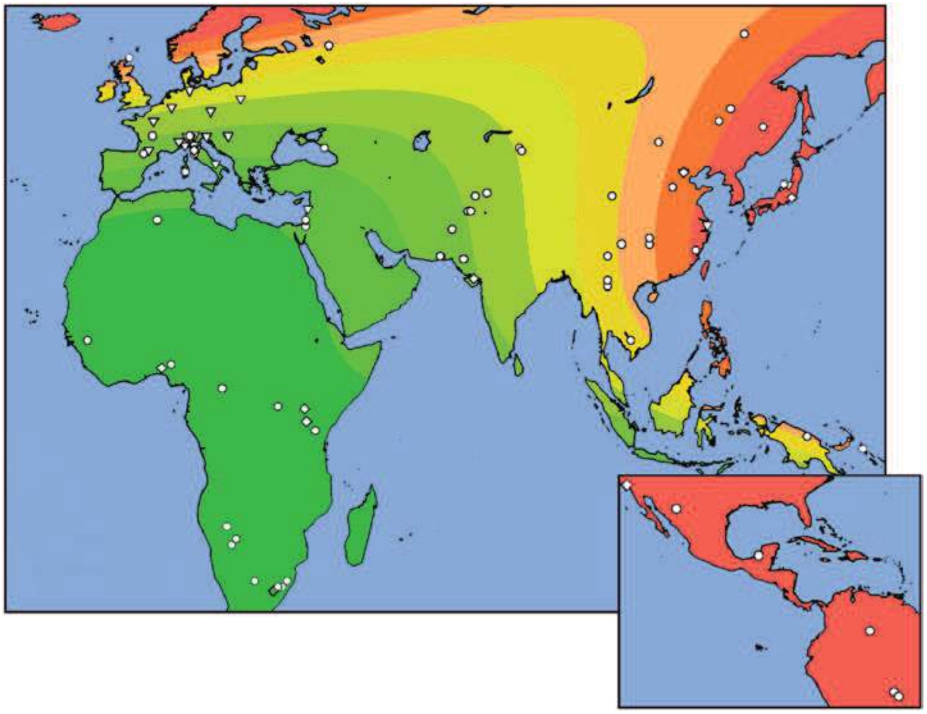

Fig. 23.2 Geographical variation in genetic risk for IgA nephropathy. Genome-wide association studies indicate a geographical gradient of risk from *green* (low risk) to *red* (high risk). (From reference 9.)

identify more individuals with urine abnormalities, but IgAN will be identified only if renal biopsy is performed. Even then, the prevalence of IgAN will be underestimated; a study of kidney donors suggests that the prevalence of IgAN with mesangial proliferative changes and glomerular C3 deposits in the general population in Japan may be 1.6%.[13] This suggests that the vast majority of patients with IgAN never come to medical attention and spontaneously remit.

Clinical Manifestations

IgA Nephropathy

The wide range of clinical presentations of IgAN varies in frequency with age (Fig. 23.3). No clinical pattern is pathognomonic of IgAN. In populations of White descent, IgAN is more common in males than females by a ratio of 3 : 1, whereas the ratio approaches 1 : 1 in most Asian populations.

Macroscopic Hematuria

In 40% to 50% of patients with IgAN, the clinical presentation is episodic macroscopic hematuria, most frequently in the second decade of life. The urine is usually brown rather than red, and clots are unusual. There may be loin pain caused by renal capsular swelling. Hematuria usually follows intercurrent mucosal infection, typically in the upper respiratory tract (the term *synpharyngitic hematuria* has been used) or occasionally in the gastrointestinal tract. Hematuria is usually visible within 24 hours of the onset of the symptoms of infection, differentiating it from the 2- to 3-week delay between infection and subsequent hematuria in postinfectious (e.g., poststreptococcal) GN. The macroscopic hematuria resolves spontaneously over a few days. Microscopic hematuria persists between attacks. Most patients have only a few episodes of frank hematuria, which become less frequent and resolve over a few years or sooner. Such episodes may be associated with acute kidney injury (AKI) characterized by tubular injury that is usually reversible.

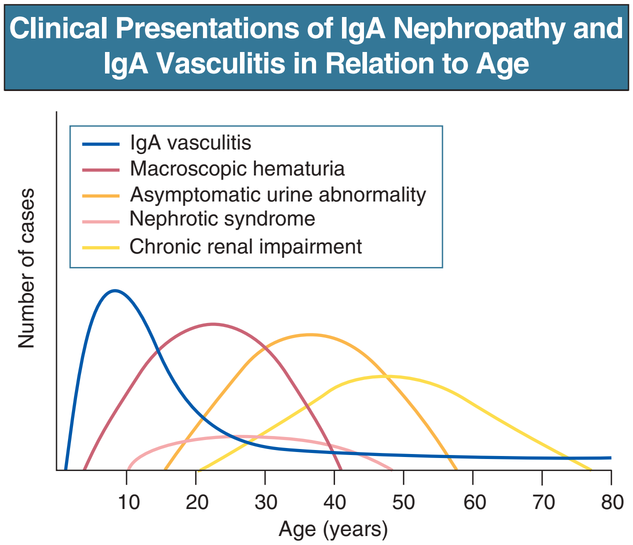

Fig. 23.3 Age in clinical presentation of IgA nephropathy and IgA vasculitis (IgAV). IGAV is most common in childhood but may occur at any age. Macrohematuria is very uncommon after age 40. The importance of asymptomatic urine abnormality as the presentation of IgAN will depend on attitudes to routine urine testing and renal biopsy. It is unclear whether patients presenting late with chronic renal impairment have a disease distinct from that of those presenting younger with macrohematuria. (Data from patients presenting in Leicester, UK, 1980-1995.)

Asymptomatic Hematuria and Proteinuria

As many as 30% to 40% of cases of IgAN are identified during routine testing of urine of asymptomatic individuals. Microhematuria with or without proteinuria (usually <2 g/24 h) is noted. The number of patients identified in this way will depend on local attitudes to urine testing, as well as on the use of renal biopsy in patients with isolated microscopic hematuria. Most patients with IgAN are asymptomatic and would be identified only when the urine is tested.

Proteinuria and Nephrotic Syndrome

It is rare for proteinuria to occur without microscopic hematuria. Whereas nephrotic-range proteinuria may occur, in particular in the presence of uncontrolled hypertension, full-blown nephrotic syndrome is uncommon, occurring in only 5% of all patients with IgAN. Nephrotic syndrome may occur early in the course of the disease, with minimal glomerular change (in such cases IgAN may coexist with minimal change disease [MCD]) or with active mesangial proliferative GN. Alternatively, it may occur as a late manifestation of advanced chronic glomerular scarring.

Acute Kidney Injury

Although AKI is uncommon in IgAN (<5% of all cases), one study reports that it may be the manifestation in up to 27% of patients older than 65 years.[14] AKI develops by three distinct mechanisms. There may be acute severe immune and inflammatory injury with necrotizing GN and crescent formation (crescentic IgAN); this may be the first presentation of IgAN, or it may be superimposed on established, less aggressive disease. Rapid deterioration in IgAN in pregnancy may be caused by crescentic transformation. Alternatively, AKI can occur with mild glomerular injury when heavy glomerular hematuria leads to tubule occlusion by red blood cells (RBCs). Third, especially in elderly patients, chronic IgAN will predispose to AKI from a variety of incidental renal insults (see Chapter 66).

Chronic Kidney Disease

Some patients already have renal impairment and hypertension when they are first diagnosed with IgAN. These patients tend to be older, and they probably have long-standing disease that previously remained undiagnosed because the patient did not have frank hematuria or undergo routine urinalysis. Hypertension is common, as in other chronic glomerular disease; accelerated hypertension occurs in 5% of patients.

Clinical Associations With IgA Nephropathy

Mesangial IgA deposition, which does not necessarily equal IgAN, is a frequent finding in autopsy studies in chronic liver disease. Although particularly associated with alcoholic cirrhosis, IgA deposition can occur in other chronic liver disease, including that caused by hepatitis B and schistosomiasis. It is thought to result from impaired clearance of IgA by the Kupffer cells, which express Fcα receptors, and hepatocytes, which express the asialoglycoprotein receptor. Clinical evidence of renal disease is more common than previously appreciated, but patients rarely develop ESRD.

A number of case reports have associated IgAN with HIV infection and AIDS. It is not clear whether the polyclonal increase in serum IgA, which is a feature of AIDS, is the predisposing factor.

There are case reports associating IgAN with many other conditions, particularly with a number of immune and inflammatory diseases (Table 23.1). Their relationship to abnormalities of the IgA immune system is not always clear, and some may represent the coincidental development of unrelated but relatively common conditions.

Pathology

Immune Deposits

Diffuse mesangial IgA is the defining hallmark of IgAN (Fig. 23.4A). C3 is co-deposited in up to 90% of cases. IgG in 40% and IgM in 40% of cases also may be found in the same distribution. IgA also may deposit along capillary loops, a pattern more common in IgAV; in IgAN, this pattern is associated with a worse prognosis. C5b-9 is found with properdin but not C4, indicating alternative complement pathway

TABLE 23.1 **Diseases Reported in Association With IgA Nephropathy: Common, Reported, and Rare**

Disease Group	Common	Reported	Rare
Rheumatic and Autoimmune Disease	Ankylosing spondylitis Rheumatoid arthritis Reiter syndrome Uveitis	Behçet syndrome* Takayasu arteritis† Myasthenia gravis	Sicca syndrome
Gastrointestinal Disease	Celiac disease	Ulcerative colitis	Crohn's disease Whipple's disease
Hepatic Disease	Alcoholic liver disease Nonalcoholic cirrhosis Schistosomal liver disease		
Lung Disease	Sarcoid		Pulmonary hemosiderosis
Skin Disease	Dermatitis herpetiformis		
Malignancy		IgA monoclonal gammopathy	Bronchial carcinoma Renal carcinoma Laryngeal carcinoma Mycosis fungoides Sézary syndrome
Infection	HIV, hepatitis B (in endemic areas)	Brucellosis	Leprosy
Miscellaneous		Wiskott-Aldrich syndrome‡	

Rare associations have been made in one or two reported cases only. In a disease as common as IgA nephropathy, it is therefore uncertain whether these are truly related.

*Behçet syndrome: Systemic vasculitis typified by orogenital ulceration and chronic uveitis.

†Takayasu arteritis: Systemic vasculitis involving the aorta and its major branches, most often found in young women.

‡Wiskott-Aldrich syndrome: X-linked disorder in which increased serum IgA is associated with the triad of recurrent pyogenic infection, eczema, and thrombocytopenia.

HIV, Human immunodeficiency virus.

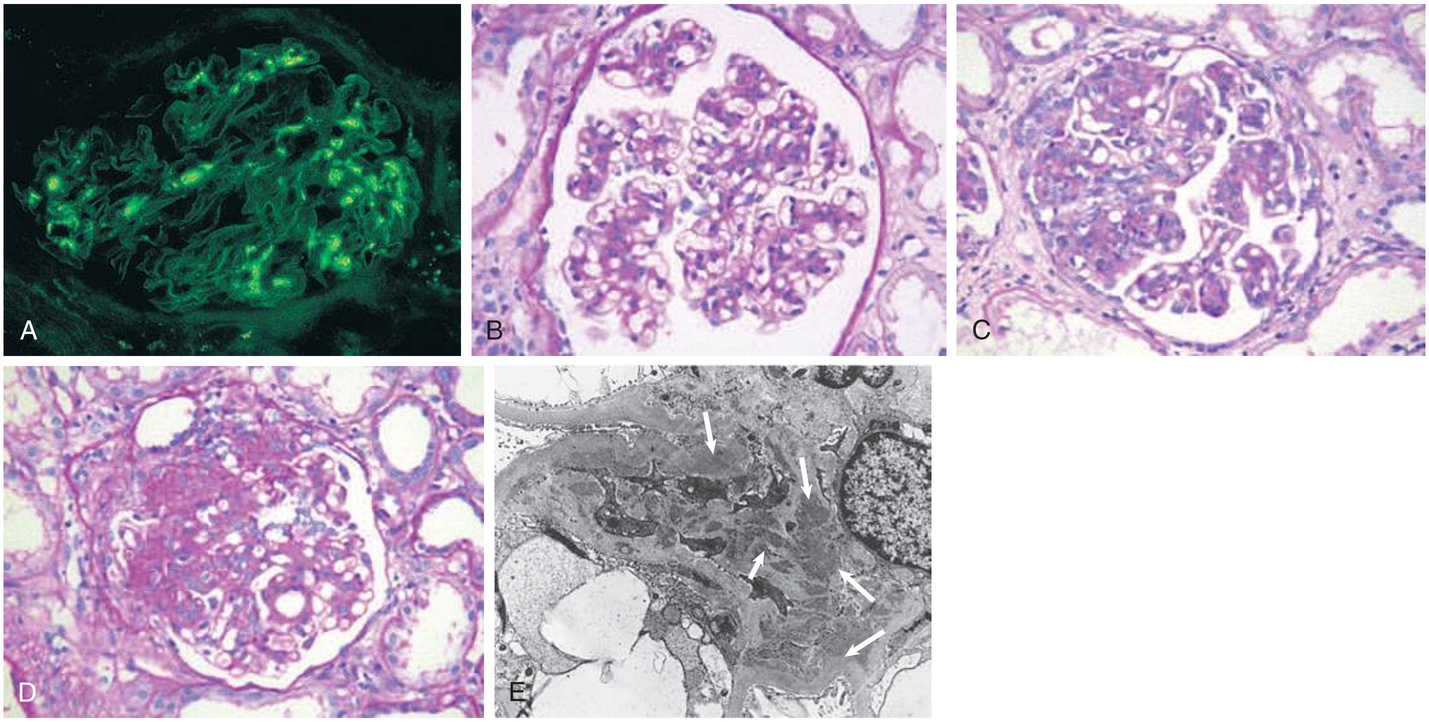

Fig. 23.4 Renal pathology in IgA nephropathy. (A) Diffuse mesangial IgAN seen on indirect immunofluorescence with fluorescein isothiocyanate–anti-IgA (magnification ×3300). (B) Diffuse mesangial hypercellularity (M1, Oxford classification). (C) Endocapillary hypercellularity (E1). (D) Segmental sclerosis (S1). (**B, C,** and **D,** Light microscopy with periodic acid–Schiff reaction; ×3300). **E,** Mesangial electron-dense deposits *(arrows)* (electron micrograph; ×316,000). (**B, C,** and **D** courtesy Professor I. Roberts.)

activation. Disappearance of IgA deposits after prolonged clinical remission has been documented in both children and adults. About one third of the patients also have deposits of sIgA in the mesangium and are characterized by more severe disease.[15]

Light Microscopy

Light microscopy changes are remarkably variable and do not correlate topographically with the IgA deposits. There can be almost normal glomerular architecture, mesangial hypercellularity that may be diffuse (see Fig. 23.4B) or segmental, or in rare cases, focal segmental necrotizing GN with extracapillary proliferation. Typical cases are characterized by an increase in mesangial cells and mesangial matrix with normal-appearing capillary loops, although endocapillary hypercellularity can occur (see Fig. 23.4C). Focal segmental or global glomerular sclerosis indicates that the disease has been ongoing for some time (see Fig. 23.4D). In addition to glomerular changes, the preglomerular arterial vessels often exhibit wall hyalinosis and subintimal fibrosis even in patients with only mild arterial hypertension. In long-standing disease, tubulointerstitial inflammation leads to interstitial fibrosis and tubular atrophy in a pattern no different from that of other progressive glomerular diseases. On occasion, IgAN and minimal change nephrotic syndrome coincide (see Differential Diagnosis), in which case light microscopy is normal but there are mesangial IgA deposits.

Morphology is of value in predicting prognosis in patients with slowly progressive disease. The Oxford (MEST) classification of IgAN is now being widely accepted.[16] This classification identifies four features of prognostic value and can be easily scored on light microscopy: mesangial hypercellularity (M1 when present, M0 when absent), endocapillary hypercellularity (E1), segmental sclerosis (S1), and three degrees of tubular atrophy and interstitial fibrosis (T0, T1, T2). Examples of these glomerular features are shown in Fig. 23.4.

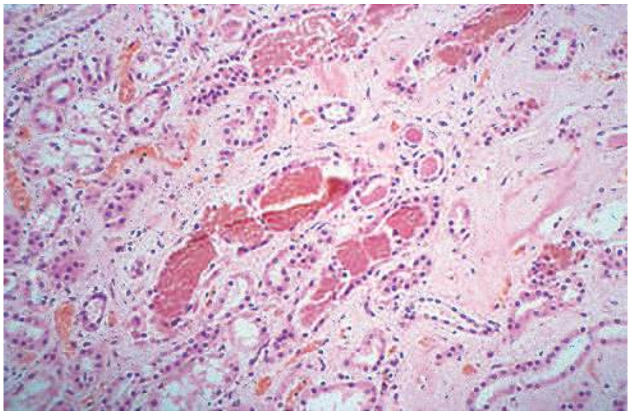

Fig. 23.5 Acute kidney injury in IgA nephropathy. Tubular occlusion by red blood cells. This appearance may be associated with only minor glomerular changes. (Hematoxylin and eosin stain; ×300.)

Histologic patterns of injury in AKI include tubular occlusion by RBCs with acute tubular epithelial injury in AKI associated with macroscopic hematuria (Fig. 23.5) or necrotizing GN and cellular crescent formation. Such crescentic IgAN may develop on a histologic background of established chronic renal injury caused by IgAN or may be the first presentation of IgAN. Small numbers of crescents may be seen in hypertensive patients with stable renal function and no other pathologic evidence of severe glomerular inflammation; the term *crescentic IgAN* should not be used for such patients, in whom the prognosis is often favorable.

Electron Microscopy

Electron-dense deposits correspond to the mesangial (or capillary loop) IgA (see Fig. 23.4E). Typically, electron-dense deposits are confined to mesangial and paramesangial areas, although subepithelial and subendothelial deposits also can be seen. Up to one third of patients will have some focal thinning of the glomerular basement membrane (GBM). On occasion, there will be extensive GBM thinning, suggesting a coincident diagnosis of thin basement membrane nephropathy (see Chapter 46).

Differential Diagnosis

The diagnosis of IgAN or IgAV nephritis requires identification of mesangial IgA in the glomeruli. Therefore it cannot be made without a renal biopsy, no matter how suggestive the clinical presentation. Serum IgA is often increased, and there may be IgA in cutaneous blood vessels in IgAN and in both affected and unaffected skin in IgAV. Neither finding, however, is reliable enough to support the diagnosis without a renal biopsy. Serum complement components are normal in most patients.

Mesangial IgA occurs in other conditions and can usually be differentiated by clinical, serologic, and histologic criteria (Box 23.1). None of the light microscopic features alone is diagnostic of IgAN.

An important differential diagnosis is IgA-dominant acute postinfectious glomerulonephritis (APIGN), in which IgA is the dominant immunoglobulin in glomerular deposits (see Chapter 55). It usually occurs in association with staphylococcal infections. Risk factors particularly include diabetes. Compared with IgAN, patients with IgA-dominant APIGN are more likely to be older and have AKI, documented staphylococcal infection, hypocomplementemia, diffuse glomerular endocapillary hypercellularity with prominent neutrophil infiltration on light microscopy, stronger immunofluorescence staining for C3 than IgA, and the presence of subepithelial humps on electron microscopy.[17]

Hematuria

Nonglomerular causes of hematuria, particularly stones and neoplasia, must be excluded by appropriate investigations (see Chapter 59). In its most characteristic clinical setting—recurrent macroscopic hematuria coinciding with mucosal infection in a man in the second or third decade of life—the diagnosis can be strongly suspected. Such a diagnosis, however, cannot be made without a biopsy because recurrent macroscopic hematuria also occurs in other glomerular diseases (e.g., Alport syndrome and MPGN), particularly in children and young adults. In young adults, thin basement membrane nephropathy is the most important differential diagnosis for isolated microhematuria.

BOX 23.1 Differential Diagnosis of Immunoglobulin a Nephropathy: Conditions Associated With Mesangial IgA Deposition

- IgA nephropathy
- IgA vasculitis

- Lupus nephritis*
- Alcoholic liver disease
- IgA monoclonal gammopathy
- Schistosomal nephropathy
- IgA-dominant Staphylococcus-associated glomerulonephritis (more common in diabetics)

*Distinguishing lupus nephritis (especially International Society of Nephrology/Renal Pathology Society classes II and III) may cause difficulty. The finding of C1q deposition is useful. It indicates classical pathway involvement found in lupus nephritis but not in IgAN.

Nephrotic Syndrome

Patients with IgAN occasionally develop nephrotic syndrome, which is indistinguishable from that in MCD. There is a sudden onset of nephrosis, with biopsy evidence of glomerular epithelial cell foot process effacement and a prompt complete remission of proteinuria in response to corticosteroids. Only hematuria and mesangial IgA deposits persist after treatment. This pattern occurs particularly in children. These patients are usually regarded as having two separate common glomerular diseases, IgAN and MCD.[18]

Other patients with IgAN may develop nephrotic syndrome with more structural glomerular damage and lack the response to corticosteroids. The clinical differential diagnosis includes common causes of nephrotic syndrome appropriate for the age of the patient (see Chapter 15).

Chronic Kidney Disease: Hypertension, Proteinuria, Renal Impairment

In this context, IgAN will be clinically indistinguishable from many forms of chronic kidney disease (CKD). The renal biopsy may be diagnostic by identifying mesangial IgA, even when structural damage is so advanced on light microscopy that it has the nonspecific features of ESRD.

Acute Kidney Injury

When AKI occurs in a patient known to have IgAN, renal biopsy should be performed unless there is rapid improvement in renal function, after at least 5 days from the onset of kidney function worsening, in response to supportive care and vigorous hydration.[19] Renal biopsy may be required to differentiate the tubular occlusion and acute tubular necrosis that occasionally follow heavy glomerular hematuria from crescentic IgAN or other coincidental causes of AKI (see Fig. 23.5).

Natural History

IgA Nephropathy

The overall prognosis of IgAN has been reevaluated in recent long-term natural history studies.[20,21] After 20 years, one fourth of patients will have ESRD and a further 20% will have progressive impairment of renal function.

Although an active approach to the investigation of microhematuria will increase the size of the cohort of patients found to have IgAN, it will include more with a good prognosis, thus altering the perceived risk for disease progression. Episodes of macrohematuria do not confer a worse prognosis. This may indicate that such episodes occur only early in the natural history of the disease and patients doing less well from the point of diagnosis in fact were identified at a later stage in their disease. This is also suggested by the adverse influence on outcome of advancing age at diagnosis.

The risk for ESRD is not uniform. As in any chronic glomerular disease, the presence of hypertension, proteinuria, and reduced glomerular filtration rate (GFR) at presentation, as well as histologic evidence of glomerular and interstitial fibrosis, identifies at the time of diagnosis those with a poor prognosis (Table 23.2). Hyperuricemia, smoking, and increased body mass index are also independent risk factors for progression. However, during follow-up, only hypertension and proteinuria, in particular time-averaged proteinuria, are reliable predictors of risk for progression. Canadian and French studies indicate

TABLE 23.2 Prognostic Markers at Presentation in Immunoglobulin A Nephropathy

Clinical	Histopathologic
Poor Prognosis	
Hypertension	Mesangial hypercellularity
Renal impairment	Endocapillary proliferation
Severity of proteinuria	Segmental glomerulosclerosis
Smoking	
Hyperuricemia	Tubular atrophy
Gross obesity	Interstitial fibrosis
Long duration of preceding symptoms	Capillary loop IgA deposits
Increasing age	Crescents (controversial)
Good Prognosis	
Recurrent macroscopic hematuria	
No Impact on Prognosis	
Gender	Intensity of IgA deposits
Serum IgA level	

None of the clinical or histopathologic adverse features, except capillary loop IgA deposits is specific to IgA nephropathy.

that risk for progression is negligible when proteinuria remains below 0.2 g/24 h with normal blood pressure.[20,21]

If a renal biopsy documents IgAN in patients with mild disease (i.e., those manifesting with isolated microhematuria, little or no proteinuria, normotension, and normal GFR), the 7- to 10-year prognosis is mostly good.[22,23] However, up to 40% of the patients will develop increasing proteinuria and up to 5% will lose GFR over this period, implying the need for regular follow-up in such patients. Large studies with long-term follow-up indicate a slow attrition.

Pathologic findings and clinical findings together inform prognosis.[24] The MEST classification of IgAN has shown that mesangial hypercellularity, endocapillary proliferation, and segmental sclerosis, as well as tubular atrophy and interstitial fibrosis, each add prognostic information even when clinical features (proteinuria, hypertension, GFR) are known at presentation and during follow-up.

Transplantation

Recurrent IgA Nephropathy

Transplant registry data show that transplant outcome is not affected for the first 10 years if IgAN is the patient's primary renal disease; thereafter, however, recurrent disease may lead to accelerated graft loss (see also Chapter 108). Mesangial IgA deposits recur in the donor transplant kidney in up to 60% of patients with IgAN.[25] They may occur within days or weeks, but the risk increases with the duration of the transplant. The deposits seem benign in the short term and are not often associated initially with light microscopy changes. In pooled series, recurrent IgAN is 30% in living related transplants versus 23% in cadaveric grafts, but this does affect graft survival only beyond 10 years after transplantation.[25] Living related donation should not be discouraged. However, any urinary abnormality in a potential related donor requires thorough evaluation, including, if necessary, a renal biopsy. Recurrence of crescentic IgAN with rapid graft failure occurs infrequently and is generally resistant to treatment.

In a few unwitting experiments, cadaver kidneys with IgA deposits have been transplanted into recipients without IgAN. In all cases, the IgA rapidly disappeared, supporting the concept that abnormalities in IgAN lie in the IgA immune system and not in the kidney.

Treatment

Although specific early treatment intervention might influence the IgA immune system abnormalities that underlie IgAN, the mechanisms of chronic disease progression are unlikely to be unique. Therefore studies of such patients with IgAN may provide information applicable to many forms of chronic GN for which IgAN is the paradigm.

The balance of risk against benefit for immunosuppressive therapy is often unfavorable in patients with IgAN, except in the unusual circumstance of crescentic IgAN.

Fig. 23.6 provides a treatment algorithm for IgAN that is based on the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[19] The approach distinguishes among the following[26]:

- The "good prognosis" patient, with minor urinary abnormalities, normal GFR, and normotension, who needs only sporadic follow-up for a prolonged period (>10 years)
- The "intermediate prognosis" patient, with significant proteinuria, hypertension, and slow reduction of GFR, who particularly benefits from comprehensive supportive care
- The "poor prognosis" patient, with a rapid loss of GFR, who may require more aggressive immunosuppression

Slowly Progressive IgA Nephropathy ("Intermediate Prognosis")

Minimal evidence exists to suggest the events of progressive glomerular injury are unique to IgAN. Comprehensive supportive therapy following the strategies outlined in Chapter 79 therefore remains central in the therapeutic approach to patients at risk for progressive IgAN (see Fig. 23.6).

Antihypertensives and proteinuria-lowering drugs. There is compelling evidence for the benefit of lowering blood pressure (BP) in the treatment of chronic progressive glomerular disease such as IgAN. In patients with IgAN, there is also evidence that casual clinic BP readings underestimate BP load, as judged by ambulatory monitoring and echocardiographic evidence of increased left ventricular mass.[27] Two prospective, controlled trials strongly support the use of angiotensin-converting enzyme (ACE) inhibitors in patients with IgAN as first-choice hypotensive agents to lower BP.[28,29] In a randomized study of IgAN, achieving a mean BP of 129/70 mm Hg prevented the decrease in renal function over 3 years seen in patients achieving mean BP of 136/76 mm Hg.[30]

Observational studies indicate that the risk for progression in IgAN decreases significantly if proteinuria can be reduced to less than 1 g/d by any therapeutic maneuver.[21] Another compelling indication for the role of lowering proteinuria in IgAN is based on the superior effectiveness of ACE inhibitors over other antihypertensive agents.[28,29]

Fish oil. The favorable effects of supplementing the diet with omega-3 fatty acids in the form of fish oil include reductions in eicosanoid and cytokine production, changes in membrane fluidity and rheology, reduced platelet aggregability, and reduced proliferation of renal cells in response to PDGF. The evidence for a beneficial action of fish oil in IgAN is weak; its suggested use in patients at risk in the 2012 KDIGO guidelines is supported by only low-level evidence.[19] However, fish oil treatment does not have the drawbacks associated with immunosuppressive treatment. Fish oil is safe except for a decrease in blood coagulability, which is not usually a practical problem, and an unpleasant taste, with flatulence, which may make compliance difficult. Some fish oil preparations contain significant amounts of cholesterol, necessitating close surveillance if such treatment is initiated. A further confirmatory study of fish oil would be of great value.

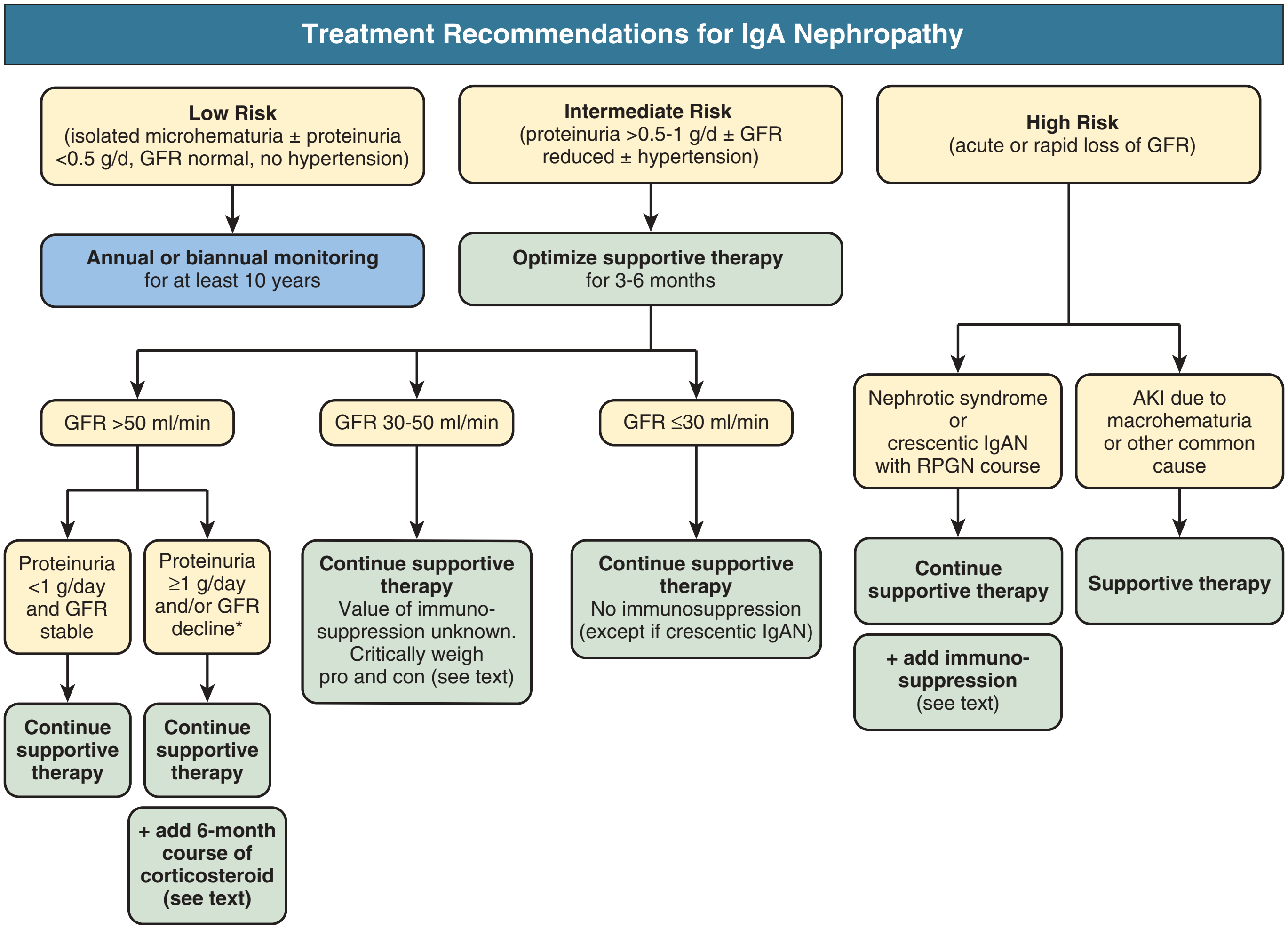
Treatment Recommendations for IgA Nephropathy
Low Risk (isolated microhematuria ± proteinuria <0.5 g/d, GFR normal, no hypertension)
Intermediate Risk (proteinuria >0.5-1 g/d ± GFR reduced ± hypertension)
High Risk (acute or rapid loss of GFR)
Annual or biannual monitoring for at least 10 years
Optimize supportive therapy for 3-6 months
GFR >50 ml/min
GFR 30-50 ml/min
GFR ≤30 ml/min
Nephrotic syndrome or crescentic IgAN with RPGN course
AKI due to macrohematuria or other common cause
Proteinuria <1 g/day and GFR stable
Proteinuria ≥1 g/day and/or GFR decline*
Continue supportive therapy Value of immuno-suppression unknown. Critically weigh pro and con (see text)
Continue supportive therapy No immunosuppression (except if crescentic IgAN)
Continue supportive therapy
Supportive therapy
+ add immuno-suppression (see text)
Continue supportive therapy
Continue supportive therapy
+ add 6-month course of corticosteroid (see text)

Fig. 23.6 Treatment recommendations for IgA nephropathy. *AKI,* Acute kidney injury; *GFR,* glomerular filtration rate; *RPGN,* rapidly progressive glomerulonephritis. (Modified from reference 26.)

Immunosuppressive or Antiinflammatory Regimens

Corticosteroids. A meta-analysis and retrospective data suggest that corticosteroids are beneficial in IgAN, in particular in adults with proteinuria exceeding 3 g/d.[31,32] However, there are also several trials that failed to demonstrate benefit from corticosteroids and dosage was somewhat lower in two of three negative versus the positive trials.[26] Several trials did not optimize supportive therapy, in particular renin-angiotensin system (RAS)-blockers, or required that such drugs be temporarily halted before the trial. The 2012 KDIGO guidelines thus suggest that corticosteroids should be initiated in high-risk patients only if proteinuria remains above 1 g/d after supportive care has been optimized for 3 to 6 months and only if GFR remains above 50 ml/min. At present, no evidence supports a more intense or complex regimen of intravenous as well as oral corticosteroid therapy over a purely oral prednisolone regimen, starting with 1 mg/kg/day for 2 months, then reduced by 0.2 mg/kg/day/month.[26]

The previously mentioned recommendations have recently been challenged by two large prospective trials of oral corticosteroids in IgAN added to optimized supportive care (STOP-IgAN and TESTING). In the German STOP-IgAN trial an extensive 6-month optimization of supportive measures abolished any subsequent benefit from high-dose corticosteroids in adult patients with IgAN with an average baseline GFR of 60 ml/min and a baseline proteinuria around 1.7 g/d.[33] The largely Chinese-based TESTING trial on high-dose corticosteroids in adults with a baseline GFR of 60 ml/min and a baseline proteinuria of 2.4 g/d was terminated early after an excess of severe, sometimes fatal infections was noted in the corticosteroid arm.[34] These two trials strongly emphasize the values of a comprehensive optimization of supportive measures in high-risk patients with IgAN.

Full-blown nephrotic syndrome may occur when MCD and IgAN coincide, in which case the nephrotic syndrome will be fully and promptly corticosteroid responsive. A trial of high-dose corticosteroid therapy analogous to that used in MCD (see Chapter 17) is therefore justified in patients with IgAN who have nephrotic syndrome associated with minimal glomerular injury.

An alternative approach to corticosteroid dosing has been evaluated: a phase II trial evaluating the role of an enteric corticosteroid (budesonide) preparation in patients with "intermediate prognosis" IgAN (NEFIGAN) showed a reduction in proteinuria and better preservation of renal function in the treated patients.[35]

Cyclophosphamide and azathioprine. Cyclophosphamide has been used in combination with warfarin and dipyridamole in two RCTs, with inconsistent results. Both showed modest reduction in proteinuria, but only one preserved renal function. Cyclophosphamide followed by azathioprine combined with prednisolone preserved renal function in patients with a poor prognosis, although BP control was suboptimal.[36] The same regimen, however, was ineffective in the STOP-IgAN trial and led to a death from pulmonary sepsis.[33] In another recent study, adding azathioprine to corticosteroids in patients with proteinuric IgAN with a GFR greater than 50 ml/min had no added benefit and only increased side effects.[37] Neither agent is therefore recommended by the 2012 KDIGO guidelines in patients with intermediate risk IgAN.[19]

Other immunosuppressive approaches. Mycophenolate mofetil (MMF) has been used in several controlled trials in high-risk patients. Three trials in White patients failed to demonstrate a benefit, whereas a study in Chinese patients noted reduced proteinuria and preservation of GFR.[26,38] Whether racial effects underlie these discrepant results remains to be clarified. In another Chinese trial, 4 of 32 patients with IgAN receiving MMF plus corticosteroids died of *Pneumocystis* pneumonia.[39] MMF is therefore not recommended by the 2012 KDIGO guidelines in patients with intermediate risk IgAN.[19]

Cyclosporine has been used in one controlled trial in IgAN.[40] Patients showed a reversible decrease in proteinuria along with a decrease in creatinine clearance, suggesting the changes were a hemodynamic effect of cyclosporine rather than an immunomodulating effect.

Rituximab (two infusions of 1 g) failed to reduce levels of undergalactosylated IgA and autoantibodies against this IgA in a small open-label trial in adult patients with high-risk IgAN and did not affect proteinuria over the course of 1 year.[41]

Pooled human immunoglobulin has given encouraging preliminary results in patients with IgAN who have an aggressive clinical course. Proteinuria was reduced, deterioration of GFR slowed, and histologic activity lessened on repeated renal biopsies.[42] No RCT is available for this approach.

Dipyridamole and warfarin. Two RCTS with dipyridamole and warfarin showed mutually inconsistent results. There was no benefit in one and preserved renal function in the other. Neither drug is currently recommended in IgAN patients.[19]

Rapidly Progressive IgA Nephropathy ("Poor Prognosis")

In this uncommon situation of rapidly progressive renal failure associated with crescentic IgAN, the risk-to-benefit ratio most strongly favors intensive immunosuppressive therapy, because, if untreated, the patient will rapidly progress to ESRD. Treatment has often combined plasma exchange with prednisolone and cyclophosphamide.[43] Early clinical response is favorable, as in other crescentic nephritis. Medium-term results, however, are disappointing; kidney survival at 5 years was only 30% and not different in immunosuppressed and nonimmunosuppressed patients.[44]

A subset of patients with circulating IgG–antineutrophil cytoplasmic antibody (ANCA) may have a more favorable response to immunosuppressive therapy similar to that seen in other ANCA-positive crescentic nephritis.[45] With no randomized controlled trials (RCTs) of treatment, it is not possible to be certain which elements of the regimen (corticosteroids, cyclophosphamide, or plasma exchange) are mandatory.

Other Therapeutic Approaches to Progressive IgA Nephropathy

Reduction of IgA production. Tonsillectomy reduces the frequency of episodic hematuria when tonsillitis is the provoking infection. In all other patients with IgAN, tonsillectomy is not routinely recommended[19]; there is no role for prophylactic antibiotics. Dietary gluten restriction, used to reduce mucosal antigen challenge, has not been shown to preserve renal function.[2]

Prevention and removal of IgA deposits. The ideal treatment of patients with IgAN would remove IgA from the glomerulus and prevent further IgA deposition. This remains a remote prospect while the pathogenesis remains incompletely understood.

Transplant recurrence. There is no evidence that newer immunosuppressive agents have modified the frequency of recurrent IgA deposits or are of value in recurrent disease. There is, however, registry evidence that transplant outcome is improved if corticosteroids are continued long term and if the immunosuppression includes MMF.[46,47] In patients with established IgAN recurrence, most clinicians merely optimize supportive care. When crescentic IgAN recurs with rapidly deteriorating graft function, treatment as for primary crescentic IgAN has been used, although evidence of its success is sparse.

IgA VASCULITIS

Definition

IgA vasculitis (IgAV), previously termed Henoch-Schönlein purpura, is a small-vessel vasculitis affecting the skin, joints, gut, and kidneys that predominantly affects children. It is defined by tissue deposition of IgA. Typically, there is clinical involvement in the skin, gut, and kidneys. The nephritis associated with IgAV is characterized by diffuse mesangial IgA deposition. Indeed, the renal histologic features of IgAV are indistinguishable from those of IgAN.

Epidemiology

In children, IgAV is usually diagnosed on clinical grounds without biopsy confirmation of tissue IgA deposition. Transient urine abnormalities are common in the acute phase. However, only those with persistent urine abnormalities or with more overt renal disease will come to renal biopsy. Therefore the incidence of IgAV is almost certainly underestimated, with many unidentified mild and transient cases. There is no information on geographical variations in IgAV.

Despite some differences in age at onset and natural history of IgAN and IgAV,[48] there is much evidence to support a close link between the two conditions. Monozygotic twins who developed IgAN and IgAV, respectively, at the same time have been described. The evolution of IgAN into IgAV in the same patient is described in both adults and children, and patients with IgAV and ESRD receiving a renal transplant may experience recurrent disease in the form of IgAN.

Pathogenesis

Many of the abnormalities of IgA production and handling reported in IgAN are also detected in IgAV, including circulating IgA-rheumatoid factors in 55% of cases, and increased serum gd-IgA1, which is found in IgAV when there is nephritis, but it is not clear if gd-IgA1 is also predictive of extrarenal manifestations of IgAV. No studies have investigated whether gd-IgA1 is in mesangial deposits in IgAV. There is no animal model for IgAV to facilitate studies of pathogenesis.

Although infective episodes precede IgAV in up to 50% of cases, no evidence indicates a role for any specific antigen.

Genetics

Subjects with IgAV have been excluded from recent large-scale genome-wide association studies in IgAN, and the genetic background to IgAV has not been systematically studied.

Clinical Manifestations

Although most prevalent in the first decade of life, IgAV may occur at any age. A palpable purpuric rash, which may be recurrent, occurs on extensor surfaces (Fig. 23.7). There may be polyarthralgia (usually without joint swelling) and abdominal pain caused by gut vasculitis. This may be severe, with bloody diarrhea if intussusception develops. In practice, the diagnosis is made by clinical criteria in the great majority of children, in whom IgAV is often a self-limiting illness. In adults, clinical features include purpura, arthritis, and gastrointestinal symptoms in 95%, 60%, and 50% of patients, respectively.[49] Renal involvement in adults with IgAV does not differ from that in isolated IgAN. Tissue confirmation of IgA deposition by renal or skin biopsy is necessary to establish the diagnosis of IgAV.

Much renal involvement in IgAV is transient. Urine abnormalities are noted during the acute presentation but may disappear. Of those

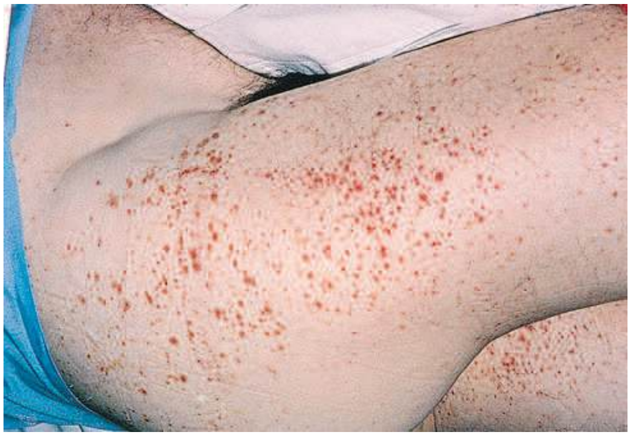

Fig. 23.7 **Henoch-Schönlein Purpura.** The rash is a palpable purpuric vasculitis on the lower limbs spreading on extensor surfaces to the buttocks and occasionally to the upper limbs. Histology shows leukocytoclastic vasculitis with IgA deposits in blood vessel walls.

referred to a nephrologist, asymptomatic urine abnormality is still the most frequent clinical manifestation. Nephrotic syndrome occurs in 20% to 30% of patients. AKI may develop as a result of crescentic GN.

Pathology

The renal histopathologic findings in IgAN and IgAV nephritis may be indistinguishable (see Fig. 23.4). The predictive value of the MEST score has not yet been shown for IgAV with renal involvement.

Differential Diagnosis

In children, the diagnosis of IgAV is usually made on the basis of clinical criteria. Confirmatory evidence of tissue IgA deposition will not be obtained unless persistence of renal disease results in a renal biopsy. In adults, the differential diagnosis is much wider and includes other forms of systemic vasculitis, requiring diagnosis by clinical, serologic, and histologic characteristics (see Chapter 25).

Natural History

The natural history for IgAV is less well defined than for IgAN. Observations are restricted to patients referred for renal biopsy, which excludes the majority of patients with minor transient renal involvement, who have an excellent prognosis. The renal prognosis is worse in adults than in children with IgAV. In adults, up to 40% will have CKD or ESRD 15 years after biopsy. One series reports an increased mortality from lung and gastrointestinal malignancy.[49]

Transplantation

IgAV can recur as isolated IgA deposits in the graft (~50% of transplants), as full-blown yet isolated IgAN, or rarely as a full recurrence of systemic involvement, including a rash. The clinical and pathologic characteristics of renal recurrence are similar to those of recurrent IgAN.[25] Delay of transplantation once ESRD is reached does not reduce the risk for IgAV recurrence.

Treatment

Many patients have transient nephritis during the early phase of IgAV, which spontaneously remits and requires no treatment. There are no prospective RCTs to guide the treatment of IgAV. Most therapeutic studies of IgAN exclude those with IgAV, so it is unclear whether the potential treatments for IgAN have a role in IgAV.[19] Commonly used treatments for IgAV are shown in Box 23.2.

BOX 23.2 Treatment Recommendations for Nephritis in IgA Vasculitis

Crescentic nephritis: Regimen is as for crescentic IgA nephropathy (see Fig. 23.6).

All other Nephritis in IgA Vasculitis (including nephrotic syndrome): Regimen is as for IgA nephropathy (see Fig. 23.6).

Hypertension: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are agents of first choice; target blood pressure: 130/80 mm Hg if proteinuria is <1 g/24 h, 125/75 mm Hg if proteinuria is >1 g/24 h.

Transplantation: Cadaveric donor may be preferable to living related donor in children (controversial).

Rapidly Progressive Chronic Kidney Disease Caused by Crescentic Nephritis

Crescentic nephritis is more common in IgAV than in IgAN, particularly early in the course of the disease. There is little specific information on treatment in adults or children, but regimens based on those for other forms of systemic vasculitis are widely used. These have included corticosteroids and cyclophosphamide, with the addition of plasma exchange or pulse methylprednisolone in some cases. However, a randomized French study in adults with severe IgAV failed to detect a benefit of cyclophosphamide plus steroids over steroids alone.[50]

Active IgA Vasculitis Without Renal Failure

There is little information about less aggressive IgAV. Corticosteroids alone, although often considered more effective than in IgAN, have never been shown to be beneficial for renal involvement in IgAV, although used with apparent benefit for extrarenal manifestations. There is no evidence that early use of corticosteroids in patients with IgAV prevents nephritis.[19] Promising findings with combination therapy of corticosteroids, cyclophosphamide, and antiplatelet agents have been reported in only small, nonrandomized studies.[19] A nonrandomized study reported that prednisolone and azathioprine preserved renal function and improved histologic appearances, but relied on historical controls.[51]

Slowly Progressive Chronic Kidney Disease

Although the renal histology and clinical course of slowly progressive IgAV and IgAN may be indistinguishable, patients with IgAV have not been included in studies of slowly progressive IgAN. Therefore there is no evidence that fish oil is beneficial in IgAV. Tight BP control with ACE inhibitors or angiotensin receptor blockers (ARBs) is recommended for proteinuric IgAV as for IgAN. The 2012 KDIGO guidelines recommend a similar indication for corticosteroids in slowly progressive IgAV as in patients with intermediate-risk IgAN.[19]

Transplant Recurrence

No treatment is known to reduce the risk for recurrence. There is some evidence that recurrence is more common and more likely to lead to graft loss in children receiving kidneys from living rather than deceased donors, although this is not confirmed in adults.[52,53] If crescentic IgAV recurs, intensive immunosuppression may be justified as for primary disease. This, however, has not been thoroughly evaluated.

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SELF-ASSESSMENT QUESTIONS

1. Based on the 2012 KDIGO guidelines, which of the following statements regarding the therapy of IgA nephropathy is correct?
   - **A.** Fish oil is not recommended for patients at risk for progressive glomerular filtration rate (GFR) loss.
   - **B.** Tonsillectomy should be routinely performed in patients at risk for progressive GFR loss.
   - **C.** In patients at risk for progressive loss of GFR, prednisolone should be given at 1 mg/kg for a minimum of 10 weeks.
   - **D.** Mycophenolate mofetil is not recommended in patients at risk for progressive GFR loss.
   - **E.** Azathioprine is recommended in patients at risk for progressive GFR loss.
2. The Oxford (MEST) classification of histopathologic changes in IgA nephropathy includes pathologic features predictive of outcome. Which of the following is *not* one of the predictive features?
   - **A.** Mesangial hypercellularity
   - **B.** Segmental glomerulosclerosis
   - **C.** Tubulointerstitial damage and fibrosis
   - **D.** Hypertensive vascular changes (nephrosclerosis)
   - **E.** Endocapillary hypercellularity
3. Which of the following statements is *true* about IgA nephropathy?
   - **A.** IgAN is more common in Europe than any other part of the world.
   - **B.** Measurement of abnormally glycosylated serum IgA is a diagnostic test for IgAN.
   - **C.** The renal pathologic features can be identical to those in IgA vasculitis (Henoch-Schönlein purpura).
   - **D.** Acute kidney injury with macrohematuria in IgA nephropathy is almost always caused by crescentic IgAN.
   - **E.** The risk for recurrence after kidney transplantation is reduced when MMF is part of the immunosuppressive regimen.
4. In IgA vasculitis (Henoch-Schönlein purpura) (IgAV), which of the following statements is *true*?
   - **A.** IgA vasculitis never occurs after age 40.
   - **B.** There is altered glycosylation of serum IgA1.
   - **C.** Delay in transplantation reduces the risk for recurrence.
   - **D.** Cyclophosphamide is of proven benefit for slowly progressive IgA vasculitis.
   - **E.** Corticosteroids given at onset of the rash reduce the risk for subsequent nephritis.

24

Anti–Glomerular Basement Membrane Disease and Goodpasture Disease

Richard G. Phelps, A. Neil Turner

The syndrome of renal failure and lung hemorrhage was associated with the name of Ernest Goodpasture by Stanton and Tange in their description of nine cases in 1958.[1,2] All nine patients presented with lung hemorrhage and acute renal failure and died within hours or days. These features had been prominent in the case of a young man who died during the influenza pandemic of 1919, whose postmortem findings were memorably reported by Goodpasture[1]: "The lungs gave the impression of having been injected with blood through the bronchi so that all the air spaces were filled" (Fig. 24.1).

Several diseases are now recognized as being associated with alveolar hemorrhage and rapidly progressive glomerulonephritis (RPGN). Nevertheless, this remains a striking clinical entity with relatively few causes and few pathogenetic mechanisms.

Because the first recognized mechanism was anti–glomerular basement membrane (anti-GBM) antibody formation and deposition, Goodpasture's name is firmly associated with anti-GBM disease (Goodpasture disease), even though this is responsible for only a proportion of patients with Goodpasture syndrome of lung hemorrhage and RPGN. The terminology used in this chapter is defined in Table 24.1.

ETIOLOGY AND PATHOGENESIS

Autoimmunity to a Component of Glomerular Basement Membrane

Goodpasture disease is caused by autoimmunity to the carboxyl terminal, noncollagenous (NC1) domain of a type IV collagen chain, α3(IV) NC1, also known as the Goodpasture antigen[3,4] (Fig. 24.2). Type IV collagen is an essential constituent of all basement membranes. In most tissues, it is composed of trimers comprising two α1 chains and one α2 chain, but there are also four tissue-specific chains, α3 through α6.[5,6] Three of these, α3 through α5, are found in GBM as well as in the basement membranes of the alveolus, the cochlea, parts of the eye (including corneal basement membrane and Bruch membrane), the choroid plexus of the brain, and some endocrine organs.

All patients with RPGN, lung hemorrhage, and anti-GBM antibodies have antibodies to α3(IV)NC1, usually binding predominantly to a single or a very restricted set of epitopes. Some patients also have antibodies to other basement membrane constituents, including other collagen IV chains, usually in low titer.

Predisposing Factors

Both environmental and genetic factors appear to be important in etiology. There are strong associations between Goodpasture disease and human leukocyte antigen (HLA) class II alleles, including *DRB1*1501* and *DR4* alleles, whereas *DR1* and *DR7* confer strong and dominant protection.[7] Some diseases and treatments predispose, as described in the following section.

Precipitating Factors

Theories of pathogenesis include precipitating factors that alter antigen processing to generate peptides that are usually destroyed or hidden, and to which tolerance is therefore deficient,[8,9] and molecular mimicry.[10] None of these is proved. Reports of temporal and geographic clustering of cases suggest an environmental trigger,[11,12] but no specific infectious agent has been consistently identified. Hydrocarbon exposure has been linked to disease onset in several striking case reports; but such exposure may simply trigger lung hemorrhage in patients who already have the disease. Furthermore, exposures of this kind are very common in the modern world. Similarly, cigarette smoking may precipitate lung hemorrhage in patients who already have circulating autoantibodies, but there is no evidence for a role in causation.

In several cases, renal trauma or inflammation has preceded the development of the disease (Box 24.1). These may alter α3(IV)NC1 turnover and metabolism qualitatively or quantitatively, providing an opportunity for self-tolerance to be broken. Qualitative changes in the basement membrane epitopes presented to T cells could be a result of overloading of the usual or recruitment of alternative processing pathways, such as extracellular processing by proteases released into inflamed glomeruli. The quantity of α3(IV)NC1 presented to T cells may be greater where there has been damage to the basement membrane, as occurs in small-vessel vasculitis (see Chapter 25). Some features suggest that an anti-GBM response may be a secondary phenomenon in some patients with vasculitis.[13,14] The association with membranous nephropathy (MN) is interesting because the thickened GBM in that disease contains increased amounts of the tissue-specific type IV collagen chains, including the Goodpasture antigen. The same could apply to a possible association with long-standing type 1 diabetes mellitus.[15]

Mechanisms of Renal Injury

The α3(IV)NC1 autoantibodies are central in the pathogenesis of Goodpasture disease[16,17] (Fig. 24.3). Antibodies eluted from the kidneys of patients who had died of Goodpasture disease rapidly bind to the GBM and cause glomerulonephritis (GN) when they are injected into monkeys.[18] The deposited antibodies are predominantly immunoglobulin G1 (IgG1). Contributions to renal injury mediated by such antibodies come from complement and from neutrophil and macrophage infiltration. T cells are essential for driving autoantibody production by T cell–dependent B cells, and, in experimental renal disease they are critical in producing glomerular crescents,[16,19] which are a usual feature of Goodpasture disease. Moreover, in mice engineered to express the human susceptibility HLA allele *DRB1*1501,* α3(IV)NC1-specific CD4 T cells are sufficient to transfer disease between animals.[20]

Agents that downregulate inflammation by inhibiting interleukin-1 or tumor necrosis factor, or that inhibit recruitment of inflammatory cells by blockade of adhesion molecules or chemoattractants, suppress injury in experimental models of anti-GBM disease. Evidence in humans and in experimental animals supports the severity of renal injury being increased by proinflammatory cytokines or by stimuli likely to elicit them, such as bacteremia.[19] Crescent formation is seen in aggressive inflammatory GN, as described in Chapter 16 (see Fig. 16.8).

Lung Hemorrhage

Lung hemorrhage in Goodpasture disease (but not in small-vessel vasculitis, the other major cause of Goodpasture syndrome) occurs only if there is an additional insult to the lung, which is usually cigarette smoke. However, infection, fluid overload, toxicity from inhaled vapors or other irritants, and the systemic effects of some cytokines are also possibilities. The higher risk of kidney disease as compared with lung hemorrhage may be because alveolar capillary endothelial cells more effectively block circulating immunoglobulin from reaching the underlying basement membrane. In the glomerulus, antibodies have more direct access to the GBM via the diaphragm-free fenestrations of glomerular endothelium. Other sites at which the Goodpasture antigen is found are not involved in Goodpasture disease, except possibly the choroid plexus, where the endothelium is again fenestrated, and more rarely the eye.

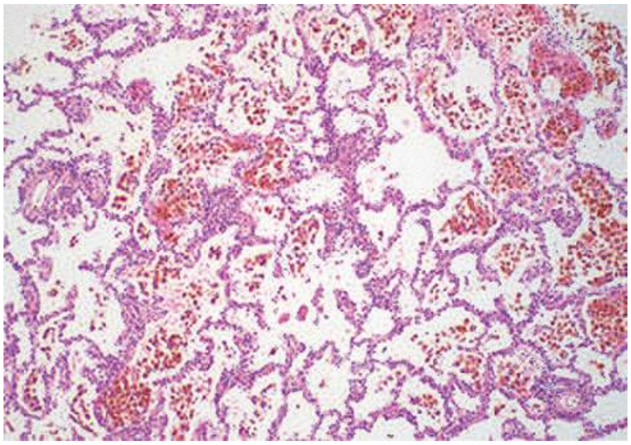

Fig. 24.1 Alveolar hemorrhage. Open lung biopsy sample in a patient with Goodpasture disease shows alveolar hemorrhage. (Courtesy Dr. E. Mary Thompson, St Mary's Hospital, London.)

EPIDEMIOLOGY

Goodpasture disease is rare, with an incidence in both White and Chinese populations approaching 1 case per 1 million population per year.[15] The incidence in Black populations appears to be lower. The incidence in other racial groups is uncertain. There is a slight male predominance. Lung hemorrhage is more common in younger patients. Age incidence is bimodal, with peaks in third and sixth decades.[15]

CLINICAL MANIFESTATIONS

Between 50% and 75% of patients present with acute symptoms of lung hemorrhage and advanced renal failure. Symptoms are usually confined to the preceding few weeks or months, but rapid progression (during days) or much slower progression (during many months) may occur. A lack of systemic symptoms, other than those related to anemia, is typical, although an apparently minor infection often triggers the clinical presentation.

Lung Hemorrhage

Lung hemorrhage may occur with renal disease or in isolation. Presenting symptoms may include cough and hemoptysis, but lung hemorrhage may result in marked iron-deficiency anemia and exertional dyspnea, even in the absence of hemoptysis. Examination findings may include pallor, dry inspiratory crackles, signs of consolidation, or respiratory distress. Recent lung hemorrhage typically is shown on the radiograph as central shadowing that may traverse fissures and give rise to the

BOX 24.1 Predisposing Events Associated With the Presentation of Goodpasture Disease

Possibly Induce Autoimmune Response and Disease

- Systemic small-vessel vasculitis affecting glomeruli
- Membranous nephropathy
- Lithotripsy of renal stones
- Urinary obstruction
- Alemtuzumab therapy for multiple sclerosis

Precipitate Pulmonary Hemorrhage

- Cigarette smoke
- Hydrocarbon exposure
- Pulmonary infection
- Fluid overload

TABLE 24.1 Definition of Terms Associated With Anti–Glomerular Basement Membrane Disease and Goodpasture Syndrome

Term	Definition	Pathogenesis
Pulmonary-renal syndrome	Renal and respiratory failure	Many causes (see Box 24.3)
Goodpasture syndrome	RPGN and alveolar hemorrhage	Several causes (see Box 24.4)
Anti-GBM disease	Disease associated with antibodies specific for (any) components of GBM	Most important are Goodpasture disease and Alport syndrome post-transplant anti-GBM disease
Goodpasture disease	Disease associated with autoantibodies specific for α3(IV)NC1 May include RPGN, lung hemorrhage, or both	Autoimmunity to α3(IV)NC1
Alport syndrome post-transplant anti-GBM disease	Glomerulonephritis associated with anti-GBM antibodies developing after renal transplantation in patients with Alport syndrome	Immunity to foreign collagen IV chains not expressed in patients with Alport syndrome, usually α3 or α5(IV)NC1

GBM, Glomerular basement membrane; *RPGN,* rapidly progressive glomerulonephritis.

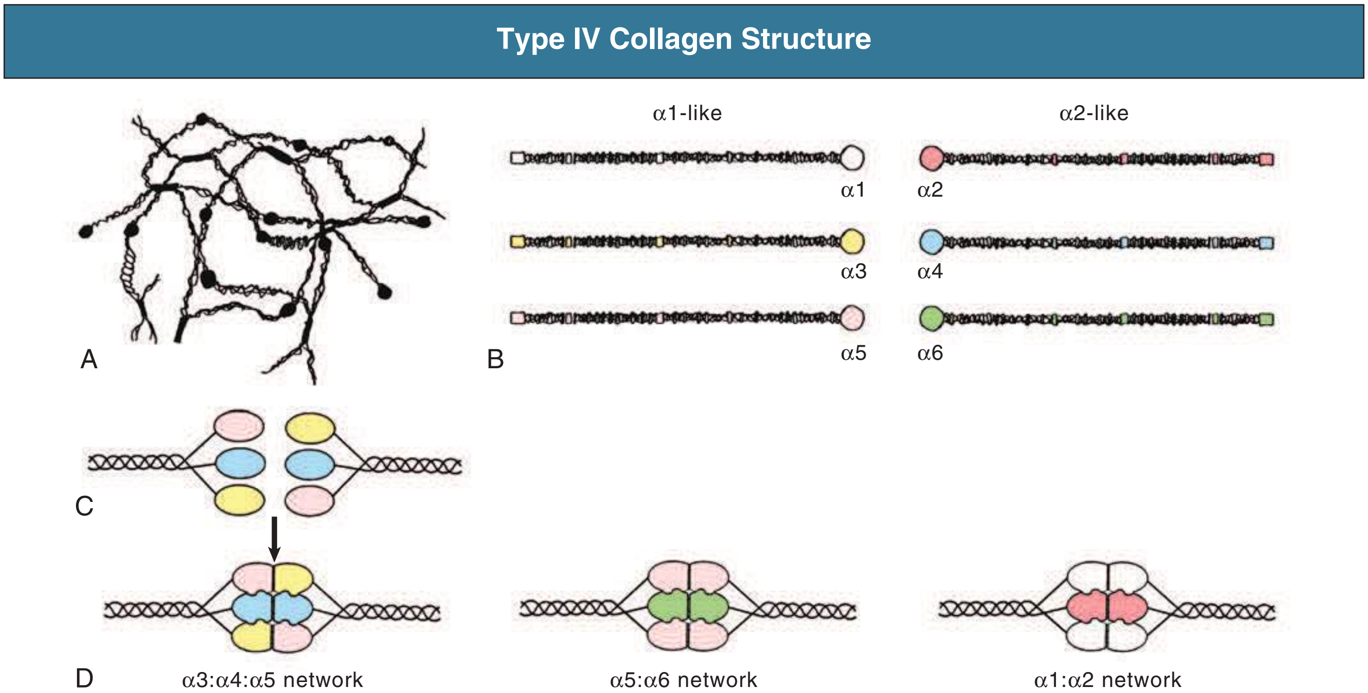

Fig. 24.2 Type IV collagen structure. (A) The type IV collagen network makes a "chicken wire" structure in the GBM. (B) Six paired type IV collagen genes, *COL4A1* to *COL4A6,* encode type IV collagen monomers α1 to α6. These associate in two or three defined monomer types per protomer (carboxyl terminal domains of α3:α4:α5 shown in (C) to form three recognized networks shown in (D) α1:α2 is present in almost all basement membranes; α3:α4:α5 is the major constituent of GBM and is a significant component of alveolar basement membrane and other locations; and α5: α6 is found in Bowman capsule, skin, esophagus, and other locations.

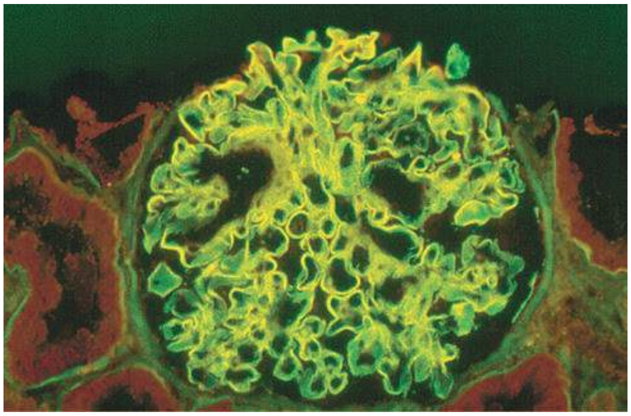

Fig. 24.3 Autoantibodies to Goodpasture antigen bound to a normal glomerulus. Direct immunofluorescence of normal kidney with sera from a patient with Goodpasture disease shows the antigen in a patient with lung hemorrhage and hematuria. (Courtesy Dr. Richard Herriot, Aberdeen Royal Infirmary, UK.)

appearance of an air bronchogram (Fig. 24.4). However, even lung hemorrhage sufficient to reduce the hemoglobin concentration may cause only minor or transient radiographic changes, and these cannot be distinguished radiologically from other causes of alveolar shadowing, notably edema or infection. The most sensitive indicator of recent lung hemorrhage is an increased uptake of inhaled carbon monoxide (DLCO). Patients with lung hemorrhage are usually current cigarette smokers.

In apparently isolated lung disease, progressive alveolar or fibrotic disease or pulmonary hemosiderosis may be suspected, although hematuria is usually found to be present if sought. This may continue for months or in rare cases recurrently for years before significant renal disease occurs.

Glomerulonephritis

Patients with GN may notice dark or red urine, but progression to oliguria is sometimes so rapid that this phase, if it occurs, is missed. In a third to half of patients, GN occurs in the absence of lung hemorrhage. In this subgroup, because systemic symptoms are generally not prominent, presentation is often late with renal failure.

Whatever the early pattern of disease, once significant renal impairment has occurred, further deterioration in renal function is usually rapid. Presentation at or shortly after acceleration of the disease process is common, and patients may demonstrate very rapid loss of renal function and life-threatening lung hemorrhage. Urinalysis always reveals hematuria (even in apparently isolated pulmonary disease), usually modest proteinuria, and dysmorphic red blood cells (RBCs) and RBC casts on microscopy. The kidneys are generally of normal size but may be enlarged. Hematuria may be substantial or associated with loin pain in acute disease.

PATHOLOGY

Renal biopsy is essential because it provides diagnostic and prognostic information. Typical appearances are of diffuse proliferative GN with variable degrees of necrosis, crescent formation, glomerulosclerosis, and tubular loss (Fig. 24.5). The degree of crescent formation and tubular loss correlates with renal prognosis. Characteristically, the crescents all appear to be of similar age and cellularity. When biopsy is performed

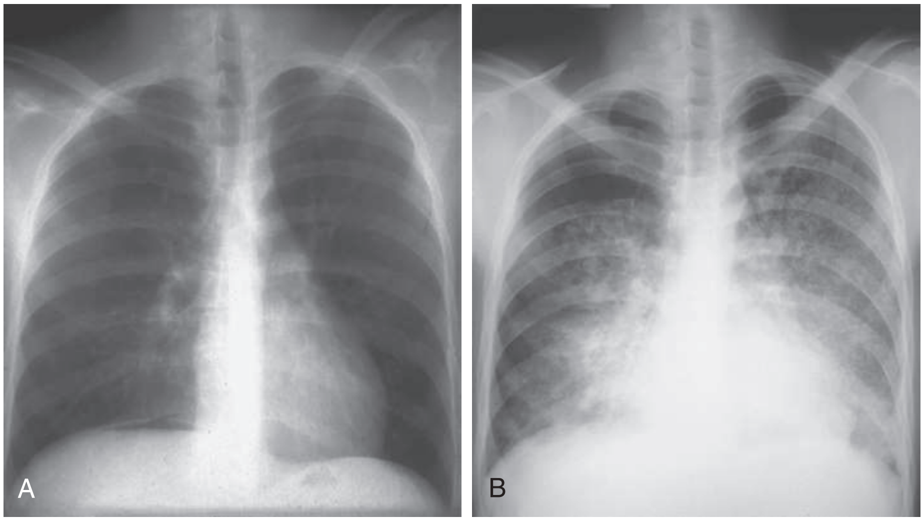

Fig. 24.4 Lung hemorrhage. (A) Patient with early pulmonary hemorrhage. The chest radiograph still appears normal. (B) Radiograph taken 4 days later shows the evolution of alveolar shadowing caused by lung hemorrhage.

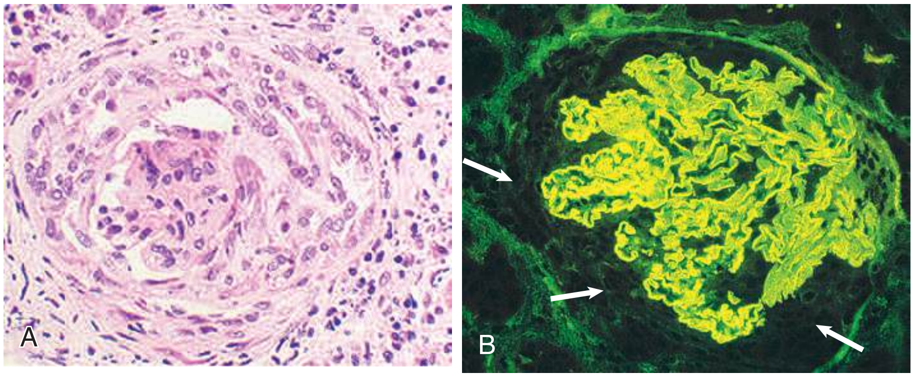

Fig. 24.5 Renal biopsy in Goodpasture disease. (A) Glomerulus from a patient with Goodpasture disease showing a recent, mostly cellular crescent. (B) Direct immunofluorescence study showing ribbon-like linear deposition of IgG along the glomerular basement membrane. The glomerular tuft is slightly compressed by cellular proliferation (exhibiting no immunofluorescence), forming a crescent *(arrows).* (Courtesy Dr. Richard Herriot, Aberdeen Royal Infirmary, UK.)

earlier in the disease, changes may be limited to focal and segmental mesangial expansion, with or without necrosis. This progresses to hypercellularity and then to more general changes, including fractures of the GBM and Bowman capsule, neutrophils in the glomeruli, and glomerular capillary thrombosis.[21]

Immunohistology

In the presence of severe glomerular inflammation, linear deposition of immunoglobulin along the GBM is pathognomonic. The immunoglobulin is usually IgG, sometimes (10% to 15%) with IgA or IgM, but, rarely, IgA alone is detected. Linear deposition of C3 is detectable in about 75% of biopsies. Linear immunofluorescence (IF) with anti-immunoglobulin reagents is occasionally seen in other conditions, usually without glomerular inflammation (Box 24.2). In most such cases, the deposited immunoglobulin is less abundant than in Goodpasture disease and is either nonspecifically deposited or bound to GBM components other than type IV collagen chains.

Circulating IgG anti-GBM antibodies are almost invariably present and may be detected and quantified by use of immobilized Goodpasture antigen in an immunoassay. The titer of anti-GBM antibody at presentation correlates with the severity of nephritis, but sometimes is at

BOX 24.2 Conditions Associated With Linear Binding of Immunoglobulin to the Glomerular Basement Membrane

Specific Binding to GBM

- Goodpasture syndrome
- Alport syndrome after renal transplantation

Nonspecific Binding to GBM

- Diabetes
- Cadaver kidneys
- Light chain disease
- Fibrillary glomerulopathy
- Systemic lupus erythematosus (possibly specific but not considered directly pathogenic)

GBM, Glomerular basement membrane.

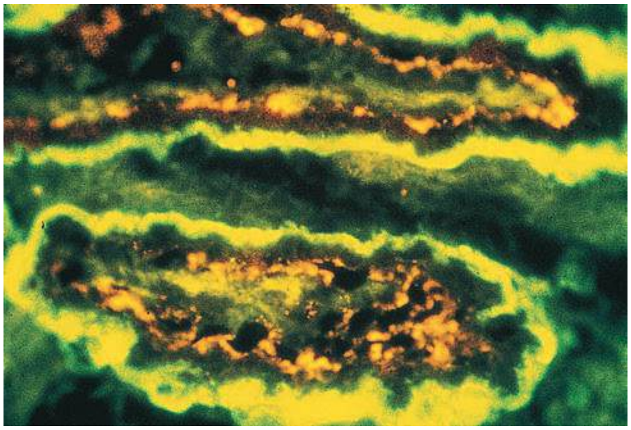

Fig. 24.6 **IgG binding to choroid plexus.** Direct immunofluorescence study showing binding of IgG to the choroid plexus of a patient who died of Goodpasture disease. (Courtesy Dr. Stephen Cashman, Imperial College, London.)

a very low level despite significant disease; interpretation may require knowledge of the local laboratory's approach to classifying assay results. Treatment and relapse are often mirrored by changes in titer.

Pathology in Other Tissues

Pathologic changes in lung tissue can be difficult to interpret because the changes, including immunoglobulin deposition, are often patchy and may be missed. Frequently, the only findings are mild, chronic inflammation and hemosiderin-laden macrophages, which are consistent with other more common pathologic diagnoses. This makes negative bronchoscopic or open-lung biopsy findings unhelpful in excluding the diagnosis.

Other tissues in which α3(IV)NC1 is expressed are rarely available for pathologic analysis, but even if antibody is deposited in these other sites, it is rarely associated with clinical disease. A number of case reports describe neurologic syndromes, particularly seizures, that may be related to antibody deposition in the choroid plexus, but may have other explanations in patients with acute kidney injury (Fig. 24.6). Other reports have described retinal detachment, in one case with antibody deposition, but again, this is rare. Placental tissue also contains the Goodpasture antigen and has been reported in a single case to act as a "sink" that binds anti-GBM antibody during pregnancy, resulting in exacerbation of glomerulonephritis after delivery.

DIFFERENTIAL DIAGNOSIS

Diagnosis of Goodpasture disease in patients who present with Goodpasture syndrome does not usually present difficulties once the possibility has been raised, although the urgency is often not appreciated. Direct IF on renal tissue and assay for circulating anti-GBM antibodies are the most rapid techniques, and renal biopsy is always indicated. Diagnosis is often delayed when patients present with subacute disease affecting the lung or the kidney in isolation. Patients with subacute lung hemorrhage may not report hemoptysis and may present with diffuse lung disease, which has many causes. Testing for hematuria is important.

Detection of Anti–Glomerular Basement Membrane Antibodies

Direct immunohistology is very sensitive for detection of anti-GBM antibody production, because the GBM selectively adsorbs and concentrates low levels of circulating antibody. However, in some circumstances, GBM may also adsorb antibody nonspecifically (see Box 24.2). Detection of anti-GBM antibodies in serum requires immunoassays based on preparations of human or animal GBM or recombinant antigen. The quality of these assays is variable. Confirmation of the specificity of anti-GBM antibodies may be obtained by Western blotting of serum onto solubilized human GBM or recombinant α3(IV)NC1, usually at a reference laboratory. Indirect immunohistology (putting patient serum onto normal kidney sections) is too insensitive for reliable diagnostic use.

False-positive results may be encountered in sera from patients with inflammatory diseases that often exhibit increased nonspecific binding. This places greater emphasis on the purity of antigen used for anti-GBM assays. False-negative results are usually encountered in patients with low titers of antibodies in association with isolated lung disease or with very early or subacute renal disease. Low titers also may be associated with anti-GBM disease that occurs after renal transplantation in patients with Alport syndrome (see later discussion).

In very advanced disease, linear antibody deposition may not be seen because of extensive destruction of GBM structure. Otherwise, deposited immunoglobulin remains detectable for some months after immunoassays have become negative.

Patients With Anti-GBM Antibodies and Other Diseases

Antineutrophil Cytoplasmic Antibody and Systemic Small-Vessel Vasculitis

Anti-GBM antibodies are sometimes detected in patients with antineutrophil cytoplasmic antibody (ANCA), especially ANCA with specificity for myeloperoxidase (see Chapter 25). Such "double-positive" patients may have a clinical course and response to treatment more typical of vasculitis than of Goodpasture disease and have possibly developed anti-GBM antibodies secondary to vasculitic glomerular damage.[8-11] Anti-GBM titers tend to be lower in ANCA-positive anti-GBM antibody–positive patients than in patients with anti-GBM antibodies alone. Recovery of renal function may be more likely if ANCAs are present, even if patients are dialysis dependent when treatment is started, although newer series have failed to detect the differences described in early reports.

Membranous Nephropathy

Anti-GBM antibodies are occasionally identified in patients with MN, usually coincident with an accelerated decline in renal function and the formation of glomerular crescents.[5,15,22] About two thirds of studies report evidence of evolution from preexisting nephrotic syndrome, and about half report a previous kidney biopsy showed typical MN. Progression to end-stage renal disease has usually been rapid, but the diagnosis has rarely been made at a stage early enough to expect intensive treatment to be successful. Three patients with Goodpasture disease later developed typical MN.

Alemtuzumab Treatment

It is now clear that treatment of multiple sclerosis (MS) with alemtuzumab, a monoclonal antibody targeting CD52 on B and T cells, is associated with the development of new autoimmunity in approximately 30% of patients, including rare cases of anti-GBM disease, sometimes as late as 4 years after treatment.[23] It remains to be established whether carriage of *DRB1*1501,* which is overrepresented in MS, influences the risk for developing anti-GBM disease after alemtuzumab therapy.

Pulmonary-Renal Syndromes

A wide variety of conditions may cause simultaneous pulmonary and renal disease. The term *pulmonary-renal syndrome* implies failure of both organs, the most common cause being fluid overload in a patient with renal failure of any cause (see Box 24.3). Then there are diseases associated with pulmonary haemorrhage and RPGN, sometimes called Goodpasture syndrome (Box 24.4).

BOX 24.3 Nonimmune Causes of Pulmonary-Renal Syndrome

With Pulmonary Edema

- Acute kidney injury with hypervolemia
- Severe cardiac failure

Infective

- Severe bacterial pneumonia (e.g., *Legionella*) with renal failure
- Hantavirus infection
- Opportunistic infections in the immunocompromised patient

Other

- Acute respiratory distress syndrome with renal failure in multiorgan failure
- Paraquat poisoning
- Renal vein/inferior vena cava thrombosis with pulmonary emboli

BOX 24.4 Causes of Lung Hemorrhage and Rapidly Progressive Glomerulonephritis

Diseases Associated With Antibodies to the GBM (20%-40% of Cases)

- Goodpasture disease (spontaneous anti-GBM disease)

Diseases Associated With Systemic Vasculitis (60%-80% of Cases)

- Granulomatosis with polyangiitis (Wegener) (common)
- Microscopic polyangiitis
- Systemic lupus erythematosus
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- IgA vasculitis (Henoch-Schönlein purpura)
- Henoch-Schönlein purpura
- Behçet syndrome
- Essential mixed cryoglobulinemia
- Rheumatoid vasculitis
- Drugs: Penicillamine, hydralazine, propylthiouracil

The two classes of disease in Box 24.4 can sometimes be differentiated clinically, but serology and renal biopsy are usually required. Renal biopsy also provides valuable prognostic information.

NATURAL HISTORY

There is some variability in the pattern of early disease. Most patients present acutely with lung hemorrhage or advanced renal failure and report that the illness developed over weeks or a few months. However, there are several reports of patients presenting with mild respiratory symptoms or incidental microhematuria, with disease progressing much more slowly during months or years; some have abruptly developed the full acute syndrome. Microhematuria preceded renal failure in all the patients who developed anti-GBM disease while being monitored after alemtuzumab treatment of MS.

Once RPGN has developed, renal function is rapidly and often irretrievably lost. Progression is often much more rapid than in RPGN occurring in other contexts, such as microscopic polyangiitis, perhaps because more glomeruli are simultaneously affected. Consequently, there is a much narrower window of opportunity for effective treatment than when other diseases cause the syndrome.

Although a severe exacerbation of lung disease usually coincides with deterioration of renal function, the natural history of isolated lung disease critically depends on continued exposure to irritants.

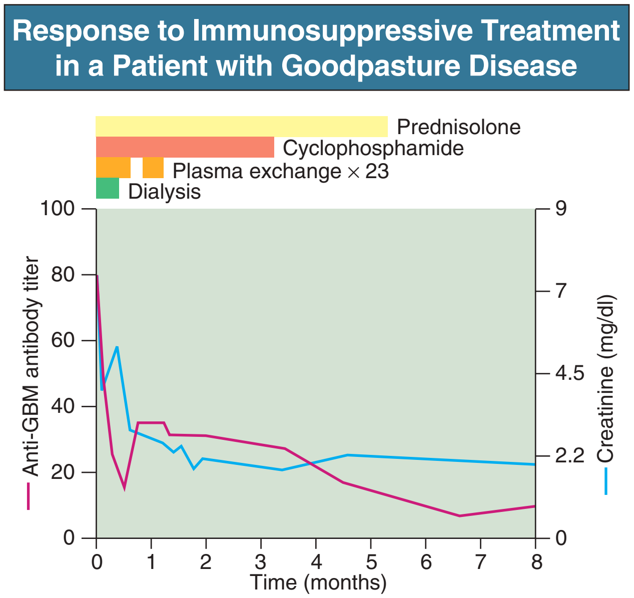
Response to Immunosuppressive Treatment in a Patient with Goodpasture Disease

Fig. 24.7 Response to immunosuppressive treatment in Goodpasture disease. The patient required dialysis but had no lung hemorrhage. The good response to treatment was unusual but not unique. The renal biopsy showed that 85% of glomeruli contained recent (mostly cellular) crescents, suggesting very acute disease, which may be indicative of a more favorable response to treatment.

TREATMENT

Immunosuppressive Regimens

Before the introduction of immunosuppressive treatment, most patients died shortly after the development of renal impairment or lung hemorrhage.[19] Lung hemorrhage now usually can be arrested within 24 to 48 hours. Renal function can be protected if impairment is mild, and even severe renal impairment can be reversed in some patients. However, dialysis-dependent patients rarely recover kidney function despite immunosuppression and should probably be immunosuppressed only if lung hemorrhage occurs.

Fig. 24.7 shows a chart recording the treatment of a patient with Goodpasture disease. Treatment recommendations for acute severe disease were devised to reduce levels of circulating pathogenic antibodies as rapidly as possible, as well as lessen their contribution to rapid glomerular destruction (Table 24.2). However, this regimen is almost certainly effective through a much broader range of mechanisms, including T cell depletion. Once the disease is controlled, immunosuppression usually can be tapered off over 3 months, and subsequent relapse is uncommon. The immune response is self-limited in the absence of immunosuppression, with antibodies disappearing over 1 to 2 years. Spontaneous remissions and effectiveness of relatively brief periods of immunosuppression are in striking contrast to the more prolonged immunosuppression generally required to prevent relapse of vasculitis and suggest a greater capacity for restoration of usual tolerance to $\alpha3$(IV)NC1[24] than to targets in vasculitis.

In RPGN with no evidence of an infective cause, immunosuppressive therapy should be started immediately, sometimes before the renal biopsy findings are available. If therapy is stopped after a few days, the patient will have incurred minimal risk (as long as pulse high-dose corticosteroids are avoided) but may have much to gain from earlier treatment.

TABLE 24.2 Treatment Regimen for Acute Goodpasture Disease

Therapy	Recommendation
Prednisolone	1 mg/kg/24 h orally. Reduce at wkly intervals to achieve one sixth of this dose by 8 wk. For a starting daily dose of 60 mg, use wkly reductions to 45, 30, 25, 20, and 15 mg; then 2 wkly to 12.5 and 10 mg. Maintain this dose to 3 mo; then taper to stop by 4 mo.
Cyclophosphamide	3 mg/kg/24 h orally, rounded down to the nearest 50 mg. Patients older than 55 yr receive a reduced dose of 2.5 mg/kg. Discontinue after 3 mo.
Plasma exchange	Daily exchange of 1 volume of plasma for 5% human albumin for 14 days or until the circulating antibody is suppressed. In the presence of pulmonary hemorrhage or within 48 hr of invasive procedure, 300 to 400 ml of fresh-frozen plasma is given at end of each treatment or according to coagulation tests.
Monitoring	Daily blood count during plasma exchange and while antibody titer remains elevated. At least twice wkly during first mo, wkly thereafter. If white blood cell count decreases to <3.5 × 10^9/l, stop cyclophosphamide until the count recovers. Resume at lower dose if cessation has been necessary. Baseline DLCO, with further measurements as indicated. Daily coagulation tests during plasma exchange to monitor for significant depletion of clotting factors. Initially, daily checks of renal and hepatic function and glucose.
Prophylaxis against complications of treatment	Oral antifungal lozenges or rinse; proton pump inhibitor. Cotrimoxazole prophylaxis against *Pneumocystis jiroveci*. Avoid nonessential lines and catheters.

DLCO, Inhaled carbon monoxide.

Plasma Exchange and Immunosuppression

The regimen described in Table 24.2 dramatically improved the outlook for patients when it was introduced in the 1970s. An early randomized trial suggested some additional benefit of plasma exchange, but the interpretation was complicated by the recipient group's less severe disease at presentation.[25] It showed that milder disease can be effectively treated with corticosteroids and cyclophosphamide alone, although the overall outcomes for all patients were not as good as described with more intensive regimens.[25] Historical evidence suggests that treatment with corticosteroids alone, or corticosteroids with azathioprine, is less effective. Plasma exchange is of value only if it is accompanied by adjunctive immunosuppressive therapy. Immunoadsorption to protein A also lowers anti-GBM antibodies rapidly and does not deplete complement components or clotting factors, and a few reports suggest that it is as effective as plasma exchange. Information is lacking on the effectiveness of newer immunosuppressive agents such as mycophenolate mofetil (MMF) or anti–B cell antibodies, which tend to have only a slow effect on antibody production but may affect antigen presentation. Therefore it is difficult to justify their use over proven therapy in the acute phase of this often rapidly progressive disease, but there may be a role in particular circumstances. Rituximab has anecdotally led to reductions in antibody titer in patients with autoimmune responses persisting or relapsing after usual therapy.[26] In contrast to advanced renal failure, in which treatment is unlikely to lead to recovery of renal function, even severe lung hemorrhage is likely to respond to treatment with full or almost full recovery of lung function.

Lung hemorrhage occurring alone tends to be relapsing and remitting, so there have been many reports of treatments (e.g., bilateral nephrectomy) that may help. Pulse methylprednisolone has been advocated, but high doses of corticosteroids fail to alter the underlying pathogenetic immune response and put the patient at increased risk for infectious and other complications. We recommend treating seriously ill patients with moderate doses of corticosteroids plus plasma exchange and cyclophosphamide.

In other acute severe diseases, daily administration of cyclophosphamide often has been superseded by pulse administration. We still prefer to use daily oral administration because it is known to work and requires only 3 months of therapy. Patients unable to take the drug orally can be given daily intravenous therapy at the usual oral dose. Dose does not need to be reduced in severe renal failure provided the white blood cell count is monitored closely, but reductions for older patients are important (see Table 24.2) and close monitoring of leukocyte counts is imperative in all patients. If pulsed therapy were chosen, the CYCLOPS (Randomised trial of daily oral versus pulse Cyclophosphamide as therapy for ANCA-associated Systemic Vasculitis) regimen would be a reasonable if untested option (see Chapter 25).

Results from all series show that recovery of renal function is unlikely if, at initiation of treatment, the patient is oliguric, has a very high proportion of glomeruli with circumferential crescents, or has a serum creatinine level above 5.5 to 6.5 mg/dl (~500 to 600 μmol/l).[27] This is a notably different experience from that encountered in systemic vasculitis or idiopathic RPGN (see Chapter 25), in which renal disease of apparently similar severity (using histology and serum creatinine) can be salvaged by similar treatment protocols.[28] This has led to the suggestion that immunosuppressive treatment should be withheld from patients with only slight chance of recovery (Table 24.3; also see later).

Supportive Treatment

The most likely cause of death in the first few days is respiratory failure caused by lung hemorrhage. Lung hemorrhage may be precipitated or exacerbated by the following:

- Fluid overload
- Smoking and other pulmonary irritants, possibly including high Fio$_2$
- Local or distant infection
- Anticoagulation used during dialysis or plasma exchange
- Thrombocytopenia, defibrination, and depletion of clotting factors as a consequence of plasma exchange

It is therefore advisable to ensure correct fluid balance, to prohibit smoking, to use the lowest fractional inspired oxygen concentration (Fio$_2$) that gives adequate oxygenation, and to minimize the use of heparin.

Plasma exchange (see Table 24.2) should be monitored by daily blood counts, calcium concentration (if regional citrate anticoagulation is used), and coagulation tests. Diminished clotting factor levels should be replenished by administration of fresh-frozen plasma or clotting factor preparations at the end of each plasma exchange session, as required.

After the first few days, the major cause of morbidity and mortality is infection. Infection carries the added risk for potentiating glomerular and lung inflammation and injury, so precautions to reduce risk, such as minimizing indwelling cannulas, are important. If leukopenia below

TABLE 24.3 **Factors in Decision to Treat Goodpasture Disease Aggressively**

	Factors Favoring Aggressive Treatment	Factors Against Aggressive Treatment
Pulmonary hemorrhage	Present	Absent
Oliguria	Absent	Present
Creatinine	<5.5 mg/dl (~500 µmol/l)	>5.5-6.5 mg/dl (~500-600 µmol/l) and ANCA negative Severe damage on kidney biopsy No desire for early kidney transplantation
Other factors	Creatinine >5.5-6.5 mg/dl (~500-600 µmol/l) *but* Rapid and recent progression ANCA positive Glomerular damage less severe than expected Crescents recent, nonfibrous Early renal transplantation desired	
Associated disease	Absent	Unusually high risk from immunosuppression

ANCA, Antineutrophil cytoplasmic antibody.

3.5×10^9/l or neutropenia develops, cyclophosphamide should be discontinued and resumed at a lower dose when the neutrophil count recovers, if necessary with the assistance of granulocyte colony-stimulating factor.

Monitoring Effect of Treatment on Disease Activity

The effect of treatment on the renal disease is monitored by following serum creatinine values. Indicators of recent lung hemorrhage include hemoptysis, decreases in hemoglobin concentration, chest radiograph changes, and increases in the Dlco, with the last being the most sensitive. Any worsening of symptoms during treatment may indicate inadequate immunosuppression, but it is frequently a consequence of intercurrent infection exaggerating immunologic injury or fluid overload or other factors precipitating lung hemorrhage.

Monitoring of anti-GBM titers during, and particularly 24 hours after, the last planned plasma exchange treatment is useful for confirming effective suppression of autoantibodies. They should be undetectable within 8 weeks, but even without treatment, autoantibodies generally become undetectable by an average of 14 months.

Duration of Treatment and Relapses

Corticosteroid treatment may be gradually reduced and cyclophosphamide discontinued at 3 months. In contrast to treatment of small-vessel vasculitis, immunosuppression longer than this is usually not necessary. Longer treatment is appropriate for patients who are positive for both anti-GBM antibody and ANCA (see later discussion). Late increases in anti-GBM level may predict clinical relapse, although antibodies are generally permanently suppressed in patients who have completed the immunosuppressive regimen. If there is recurrence, success has been achieved by treating as at first presentation.

Electing Not to Treat

Advanced renal failure, frequently already established at presentation, is generally not salvaged by any current treatment.[27,29,30] Furthermore, the immunosuppressive regimen outlined carries significant risks and careful monitoring is required. For these reasons, it may be reasonable not to initiate immunosuppression in patients who present with advanced renal failure without lung hemorrhage. The decision not to treat is strengthened if the renal biopsy specimen shows widespread glomerulosclerosis and tubular loss and the patient is dialysis dependent at presentation (see Table 24.3). The risk for development of late lung hemorrhage in these patients seems to be low but warrants particular care to avoid the major precipitating factors, smoking and pulmonary edema, in at least the first few months. However, patients who are dialysis dependent usually should be treated if the renal histopathologic changes are unexpectedly mild or very recent (highly cellular crescents, even if 100% of glomeruli are involved, or acute tubular necrosis). Several reports describe good outcomes in these patients even after prolonged oliguria.

Treatment of Double-Positive Patients

Patients with both ANCA and anti-GBM antibodies may have other extrarenal disease requiring treatment (see Table 24.3). There is conflicting evidence as to whether their renal prognosis is the same as or better than that of other patients with anti-GBM antibodies. Earlier series suggested a better prognosis, but this was not confirmed in two later reports.[13,14] Because of the risk for serious disease in other organs, double-positive patients should usually receive an immunosuppressive regimen similar to that given for small-vessel vasculitis, with continuing immunosuppression with azathioprine after 3 months of cyclophosphamide (see Chapter 25).

TRANSPLANTATION

Renal transplantation in patients who have had Goodpasture disease carries the additional risk for disease recurrence. Recurrence with consequent loss of the graft has been reported and appears more likely when circulating anti-GBM antibodies are still detectable at transplantation. Therefore it is reasonable to delay transplantation until circulating anti-GBM antibodies have been undetectable for 6 months and to monitor graft function, urinary sediment, and circulating anti-GBM antibody levels to detect recurrent disease (see Chapter 108). Biopsy samples of well-functioning grafts sometimes show linear deposition of immunoglobulin on the GBM without clinical or histologic disease or apparently an adverse prognosis.

ALPORT SYNDROME POST-TRANSPLANT ANTI–GLOMERULAR BASEMENT MEMBRANE DISEASE

Patients with Alport syndrome have mutations in a gene encoding one of the tissue-specific type IV collagen chains, usually α5. Because these chains assemble with each other during biosynthesis, the resulting phenotype in the case of most mutations often has all the tissue-specific chains (α3 through α5) missing from the basement membranes, where they are normally coexpressed. Altered expression may lead to absent or inadequate immunologic tolerance to these proteins and to preservation of the capacity to mount a powerful (allo)immune response to the type IV collagen chains expressed in a normal donor kidney after renal transplantation. Most patients with Alport syndrome accommodate renal transplants with conventional immunosuppression without development of anti-GBM nephritis. However, development of low titers of anti-GBM antibodies is shown by many such patients having linear deposition of IgG on the GBM of the transplanted kidney on direct IF, without disease. This alone does not justify treatment.

Up to 2% of patients with Alport develop RPGN in the transplanted kidney. It is clinically indistinguishable from spontaneous anti-GBM disease but without lung hemorrhage. This is more likely if the patient has a large gene deletion causing the disease rather than a point mutation, with the inference that the immune system has never been exposed to the mature protein. Typically, graft function is lost despite treatment for presumed acute rejection. Disease is usually encountered some months or longer after a first renal transplant, after weeks in a second, and after days in a third.[29] However, regrafting has been successful in two cases known to us and in two further cases in the literature. If the disease is recognized early, there are sound theoretical reasons for treating with the regimen recommended for Goodpasture disease, but there are few data on its effectiveness.[31]

In contrast to spontaneous Goodpasture disease, the specificity of anti-GBM antibodies in Alport post-transplant anti-GBM disease is not always to α3(IV)NC1. In many patients, possibly in most, the autoantibodies are specific for α5(IV)NC1, encoded by the *COL4A5* gene usually implicated in causation of the disease.[32] This is important because immunoassays for anti-GBM antibodies are optimized for detection of the anti-α3(IV)NC1 antibodies of spontaneous Goodpasture disease and they may have low sensitivity for anti-α5(IV)NC1 antibodies. In the absence of widely available assays for these uncommon antibodies, renal biopsy with immunohistology is the only reliable method of diagnosis.

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SELF-ASSESSMENT QUESTIONS

1. A 65-year-old man presenting with acute renal failure and pulmonary hemorrhage was diagnosed after appropriate investigation as having Goodpasture (anti–glomerular basement membrane [GBM]) disease and treated with plasma exchange (10 × 4 liters over 2 weeks), oral cyclophosphamide (150 mg/day) and prednisolone (week 1: 60 mg/day; week 2: 45 mg/day; week 3: 30 mg/day; week 4: 25 mg/day; week 5: 20 mg/day; week 6: 15 mg/day; weeks 7 and 8: 20 mg alternate days). Cyclophosphamide (CYP) had to be omitted for 5 days, then restarted at 100 mg/day in week 4 because of neutropenia.

   At review 3 months after treatment commenced, the patient is entirely well with estimated glomerular filtration rate (eGFR) of 36 ml/min, Hb of 110 g/l, and white blood cell count of 2.4×10^3 per μl. Anti-GBM antibodies remain detectable just above the reporting threshold of the local assay. How should his immunosuppression be managed?
   - **A.** Replace CYP with azathioprine or mycophenolate mofetil (MMF), and maintain with steroids to at least 1 year
   - **B.** Discontinue CYP and steroids with close outpatient monitoring
   - **C.** Continue CYP at reduced dose with prednisolone (10 mg/day) or equivalent to at least 1 year
   - **D.** Reinstitute plasmapheresis
2. A 45-year-old nonsmoking executive collapses at a meeting and in the emergency room is found to have a serum creatinine of 1800 μmol/l, Hb 90 g/l, K 7.2 mmol/l, BP 165/92, and normal-sized unobstructed kidneys on ultrasound scan. After appropriate acute dialysis and BP control, a renal biopsy sample is taken, which shows severe crescentic glomerulonephritis affecting 32/32 sampled glomeruli. On silver staining, breaks could be seen in multiple capillary loops and in the Bowman capsule of most glomeruli. Linear deposition of IgG along the residual GBM and strong positivity for serum anti-GBM antibodies establishes a diagnosis of Goodpasture disease. ANCA is negative, and there is no evidence of lung hemorrhage. What treatment would you recommend for this patient with Goodpasture disease?
   - **A.** Plasma exchange, CYP, and oral prednisolone for at least 3 months
   - **B.** Plasma exchange, CYP, and oral prednisolone with plan for early
   - **C.** Close monitoring with a goal of avoiding immunosuppression
   - **D.** CYP, and oral prednisolone for at least 3 months
3. A 26-year-old man has a deceased donor renal transplant after 10 months on hemodialysis. His renal failure is of unknown cause. Eight months post-transplant, kidney function is found to have deteriorated dramatically with creatinine rising from 130 to 800 μmol/l at routine clinic visits 3 weeks apart. A biopsy shows 100% crescentic nephritis with strong linear binding of IgG to the GBM. Serum anti-GBM titers are negative. The most likely diagnosis is:
   - **A.** Anti-GBM (Goodpasture) disease
   - **B.** Alport anti-GBM disease
   - **C.** Antibody-mediated rejection
   - **D.** Polyomavirus infection

25

Renal and Systemic Vasculitis

J. Charles Jennette, Ronald J. Falk

DEFINITION

The kidneys are targets for a variety of systemic vasculitides, especially those that affect small vessels.[1-4] This is not surprising given the large number and variety of renal vessels. Vasculitis involving the kidneys can produce a wide variety of clinical manifestations, depending mainly on the type of renal vessel affected. Vasculitides can be categorized as large-vessel vasculitis, medium-vessel vasculitis, and small-vessel vasculitis (Figs. 25.1 and 25.2). The 2012 Chapel Hill Consensus Conference definitions are used throughout the chapter (Table 25.1).[4]

Several of the vasculitides listed in Fig. 25.2 are covered in other chapters and are not reviewed in detail here except in the context of differential diagnosis, for example, cryoglobulinemic vasculitis (Chapter 21), immunoglobulin A (IgA) vasculitis (Henoch-Schönlein purpura, Chapter 23), and anti–glomerular basement membrane (anti-GBM) disease (Chapter 24). Nephrologists most often encounter patients with small-vessel vasculitides because these often cause glomerulonephritis (GN). Therefore small-vessel vasculitis is the primary focus of this chapter.

Small-Vessel Vasculitis

Small-vessel vasculitis is necrotizing vasculitis that affects predominantly vessels smaller than arteries, including capillaries, venules, and arterioles; however, arteries, especially small arteries, also may be involved.[4] The most common renal target for small-vessel vasculitis is glomerular capillaries, and therefore the most common renal clinical manifestations are those of GN.

Medium-Vessel Vasculitis

Medium-vessel vasculitis is necrotizing arteritis that affects predominantly major visceral arteries.[4] In the kidneys, the interlobar arteries and arcuate arteries are affected most frequently, although any arteries from the main renal artery to the smallest interlobular arteries may be affected. Inflammation and necrosis of arteries may result in thrombosis or rupture, which causes renal infarction and hemorrhage, respectively.

Large-Vessel Vasculitis

Large-vessel vasculitis is chronic granulomatous arteritis that affects the aorta and its major branches more often than other forms of vasculitis.[4] When there is renal involvement, the ostia of the renal arteries and the main renal arteries are most often affected. The most common clinical renal manifestation is renovascular hypertension.

SMALL-VESSEL PAUCI-IMMUNE VASCULITIS

Small-vessel vasculitis can be divided into *immune complex* small-vessel vasculitis with moderate to marked vessel wall deposits of immunoglobulin and *pauci-immune* small-vessel vasculitis with few or no immune deposits in vessel walls.[4] Pauci-immune small-vessel vasculitis often is associated with circulating antineutrophil cytoplasmic autoantibodies (ANCAs).[1] The ANCA-associated vasculitides share an indistinguishable form of necrotizing small-vessel vasculitis that affects capillaries, venules, arterioles, and small arteries.[1-5] Some patients with *ANCA-associated vasculitis* (AAV) have no evidence of involvement of arteries, even though they have involvement of glomerular capillaries, causing GN; pulmonary alveolar capillaries, causing pulmonary hemorrhage; or dermal venules, causing purpura. The clinicopathologic variants of pauci-immune small-vessel vasculitis are categorized on the basis of clinical, laboratory, and pathologic findings, as follows[4]:

- *Microscopic polyangiitis* (MPA) is pauci-immune small-vessel vasculitis occurring in the absence of evidence for necrotizing granulomatous inflammation.
- *Granulomatosis with polyangiitis* (Wegener) (GPA) is pauci-immune vasculitis associated with necrotizing granulomatous inflammation, most often affecting the respiratory tract.
- *Eosinophilic granulomatosis with polyangiitis* (Churg-Strauss) (EGPA) is pauci-immune vasculitis associated with asthma, eosinophilia, and necrotizing granulomatous inflammation.

MPA, GPA, and, less frequently, EGPA share an indistinguishable pattern of GN that is the expression of the vasculitis in glomerular capillaries.[1] In the acute phase, the GN usually has necrosis and crescents, and an absence or paucity of immunoglobulin deposition, and is often designated *pauci-immune crescentic glomerulonephritis*. When occurring in the apparent absence of systemic vasculitis, pauci-immune crescentic GN is sometimes referred to as *renal-limited vasculitis*.

Pathogenesis

MPA, GPA, EGPA, and renal-limited pauci-immune crescentic GN are all associated with ANCAs.[4-6] The most common antigen specificities of ANCAs in patients with vasculitis and GN are for proteinase 3 (PR3) and myeloperoxidase (MPO).[7,8]

The strong association of ANCAs with this distinctive form of small-vessel vasculitis suggests that ANCAs are involved in the pathogenesis.[4-6] The report of a neonate who developed GN and pulmonary hemorrhage possibly caused by transplacental passage of MPO-ANCA IgG is intriguing but has not been substantiated by additional reports.[9] The observation that ANCA titers correlate with disease activity also suggests a pathogenic role; however, this correlation is not strong and some patients with clinically and pathologically typical MPA, GPA, or renal-limited pauci-immune crescentic GN are negative using conventional serologic testing for ANCAs. MPO-ANCA epitope specificity determines not only the pathogenicity but also the detectability and clinical predictive value of circulating MPO-ANCA.[10] For example, ANCAs with certain epitope specificities occur only in patients with active disease, whereas other

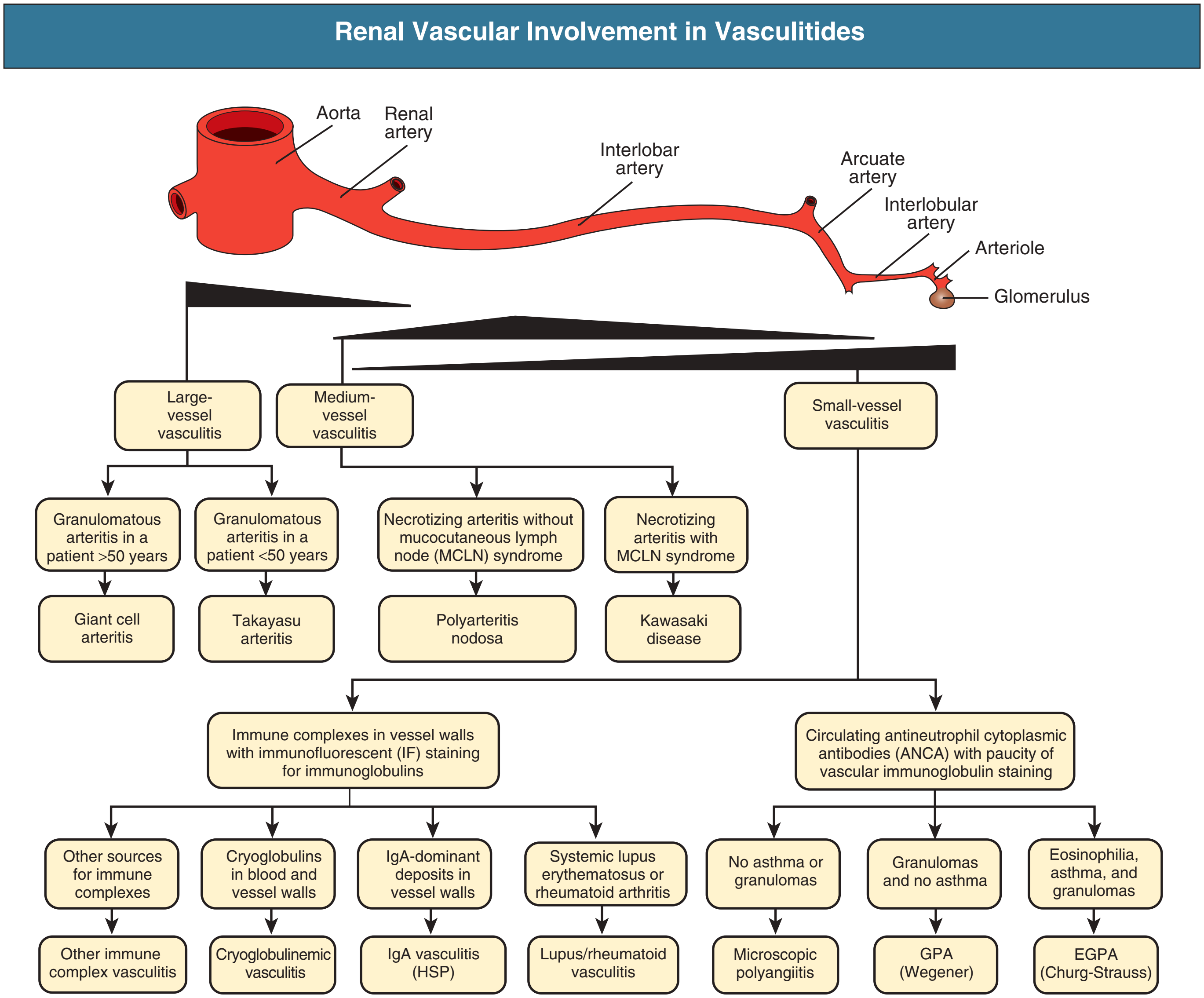
Renal Vascular Involvement in Vasculitides
Aorta
Renal artery
Interlobar artery
Arcuate artery
Interlobular artery
Arteriole
Glomerulus
Large-vessel vasculitis
Medium-vessel vasculitis
Small-vessel vasculitis
Granulomatous arteritis in a patient >50 years
Granulomatous arteritis in a patient <50 years
Necrotizing arteritis without mucocutaneous lymph node (MCLN) syndrome
Necrotizing arteritis with MCLN syndrome
Giant cell arteritis
Takayasu arteritis
Polyarteritis nodosa
Kawasaki disease
Immune complexes in vessel walls with immunofluorescent (IF) staining for immunoglobulins
Circulating antineutrophil cytoplasmic antibodies (ANCA) with paucity of vascular immunoglobulin staining
Other sources for immune complexes
Cryoglobulins in blood and vessel walls
IgA-dominant deposits in vessel walls
Systemic lupus erythematosus or rheumatoid arthritis
No asthma or granulomas
Granulomas and no asthma
Eosinophilia, asthma, and granulomas
Other immune complex vasculitis
Cryoglobulinemic vasculitis
IgA vasculitis (HSP)
Lupus/rheumatoid vasculitis
Microscopic polyangiitis
GPA (Wegener)
EGPA (Churg-Strauss)

Fig. 25.1 Renal vasculitis. Predominant distribution of renal vascular involvement by a variety of vasculitides. The heights of the trapezoids represent the relative frequency of involvement of different portions of the renal vasculature by the three major categories of vasculitis. *EGPA,* Eosinophilic granulomatous polyangiitis; *GPA,* granulomatous polyangiitis; *HSP,* Henoch-Schönlein purpura.

MPO-ANCA epitope specificities occur not only in patients with active disease but also in patients in remission and even in healthy controls (natural ANCAs), although at very low titers. Some patients with AAV who are negative by conventional serologic testing have MPO-ANCA with very restricted epitope specificity that can be detected with special unmasking techniques.[10]

The pathogenic potential of ANCAs is supported by the observation that administration of certain drugs, such as propylthiouracil, hydralazine, and penicillamine, can induce AAV.[11] Cocaine adulterated with levamisole also can induce AAV associated with high titers of MPO-ANCA, PR3-ANCA, and ANCA specific for another neutrophil granule protein elastase.[11] Levamisole-induced vasculitis has frequent cutaneous leukocytoclastic angiitis and upper respiratory tract involvement, but rarely renal or lung involvement.

A number of in vitro observations suggest mechanisms by which ANCAs can cause vascular injury.[5,6] Priming of neutrophils by cytokines, as would occur with a viral infection, causes neutrophils to increase expression of ANCA antigens on their surfaces, where they are accessible to interact with ANCAs. Cytokine-primed neutrophils that are activated by ANCAs release lytic enzymes from granules, generate toxic oxygen metabolites, and kill cultured endothelial cells. ANCA-antigen complexes adsorb onto endothelial cells, where they could participate in in situ immune complex formation. ANCA activation of neutrophils is mediated to a minor degree by both $F(ab)'_2$ binding to neutrophils and to a greater degree by Fc receptor engagement. Neutrophils that have been activated by ANCAs adhere to endothelial cells and release mediators of inflammation and cell injury. These events cause vasculitis as a result of neutrophils adhering to, penetrating, and destroying vessel walls (Fig. 25.3).

The ability of ANCA IgG to cause pauci-immune necrotizing and crescentic GN and vasculitis has been demonstrated in multiple animal models induced with MPO-ANCA, although no widely accepted model of PR3-ANCA disease has been developed.[6] Wild-type or immunodeficient mice that are injected with anti-MPO antibodies intravenously

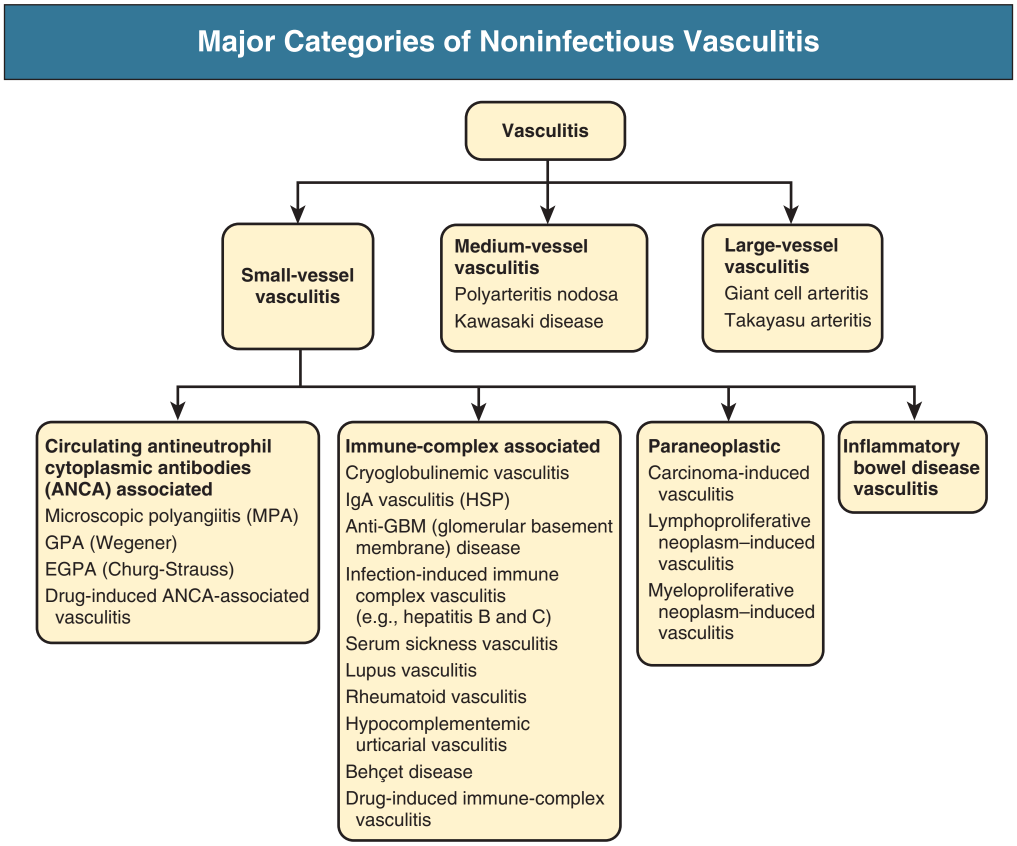
Major Categories of Noninfectious Vasculitis
Vasculitis
Small-vessel vasculitis
Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Large-vessel vasculitis
Giant cell arteritis
Takayasu arteritis
Circulating antineutrophil cytoplasmic antibodies (ANCA) associated
Microscopic polyangiitis (MPA)
GPA (Wegener)
EGPA (Churg-Strauss)
Drug-induced ANCA-associated vasculitis
Immune-complex associated
Cryoglobulinemic vasculitis
IgA vasculitis (HSP)
Anti-GBM (glomerular basement membrane) disease
Infection-induced immune complex vasculitis (e.g., hepatitis B and C)
Serum sickness vasculitis
Lupus vasculitis
Rheumatoid vasculitis
Hypocomplementemic urticarial vasculitis
Behçet disease
Drug-induced immune-complex vasculitis
Paraneoplastic
Carcinoma-induced vasculitis
Lymphoproliferative neoplasm–induced vasculitis
Myeloproliferative neoplasm–induced vasculitis
Inflammatory bowel disease vasculitis

Fig. 25.2 Major categories of noninfectious vasculitis. Not included are vasculitides that are known to be caused by direct invasion of vessel walls by infectious pathogens, such as rickettsial vasculitis and neisserial vasculitis. *EGPA,* Eosinophilic granulomatous polyangiitis; *GPA,* granulomatous polyangiitis; *HSP,* Henoch-Schönlein purpura.

develop pauci-immune focal necrotizing GN with crescents.[12] A rat model of pauci-immune necrotizing and crescentic GN has been developed by immunizing rats with human MPO, resulting in the development of antibodies that cross-react with rat MPO and are able to induce pauci-immune glomerular necrosis and crescents.[13] MPO-ANCA GN in mice is mediated by neutrophil activation, modulated by the Fc γ receptor repertoire, and can be prevented by neutrophil depletion.[6,12] Activation of the alternative complement pathway plays a role in amplifying ANCA-induced inflammation.[14] ANCA-activated neutrophils release factors that activate the alternative complement pathway, resulting in the generation of C5a, which is strongly chemotactic for neutrophils and primes neutrophils to facilitate further activation by ANCAs.[15] The relevance of these experimental observations in patients is supported by a report that patients with AAV have increased plasma levels of alternative pathway activation markers C3a, C5a, soluble C5b-9, and Bb during active disease but no remission, and that the plasma level of Bb correlated with percentage of cellular crescents in the renal biopsy samples and with Birmingham Vasculitis Activity Scores.[16] Clinical trials are underway to identify a role for blockade of complement activation in the treatment of AAV.

Thus the clinical and experimental data indicate that ANCAs can activate neutrophils and cause vasculitis, especially if there are concurrent synergistic proinflammatory stimuli. The requirement for a synergistic neutrophil-priming inflammatory process may be reflected in the frequent association of the onset of ANCA small-vessel vasculitis with an influenza-like syndrome.[17]

The basis for the ANCA autoimmune response is less well understood but involves having human leukocyte antigen (HLA) molecules with specific molecular recognition capabilities to initiate the PR3 or MPO autoimmune response.[18,19] This also may entail abnormally high expression of *MPO* and *PR3* genes in leukocytes and recognition of autoantigen complementary (antisense) peptides that initiates an immune response that induces anti-idiotypic antibodies that react with sense peptides (autoantigen epitopes).[6]

Epidemiology

GPA, MPA, and EGPA usually begin during the fifth, sixth, and seventh decades of life, with a peak incidence of 65 to 75 years, but may occur at any age. There is a slight male predominance. AAV has geographical and race/ethnic differences in prevalence.[20] In the United Kingdom, GPA (148 per million) is more common than MPA (65 per million), and MPA is more common than EGPA (46 per million). In France, the prevalence of AAV is twice as high in Europeans (105 per million) compared with non-Europeans (53 per million). In North America, the incidence is disproportionately greater in Whites than in African Americans, which may be caused by HLA differences.[21]

In the United Kingdom and northern Europe, PR3-ANCA (usually associated with GPA) is more common than MPO-ANCA; however, in Southern Europe, Asia, and India, MPO ANCA and MPA are more common than PR3-ANCA and GPA.[20] In the United States there is a similar trend with more PR3-ANCA and GPA in northern states and more MPO-ANCA-and MPA in southern states. Geographical and racial

TABLE 25.1 Names and Definitions of Vasculitis

Category/Name	Definition
Large-Vessel Vasculitis	
Takayasu arteritis	Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually in patients younger than 50 yr.
Giant cell arteritis	Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with predilection for branches of carotid and vertebral arteries; often involves temporal artery. Onset usually in patients older than 50 yr and often associated with polymyalgia rheumatica.
Medium-Vessel Vasculitis	
Polyarteritis nodosa	Necrotizing arteritis of medium or small arteries without GN or vasculitis in arterioles, capillaries, or venules and not associated with ANCA.
Kawasaki disease	Arteritis associated with mucocutaneous lymph node syndrome and predominantly affecting medium and small arteries; coronary arteries are often involved; aorta and large arteries may be involved. Usually occurs in infants and young children.
Small-Vessel Vasculitis	
ANCA-Associated Small-Vessel Vasculitis	
Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (capillaries, venules, arterioles, small arteries), associated with MPO-ANCA or PR3-ANCA. Not all patients have ANCA. Add prefix indicating ANCA reactivity, e.g., PR3-ANCA, MPO-ANCA, ANCA-negative.	
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (capillaries, venules, arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing GN is common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
Granulomatosis with polyangiitis (Wegener) (GPA)	Necrotizing granulomatous inflammation usually involving upper and lower respiratory tract and necrotizing vasculitis affecting predominantly small to medium vessels (capillaries, venules, arterioles, arteries, veins). Necrotizing GN is common.
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia. ANCA is more common when GN is present.
Immune Complex Small-Vessel Vasculitis	
Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels (capillaries, venules, arterioles, small arteries). GN is common.	
Anti–glomerular basement membrane (anti-GBM) disease	Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti–basement membrane autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes GN with necrosis and crescents.
Cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with cryoglobulins in serum. Skin, glomeruli, and peripheral nerves are often involved.
IgA vasculitis (IgAV) (Henoch-Schönlein purpura)	Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract and frequently causes arthritis. GN indistinguishable from IgA nephropathy may occur.
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)	Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (capillaries, venules, arterioles) and associated with anti-C1q antibodies. GN, arthritis, obstructive pulmonary disease, and ocular inflammation are common.

Modified from reference 71.
ANCA, Antineutrophil cytoplasmic antibody; *GN,* glomerulonephritis; *IgA,* immunoglobulin A.
Adopted by the 2012 chapel hill consensus conference on the nomenclature of systemic vasculitis. Note that all three categories affect arteries, but only small-vessel vasculitis has a predilection for vessels smaller than arteries.

differences may be related to HLA differences, which can influence the prevalence of PR3-ANCA and MPO-ANCA.[18,19]

Clinical Manifestations

Generalized nonspecific manifestations of systemic inflammatory disease, such as fever, malaise, anorexia, weight loss, myalgias, and arthralgias, often are present. Many patients with vasculitis trace the onset of their disease to a flu-like illness.[17]

The clinical manifestations of GPA, MPA, and EGPA are extremely varied because they are influenced by the organs affected by vasculitis. The three categories of vasculitis share features caused by the small-vessel vasculitis, and patients with GPA and EGPA have the additional features that define each of these syndromes.[4,22,23]

Renal involvement occurs often in GPA and MPA and is uncommon in EGPA (Table 25.2). The most common renal manifestations are hematuria, proteinuria, and renal failure. The renal failure often has

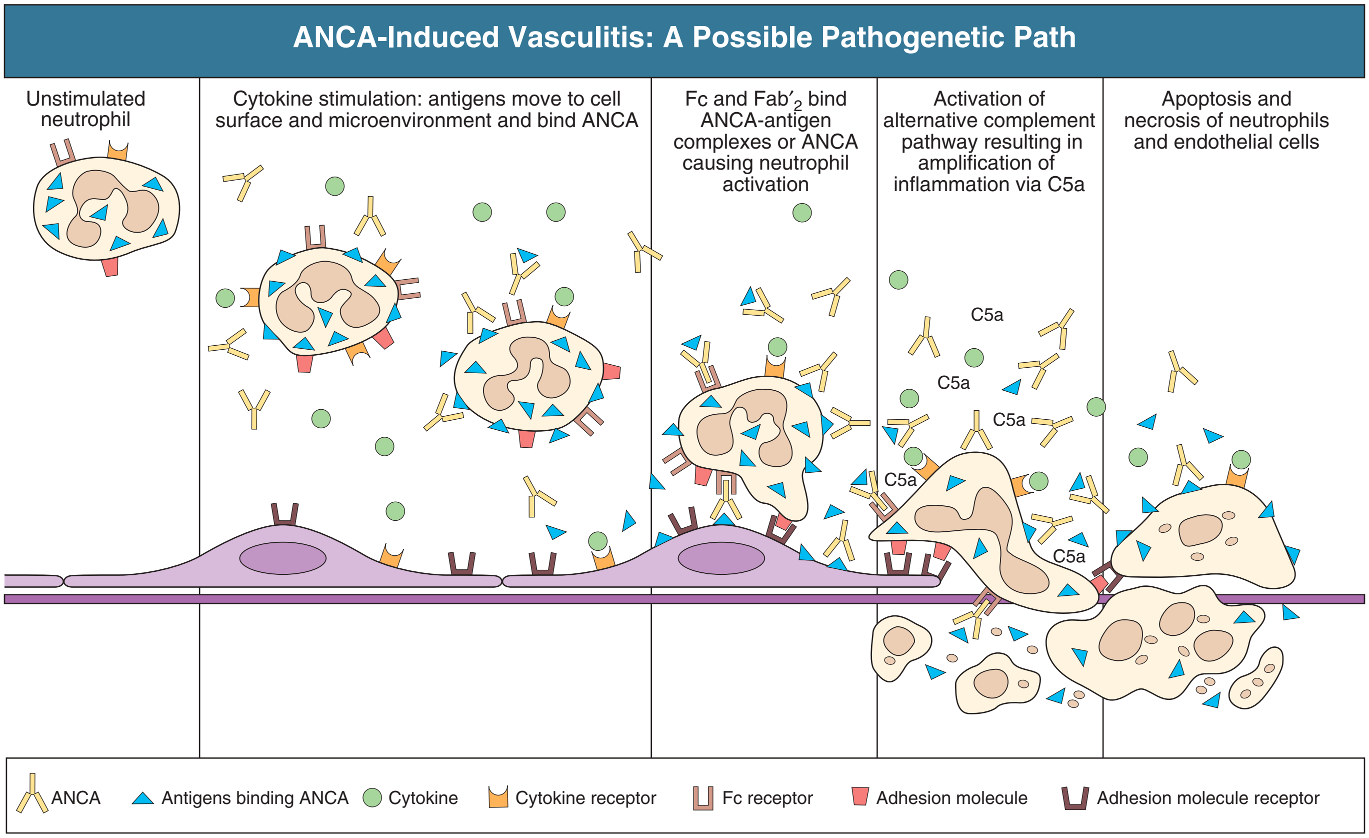
ANCA-Induced Vasculitis: A Possible Pathogenetic Path
Unstimulated neutrophil
Cytokine stimulation: antigens move to cell surface and microenvironment and bind ANCA
Fc and Fab′$_2$ bind ANCA-antigen complexes or ANCA causing neutrophil activation
Activation of alternative complement pathway resulting in amplification of inflammation via C5a
Apoptosis and necrosis of neutrophils and endothelial cells
C5a
C5a
C5a
C5a
C5a
ANCA
Antigens binding ANCA
Cytokine
Cytokine receptor
Fc receptor
Adhesion molecule
Adhesion molecule receptor

Fig. 25.3 Vasculitis induced by antineutrophil cytoplasmic antibody (ANCA). Hypothetical sequence of pathogenetic events.

TABLE 25.2 Organ System Involvement in Small-Vessel Vasculitis

	FREQUENCY OF INVOLVEMENT (%)				
Organ System	**Microscopic Polyangiitis**	**GPA (Wegener)**	**EGPA (Churg-Strauss)**	**IgA Vasculitis (HSP)**	**Cryoglobulinemic Vasculitis**
Kidney	90	80	20	50	55
Skin/cutaneous	40	40	40	90	90
Lungs	50	90	90	<5	<5
Ear, nose, throat	35	90	70	<5	<5
Musculoskeletal	60	60	50	75	70
Neurologic	30	50	40	10	40
Gastrointestinal	50	50	40	60	30

EGPA, Eosinophilic granulomatosis with polyangiitis; *GPA,* granulomatosis with polyangiitis; *HSP,* Henoch-Schönlein purpura; *IgA,* immunoglobulin A.

the characteristics of rapidly progressive glomerulonephritis (RPGN) in GPA and MPA but usually is less severe in EGPA. A cohort of more than 300 patients with pauci-immune crescentic GN evaluated at renal biopsy had a mean age of 56 years (range 2 to 92 years), male-to-female ratio of 1.0:0.9, mean serum creatinine concentration of 6.5 mg/dl (range 0.8 to 22.1 mg/dl; 69 to 1900 μmol/L), and proteinuria of 1.9 g/day (range 0.1 to 18 g/day).[24]

Cutaneous involvement occurs frequently in small vessel vasculitis. Purpura is a manifestation of GPA, MPA, and EGPA (Fig. 25.4). The purpura is most common on the lower extremities and tends to occur as recurrent crops. The purpura may be accompanied by small areas of ulceration. Nodular cutaneous lesions are more frequent in GPA and EGPA than MPA. Nodules can be caused by dermal or subcutaneous arteritis and granulomatous inflammation.

Upper respiratory tract involvement is most common in GPA and EGPA but also occurs in MPA.[25] In all three categories, patients can have pulmonary hemorrhage caused by alveolar capillaritis. Patients with GPA and to a lesser extent EGPA also can have pulmonary injury caused by necrotizing granulomatous inflammation, which may be detected radiographically as nodular or cavitating lesions. By definition, patients with MPA do not have granulomatous respiratory tract lesions.[4]

Manifestations of upper respiratory tract disease include subglottic stenosis, sinusitis, rhinitis, nasal septal collapse, otitis media, and ocular inflammation. These features are most common in GPA but may occur

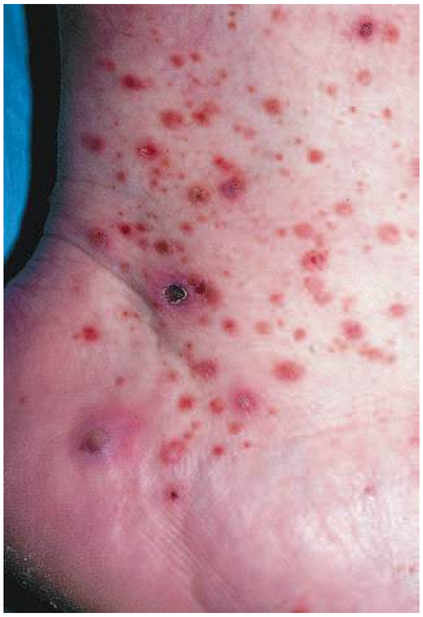

Fig. 25.4 Cutaneous vasculitis. Ankle of a patient with small-vessel vasculitis, showing purpura and a few small ulcers.

in EGPA and MPA. The upper respiratory inflammation in MPA is caused by angiitis alone, without granulomatous inflammation. Destruction of bone, for example, resulting in septal perforation and saddle nose, results from necrotizing granulomatous inflammation and therefore does not occur in MPA.

Cardiac disease is identified in approximately 50% of patients with EGPA (usually myocarditis) but in less than 20% of patients with GPA or MPA. Cardiac manifestations in GPA and MPA are predominantly transient heart block and ventricular hypokinesis that respond to immunosuppressive treatment, although infarction, endocarditis, pericarditis, and severe life-threatening myocarditis may occur.

Peripheral neuropathy, usually with a mononeuritis multiplex pattern, is the most common neurologic manifestation. Central nervous system involvement is less common and most often results from vasculitis within the meninges. Gastrointestinal involvement typically causes abdominal pain and blood in the stool, with mesenteric ischemia and rarely intestinal perforation. Vasculitis in the pancreas and liver can mimic pancreatitis and hepatitis symptomatically and cause elevated serum pancreatic and liver enzymes.

Antineutrophil Cytoplasmic Autoantibody

Serologic testing for ANCAs is a useful diagnostic procedure for pauci-immune small-vessel vasculitis and pauci-immune crescentic GN but should be interpreted in the context of other characteristics of the patient, and the performance characteristics of the assay system.[7,26-28] The antigen specificity of ANCA for PR3 versus MPO not only is helpful for diagnosis but has predictive value with respect to clinical course and outcome.[8,28] Laboratory testing for ANCA should include both indirect immunofluorescence microscopy assay (IFA) and enzyme immunoassay (EIA).[27] IFA using normal human neutrophils as substrate produces two major staining patterns (Fig. 25.5): cytoplasmic (C-ANCA), in which staining occurs diffusely throughout the cytoplasm, and perinuclear (P-ANCA). By EIA, most C-ANCAs have specificity for proteinase 3 (PR3-ANCA) and most P-ANCAs have specificity for myeloperoxidase (MPO-ANCA). For adequate diagnostic accuracy, all serologic testing for ANCAs should include an immunochemical analysis for antigen specificity, such as an EIA.[7,27,28] High-quality EIA alone can be used alone as a screening test for AAV.[28] Although positive results are rare in completely healthy individuals, approximately one fourth of patients with other inflammatory renal diseases (especially lupus) have a false-positive IFA result (usually with a P-ANCA pattern) and approximately 5% have a false-positive EIA result (usually at low titer).[27]

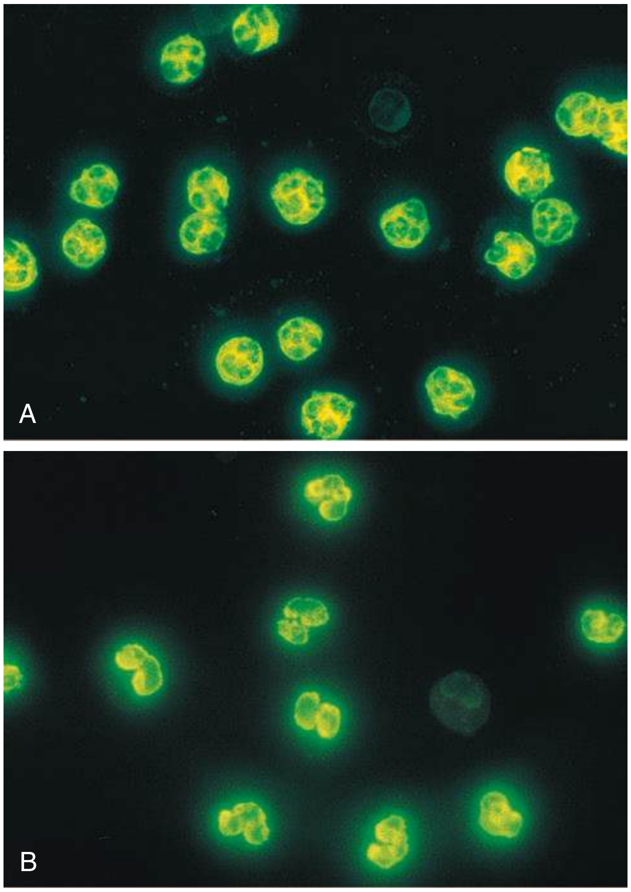

Fig. 25.5 Antineutrophil cytoplasmic antibodies (ANCAs). Indirect immunofluorescence staining pattern of alcohol-fixed normal human neutrophils. (A) Cytoplasmic pattern caused by ANCAs with specificity for proteinase 3. (B) Perinuclear pattern caused by ANCAs with specificity for myeloperoxidase (anti-IgG). (Original magnification, ×250.)

ANCA testing has good sensitivity for AAV (80% to 90%). The specificity and predictive value depend on the population of patients and the quality of the assay.[7] Although ANCAs are most frequent in patients with pauci-immune crescentic GN, one fourth to one third of patients with anti-GBM crescentic GN and one fourth of those with idiopathic immune complex crescentic GN with 50% or more crescents are ANCA positive.[24,29] Some of these patients have well-recognized types of immune complex GN complicated by ANCAs, such as membranous nephropathy and IgA nephropathy, whereas others have non-lupus IgG-dominant immune complex disease that cannot be categorized further. Patients with concurrent ANCAs and anti-GBM antibodies have a worse prognosis than patients with ANCAs alone. The anti-GBM antibodies typically disappear after treatment and do not recur, whereas ANCAs and associated vasculitis may recur.

Table 25.3 provides an estimate of the relative frequencies of PR3-ANCA/C-ANCA and MPO-ANCA/P-ANCA in the different clinical phenotypes of AAV, although this is influenced by geographical and racial influences, as discussed earlier.[5,20] PR3-ANCA/C-ANCA are most prevalent in GPA, and MPO-ANCA/P-ANCA are most prevalent in

TABLE 25.3 Antineutrophil Cytoplasmic Antibody in Small-Vessel Vasculitis

	FREQUENCY (%)		
Disorder	**Proteinase 3 (PR3, usually c-ANCA)**	**Myeloperoxidase (MPO, usually p-ANCA)**	**Negative**
Granulomatosis with polyangiitis (Wegener)	70	25	5
Microscopic polyangiitis	40	50	10
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	5	40	55
Renal-limited pauci-immune crescentic GN	20	70	10

GN, Glomerulonephritis.

Approximate frequency of antibody in small-vessel vasculitis (ANCA) with specificity for proteinase 3 (PR3/c-ANCA) and for myeloperoxidase (MPO/p-ANCA) in patients with different categories of pauci-immune small-vessel vasculitis and crescentic glomerulonephritis.

renal-limited pauci-immune crescentic GN and EGPA. Patients with MPA have a more equal distribution of PR3-ANCA/C-ANCA and MPO-ANCA/P-ANCA, although this varies among geographical regions.[20] Patients with EGPA have the lowest overall frequency of ANCAs, but the frequency of ANCAs is much higher in EGPA patients with GN (75%) than in those with no GN (26%).[30] The ANCA specificity correlates with clinical symptoms, with PR3-ANCA having the highest frequency (~90% when ANCA present) in patients who have destructive upper respiratory tract disease, especially saddle nose.[25]

Changes in ANCA titers over time may correlate with disease activity but are not dependable markers and thus must be interpreted with caution.[7,27,28,31] In general, titers decrease with treatment and increase before or at disease recurrence. An increase in ANCA titer should prompt careful evaluation of the patient for corroborating evidence of exacerbation, but most physicians do not modify treatment based on an increase in titer without accompanying clinical signs. There is evidence that epitope-specific assays may provide much better correlation with and prediction of disease outcome.[10] MPO-ANCAs with certain epitope specificities occur only in patients with active disease, disappear with remission, and reappear during relapse, whereas MPO-ANCAs with other specificities remain during disease remission.

From 10% to 20% of patients with pauci-immune necrotizing and crescentic GN and pauci-immune small-vessel vasculitis will be ANCA negative. The clinicopathologic and outcome characteristics of these patients are indistinguishable from those of ANCA-positive patients.[32] In the same epitope-specific assays previously mentioned, some patients with AAV who are negative by current clinical assays have MPO-ANCA with restricted epitope specificity that can be detected with sensitive assays that remove a masking factor.[10]

ANCAs may be positive but not associated with vasculitis in inflammatory conditions other than vasculitis, including inflammatory bowel disease (IBD), rheumatoid disease, chronic inflammatory liver disease, bacterial endocarditis, and cystic fibrosis. In IBD, specificity of the ANCAs usually is not against PR3 or MPO but against other neutrophil antigens, including lactoferrin, cathepsin G, and anti–bactericidal/permeability-increasing protein (BPI).[27,28]

Pathology

The acute vascular lesion of the pauci-immune small-vessel vasculitides is segmental fibrinoid necrosis, often accompanied by leukocyte infiltration and leukocytoclasia[1,33-35] (leukocyte fragmentation; Figs. 25.6 and 25.7). The earliest vasculitic lesions have infiltrating neutrophils that are quickly replaced by predominantly mononuclear leukocytes. The acute necrotizing lesions evolve into sclerotic lesions and may be complicated by thrombosis.

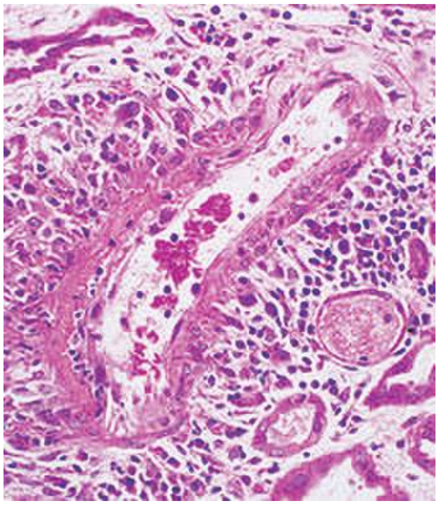

Fig. 25.6 Necrotizing arteritis of interlobular artery in patient with ANCA-associated small-vessel vasculitis. There is segmental fibrinoid necrosis with adjacent perivascular leukocyte infiltration. (Hematoxylin and eosin [HE] stain, ×50.)

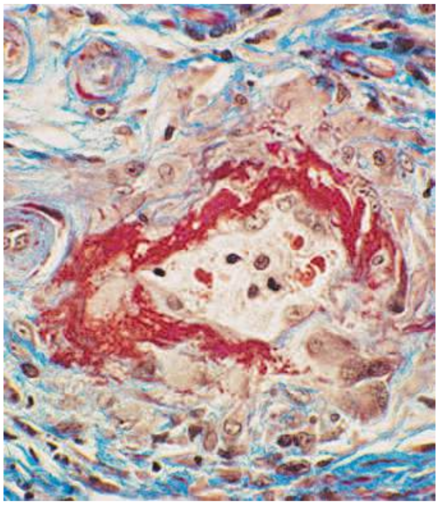

Fig. 25.7 Necrotizing arteritis of interlobular artery in patient with ANCA-associated small-vessel vasculitis. The fibrinoid necrosis is indicated by the *red* staining. (Masson trichrome, ×100.)

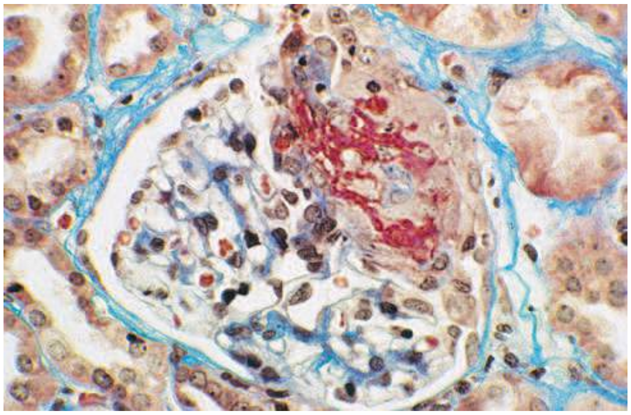

Fig. 25.8 Segmental glomerular necrosis and crescent formation in patient with ANCA-associated small-vessel vasculitis. The fibrinoid material is *red.* The uninvolved segments appear normal. (Masson trichrome, ×150.)

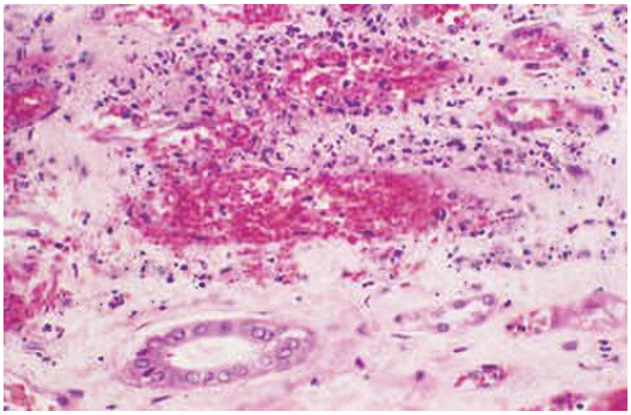

Fig. 25.10 Medullary leukocytoclastic angiitis involving vasa recta in a patient with granulomatosis with polyangiitis. (HE stain, ×150.)

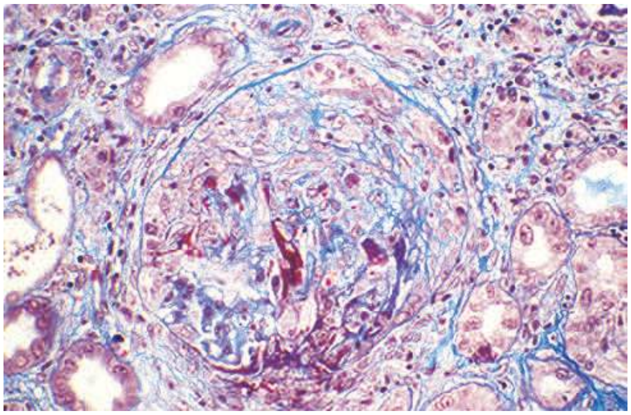

Fig. 25.9 Global glomerular necrosis and circumferential crescent formation in a glomerulus from patient with ANCA-associated small-vessel vasculitis. (Masson trichrome, ×150.)

These focal necrotizing lesions can affect many different vessels, thus causing many different signs and symptoms. For example, involvement of glomerular capillaries causes nephritis; of alveolar capillaries, pulmonary hemorrhage; of dermal venules, purpura; of upper respiratory tract mucosal venules, rhinitis and sinusitis; of abdominal visceral arteries, abdominal pain; and of epineural arteries, mononeuritis multiplex.

A shared glomerular lesion of the pauci-immune small-vessel vasculitides is a necrotizing GN, usually with resultant crescent formation.[1,33-35] Early mild lesions have segmental fibrinoid necrosis with or without an adjacent small crescent (Fig. 25.8). Severe acute lesions may have essentially global necrosis with large circumferential crescents (Fig. 25.9). In a cohort of 181 renal biopsy specimens from patients with ANCA-associated GN, 90% had glomerular crescents that on average affected 50% of glomeruli, with half having crescents in more than 50% of glomeruli.[24] Non-necrotic segments within segmentally injured glomeruli (see Fig. 25.8) and glomeruli without necrosis typically have slight or no histologic abnormalities.

As mentioned previously, approximately one fourth of patients with anti-GBM crescentic GN and one fourth of patients with immune complex–mediated crescentic GN will be ANCA positive.[24] By contrast, less than 5% of patients with immune complex GN who do not have crescents will be ANCA positive. Therefore, even in patients with immune complex GN, the presence of ANCAs is associated with an increased incidence of crescents (and also inflammation in vessels other than glomerular capillaries). A histopathologic classification has been proposed for AAV GN: sclerotic class (≥50% globally sclerotic glomeruli), focal class (≥50% normal glomeruli), crescentic class (≥50% of glomeruli with cellular crescents), or mixed class if none of these features predominated.[35] Renal survival at 5 years was 93% for the focal class, 76% for crescentic class, 61% for mixed class, and 50% for sclerotic class. Validation studies are underway to better understand the utility of this classification.

In addition to GN, patients with AAV also may have renal arteritis, most often affecting interlobular arteries (see Figs. 25.6 and 25.7), and medullary angiitis affecting the vasa recta (Fig. 25.10). The medullary angiitis may be severe enough to cause papillary necrosis, although this is a rare complication.

Patients with GPA and EGPA have pathologic lesions in addition to the necrotizing small-vessel vasculitis.[1,3,4] The necrotizing granulomatous inflammation of GPA occurs most often in the respiratory tract and is characterized by zones of necrosis surrounded by mixed infiltrates of neutrophils, lymphocytes, monocytes, and macrophages, often including scattered multinucleated giant cells. In patients with GPA and EGPA, extravascular granulomatous inflammation is rare in kidneys and even rarer in kidney biopsy specimens. Varying numbers of eosinophils may be present in the lesions of GPA, but these are more conspicuous in the necrotizing granulomatous inflammation of EGPA. Eosinophils also are typically conspicuous in the vasculitic lesions of EGPA, but this is not a pathognomonic observation because numerous eosinophils may be present in the vasculitic lesions of GPA, MPA, polyarteritis nodosa (PAN), and other vasculitides.

Differential Diagnosis

ANCA-associated small-vessel vasculitis must be differentiated from other forms of small-vessel vasculitis that can produce the same signs and symptoms.[1,3,4] In addition, an attempt should be made to distinguish MPA, GPA, and EGPA, although in some patients this cannot be accomplished conclusively and is not required for initiation of therapy. In addition to clinicopathologic classification, patients should be categorized as MPO-ANCA, PR3-ANCA, or ANCA-negative, because the serotype has independent predictive value about clinical course and outcome.[5,8,25] Pathologic confirmation of the granulomatous inflammation seen in ANCA disease is particularly difficult because small biopsy specimens often show only nonspecific acute and chronic inflammation and necrosis. Thus findings other than histologic lesions, such as nodular or cavitating lung lesions observed radiographically or destructive bone lesions in the nasal septum, often must be used as markers of necrotizing

TABLE 25.4 Differential Diagnostic Features of Select Forms of Small-Vessel Vasculitis

Features	Microscopic Polyangiitis	GPA (Wegener)	EGPA (Churg-Strauss)	IgA Vasculitis (HSP)	Cryoglobulinemic Vasculitis
Vasculitic signs and symptoms*	+	+	+	+	+
IgA-dominant immune deposits	—	—	—	+	—
Cryoglobulins in blood and vessels	—	—	—	—	+
ANCAs in blood	+	+	+	—	—
Necrotizing granulomas	—	+	+	—	—
Asthma and eosinophilia	—	—	+	—	—

Modified from reference 3.
*These vasculitides can manifest any of the shared features of small-vessel vasculitides, such as nephritis, purpura, abdominal pain, peripheral neuropathy, myalgias, and arthralgias. Each is distinguished by the presence and, just as important, by the absence of certain specific features.
ANCAs, Antineutrophil cytoplasmic antibodies; *EGPA,* eosinophilic granulomatosis with polyangiitis; *GPA,* granulomatosis with polyangiitis; *HSP,* Henoch-Schönlein purpura.

granulomatous inflammation to categorize patients. Because of the toxicity of the treatment, even in a patient with substantial clinical and serologic evidence of ANCA disease, pathologic confirmation of vasculitis is warranted. This can be accomplished with biopsy of many different involved sites, including skin, muscle, nerve, gut, and kidney. When the patient has substantial renal involvement, renal biopsy findings also can be useful for predicting response to treatment and clinical outcome.[33-35]

All forms of small-vessel vasculitis listed in Fig. 25.2 are capable of producing clinically indistinguishable overlapping features of disease, such as nephritis, purpura, peripheral neuropathy, myalgias, arthralgias, and abdominal pain. Table 25.4 lists a number of features that help distinguish several important categories of small-vessel vasculitis.[3] Accurate differentiation is very important for proper patient management because the natural histories and appropriate treatments vary greatly. For example, a patient presenting with nephritis, arthralgias, and abdominal pain could have IgA vasculitis (IgAV, formerly Henoch-Schönlein purpura), MPA, cryoglobulinemic vasculitis, or several other small-vessel vasculitides. A number of serologic and pathologic observations are useful for reaching the correct diagnosis (see Table 25.4). A positive ANCA assay (confirmed by EIA to be MPO-ANCA or PR3-ANCA) supports a diagnosis of MPA or one of the other pauci-immune small-vessel vasculitides. A negative ANCA assay and positive cryoglobulin assay (especially accompanied by hypocomplementemia and positive hepatitis C serology) support a diagnosis of cryoglobulinemic vasculitis. A negative ANCA assay, negative cryoglobulin assay, and normal complement levels support a diagnosis of IgAV, especially in a patient younger than 21 years. The age of a patient influences the likelihood of a specific diagnosis. For example, approximately 80% of children younger than 10 years who have purpura, nephritis, and arthralgias will have IgAV, whereas approximately 80% of adults older than 60 years with the same symptoms will have an AAV. However, each disease can occur at any age.

Exposure to drugs that may provoke AAV must be considered, including penicillamine, hydralazine, and propylthiouracil,[11] as well as cocaine adulterated with levamisole.[11] Cholesterol embolization also can mimic the clinical features of small-vessel vasculitis with lower extremity rash or livedo reticularis, but ANCA assay is negative. The differential diagnosis of lung hemorrhage and nephritis includes anti-GBM disease, alone or with ANCA disease.

Natural History

Before the advent of immunosuppressive therapy, the survival of patients with MPA and GPA was poor, with most patients dying in less than 1 year. With adequate immunosuppressive therapy, 5-year renal and patient survival is 65% to 75%.[5,36,37] The likelihood of success of long-term maintenance of renal function is inversely correlated with the serum creatinine concentration when therapy begins, which indicates the importance of early diagnosis and prompt initiation of appropriate treatment. The likelihood of patient survival increases with early treatment of pulmonary hemorrhage and sepsis and avoidance of overimmunosuppression leading to life-threatening infections. Adverse events from therapy, including infections, are the leading cause of death in the year after diagnosis.[36] Older age, higher serum creatinine concentration at presentation, pulmonary hemorrhage, and especially dialysis-dependent renal failure correlate with an overall poor outcome. However, even dialysis-dependent renal failure may resolve with aggressive early therapy. Respiratory tract disease and PR3-ANCA are predictors of higher relapse rates.[37] Pathologic features that correlate with renal outcome include histologically normal glomeruli, glomerular sclerosis, interstitial leukocyte infiltration, tubular necrosis, and tubular atrophy.[35] Increased numbers of histologically normal glomeruli or glomeruli with cellular crescents correlated with a better prognosis than higher proportions of globally sclerotic glomeruli, suggesting that active inflammatory lesions may be suppressed if not reversed by treatment, whereas chronic injury at initiation of treatment may be irreversible.

When severe GN is present, the renal prognosis is similar for patients with MPA, GPA, or EGPA, and renal-limited pauci-immune crescentic GN. Renal involvement, however, is much less common and usually less severe in patients with EGPA. Cardiac involvement is the most frequent cause of death in patients with EGPA, but only rarely causes mortality in MPA or GPA. GPA has a broad spectrum of clinical manifestations, from localized indolent disease to fulminant multisystem disease. For example, some patients have disease limited to the upper respiratory tract or the upper and lower respiratory tract. Such limited disease may have a more benign natural history than systemic disease with substantial renal involvement and may warrant less aggressive treatment.

Patients with MPO-ANCA have a slightly better renal outcome than those with PR3-ANCA, even though they have more renal impairment and more chronic renal pathologic changes at presentation. Patients with PR3-ANCA have more extrarenal organ manifestations (especially respiratory tract disease), higher chance for relapse, and higher mortality than patients with MPO-ANCA. Regardless of the category of ANCA disease, the best clinical predictor of renal outcome is the glomerular filtration rate (GFR) at diagnosis.

Treatment

This section focuses on patients with ANCA-associated small-vessel vasculitis affecting the kidneys, aiming not to overtreat mild disease

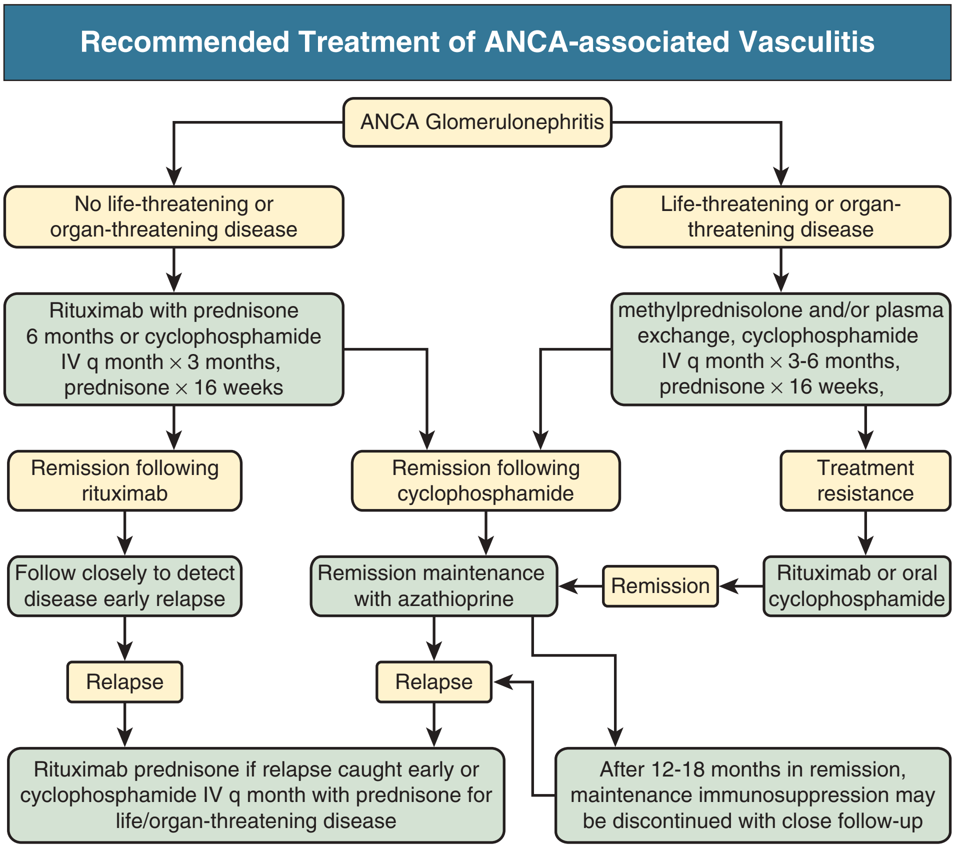
Recommended Treatment of ANCA-associated Vasculitis
ANCA Glomerulonephritis
No life-threatening or organ-threatening disease
Life-threatening or organ-threatening disease
Rituximab with prednisone 6 months or cyclophosphamide IV q month × 3 months, prednisone × 16 weeks
methylprednisolone and/or plasma exchange, cyclophosphamide IV q month × 3-6 months, prednisone × 16 weeks,
Remission following rituximab
Remission following cyclophosphamide
Treatment resistance
Follow closely to detect disease early relapse
Remission maintenance with azathioprine
Remission
Rituximab or oral cyclophosphamide
Relapse
Relapse
Rituximab prednisone if relapse caught early or cyclophosphamide IV q month with prednisone for life/organ-threatening disease
After 12-18 months in remission, maintenance immunosuppression may be discontinued with close follow-up

Fig. 25.11 Recommended treatment for ANCA-associated vasculitis.

and not to undertreat severe disease. GN that is severe enough to cause renal impairment is an indication for immunosuppressive treatment in patients with GPA, MPA, EGPA, and renal-limited pauci-immune crescentic GN. Patients with AAV who have concurrent immune complex disease should be treated similarly to patients with AAV alone. Patients with AAV who have concurrent anti-GBM disease should be treated similarly to patients with anti-GBM disease alone. Treatment involves three phases: induction of remission, maintenance of remission, and treatment of relapse (Fig. 25.11).

Induction Therapy

The standard induction therapy for AAV combines corticosteroids with an immunomodulatory agent such as cyclophosphamide or rituximab.[5,37-50] Combined treatment with corticosteroid and cyclophosphamide induces remission in approximately 75% of patients at 3 months and 90% at 6 months. The specifics of combined induction regimens vary with respect to agents, doses, route of administration, and duration. One induction approach is to begin with methylprednisolone 7 mg/kg/day intravenously (IV) for 3 days, followed by oral prednisone 1 mg/kg/day, tapering to an alternate-day regimen and discontinuing within 3 to 6 months.[39] Alternatively, the corticosteroids can be administered as prednisolone 1 mg/kg/day tapered to 0.25 mg/kg/day by 3 months.[43] The corticosteroid treatment is combined with oral cyclophosphamide 2 mg/kg/day or cyclophosphamide at 0.5 g/m^2 IV per month adjusted upward to 1 g/m^2 on the basis of the leukocyte count after 2 weeks, with a target nadir of 3000 cells/mm^3. The dose of oral cyclophosphamide can be reduced by 25 mg for patients older than 60. A comparison by the European Vasculitis Study Group (CYCLOPS trial) indicated that intravenous cyclophosphamide results in the same remission rates as oral cyclophosphamide while reducing the total dose of cyclophosphamide.[47]

The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved rituximab for use as induction therapy for AAV based on the results of two randomized controlled trials (RCTs) noting that rituximab-based cyclophosphamide-sparing strategies were comparable to traditional cyclophosphamide induction protocols.[45,46] The Rituximab for ANCA-Associated Vasculitis (RAVE) trial noted no difference in remission off all therapy in 6 months between patients treated with four infusions of 375 mg/m^2 rituximab plus prednisone and those receiving oral cyclophosphamide with prednisone (64% in rituximab arm, 55% in cyclophosphamide arm). The RITUXVAS trial compared 6 to 10 infusions of cyclophosphamide followed by maintenance therapy with azathioprine to four infusions of 375 mg/m^2 rituximab in combination with two infusions of cyclophosphamide without maintenance therapy. There was no difference in remission rates at 12 months between the groups. In both RAVE and RITUXVAS, enthusiasm is tempered by higher adverse event rates, including infection and neoplasms, that may signify no improvement in safety over cyclophosphamide. This is somewhat disappointing because there was hope that targeted B cell therapy would have fewer adverse events than broader spectrum immunosuppression. Rather than using four infusions of rituximab, our current approach is to use two 1-g doses 14 days apart. Of note, in the current health care systems in many countries, the cost and insufficient reimbursement for rituximab may be problematic.

Plasma exchange may be of benefit in patients with life-threatening pulmonary hemorrhage[48] and patients who have dialysis-dependent renal failure at presentation.[49] With pulmonary hemorrhage, 20 of 20 patients treated with early plasma exchange had resolution of pulmonary bleeding compared with a 50% mortality in historical controls.[48] A trial by the European Vasculitis Study Group (MEPEX) evaluated the efficacy of intravenous methylprednisolone as induction therapy or plasma exchange in patients who had a serum creatinine of more than 500 µmol/l.[49] Results from this study suggest that plasma exchange compared with pulse methylprednisolone in this population increases the rate of recovery from renal failure. Patient survival and adverse events were similar in patients who did or did not receive plasma exchange. Plasma exchange was associated with a 24% reduced risk for progression to end-stage renal disease (ESRD), from 43% to 19% at 1 year.

Maintenance Therapy

The duration of induction therapy and the intensity of maintenance therapy should be decreased as much as possible to reduce toxic side effects. This is a difficult challenge because of the tendency of AAV to recur. A number of approaches have been used to reduce the cyclophosphamide dose, such as giving less cyclophosphamide through intravenous rather than oral schedules, substituting a less toxic maintenance drug after 3 to 6 months, and discontinuing therapy earlier in patients with lower risk for relapse. Intravenous cyclophosphamide regimens afford one third to one half the total dose of cyclophosphamide given in oral regimens. Long-term follow-up, however, notes longer time to relapse in the oral cyclophosphamide treated group, at the cost of increased leukopenia.[50] Another approach to reducing cyclophosphamide dose is to substitute azathioprine after 3 to 6 months of therapy.[43] In the European Vasculitis Study Group (CYCAZAREM) trial, cyclophosphamide was replaced with azathioprine 2 mg/kg/day after 3 to 6 months with no change in the relapse rate at the end of the study.[43] Azathioprine 2 mg/kg/day has been compared with mycophenolate mofetil (MMF) 2 g/day in a randomized control fashion, noting that relapses were more common in the MMF group compared with the azathioprine group (unadjusted hazard ratio [HR] for MMF 1.69; 95% confidence interval [CI] 1.06 to 2.70). Adverse events, disease activity score, GFR, and proteinuria did not differ between the groups.[51]

Cyclophosphamide dose also could be reduced by alternative induction therapies. The French Vasculitis Study Group examined methotrexate compared with azathioprine as maintenance therapy in patients with GPA and MPA.[52] In this study, methotrexate was as effective as azathioprine for maintenance of remission, but methotrexate did not have fewer side effects. But methotrexate should not be used in patients with low GFR. An attractive alternative is to stop all immunosuppressive therapy at 6 to 12 months if the patient is in full remission, especially if the patient is at lower risk for relapse.[37]

Rituximab is another option for maintenance of remission.[52,53] The MAINRITSAN trial compared rituximab to azathioprine for maintenance in patients with MPA and GPA in remission after induction treatment with cyclophosphamide and glucocorticoids. Rituximab was more effective than azathioprine for preventing relapse, including renal relapse.[52] Rituximab has a significant amount of immunogenic mouse protein as part of its structure, so a growing number of patients have become sensitized to this biologic agent, and some have developed serum sickness–like disease. If sensitivity develops as a result of use for maintenance, if these patients need rituximab for clinical disease activity, it may not be an option. The expense of rituximab may become prohibitive for some patients.

The role of antimicrobial agents such as trimethoprim-sulfamethoxazole in maintenance of remission is controversial. Some studies have suggested a benefit, but others have not because of an increased likelihood of relapse.[54] Trimethoprim-sulfamethoxazole (TMP-SMX) may be useful adjunct therapy, especially in patients with upper respiratory tract disease, but should not be used in the absence of immunosuppressive drugs with more proven efficacy (e.g., cyclophosphamide, azathioprine) for induction or maintenance therapy for systemic vasculitis or GN.

Relapse Therapy

Approximately one fourth to one half of patients with AAV will experience a relapse within several years. Relapses are diagnosed on the basis of clinical and pathologic evidence of recurrent disease, not by an increase in ANCA titer alone.[31] However, an increase in ANCA titer increases the likelihood of a relapse, and some advocate preemptive immunosuppressive therapy if the ANCA titer increases by at least fourfold.[31] We prefer to identify clear-cut clinical or pathologic evidence of relapse before increasing immunosuppressive therapy.[39]

Observational data suggest that the best treatment for relapses may be rituximab. There is evidence that use of rituximab for relapse is superior to cyclophosphamide.[45] Reinstitution of treatment similar to an induction regimen is used most often, but less intensive or less toxic therapy may be adequate.[39] Lifetime exposure to cyclophosphamide is a consideration when selecting treatment for relapses. In addition to rituximab or cyclophosphamide, a number of therapies can be used in the treatment of relapse, including azathioprine, MMF, methotrexate, or combinations of these drugs tailored to the individual patient with recalcitrant disease.

In some individuals, long-term therapy may not be required, especially if there is a very low risk for relapse. In prospective observational studies from the Glomerular Disease Collaborative Network, the relative risk for relapse was increased in those individuals who had PR3-ANCA and respiratory tract disease.[37] Patients had more than a threefold risk for relapse compared with those individuals with MPO-ANCA and without lung or ear, nose, and throat disease. In a follow-up study, this model of relapsing disease was investigated in a separate registry in France, in which PR3-ANCA and lung disease was the most important predictive marker.[55] Thus, in those who have a much smaller risk for relapse, all therapy may be stopped, provided the patient and physician pursue a monitoring course in which the risk for early relapse is detected (e.g., home urinary dipstick testing to monitor for recurrence of hematuria). The risk for relapse is about 10% to 15% even with remission maintenance therapy.

Transplantation

Renal transplantation is not contraindicated in patients with ESRD caused by AAV. In a multicenter experience, the vasculitis relapse rate was 0.02 per patient per year[56] (see Chapter 108). A positive ANCA titer at the time of transplantation does not increase the risk for recurrent disease in the transplant.[57] Recurrent ANCA GN in a renal transplant responds similarly to recurrent disease in native kidneys. As with native kidney disease, an increase in ANCA titer and an active urine sediment should suggest recurrent GN, but the diagnosis requires pathologic confirmation. ANCA GN recurrence in a transplant usually is treated with cyclophosphamide and corticosteroids. Rituximab also has been used successfully and avoids increasing the risk for cyclophosphamide toxicity.[58]

POLYARTERITIS NODOSA

PAN is a systemic necrotizing arteritis that affects predominantly main visceral arteries and their intraparenchymal branches.[2,23,59] The Chapel Hill nomenclature system limits the diagnosis of PAN to patients who have only arteritis.[4] The presence of vasculitis in capillaries and venules excludes a diagnosis of PAN and indicates some form of small-vessel vasculitis. Thus GN excludes a diagnosis of PAN. When PAN is distinguished from MPA by this approach, the two categories of vasculitis have not only different pathologic characteristics but also different clinical features and natural histories, which justifies the nosologic distinction between PAN and MPA.[60]

Pathogenesis

The etiology and pathogenesis of PAN are unknown and probably are diverse.[2] When PAN is separated from MPA, the latter but not the former is associated with ANCAs. An immune complex trigger for PAN has been proposed but has not been confirmed as the major pathogenetic process. A minority of patients have hepatitis B virus (HBV) infection, suggesting that the HBV infection is producing immune complexes that are localizing in arterial walls and inducing inflammation.[2] However, the evidence that HBV infection is causing vascular immune complex deposition is stronger in certain forms of GN and small-vessel vasculitis than in PAN.

Epidemiology

When defined by the Chapel Hill nomenclature system, PAN has a low prevalence of approximately 1.5 per million.[20] The prevalence is higher in regions that have higher levels of endemic hepatitis B virus infection, which can cause PAN. PAN affects males and females equally and is found in all races. Onset occurs most frequently between ages 40 and 60 years.

Clinical Manifestations

The usual clinical presentation of PAN includes nonspecific constitutional symptoms, such as fever, malaise, arthralgias, myalgias, and weight loss, as well as manifestations of arteritis.[34,60,61] Peripheral neuropathy, typically in the form of a mononeuritis multiplex, is a common manifestation. This is caused by inflammation of small epineural arteries and is clinically indistinguishable from the peripheral neuropathy caused by other forms of vasculitis that can affect epineural arteries, such as MPA, GPA, and EGPA. Gastrointestinal involvement occurs in about half of patients, usually manifesting as abdominal pain and blood in the stool. Bowel infarction is uncommon and perforation rare. Renal involvement produces infarction and hemorrhage, as indicated by flank pain and hematuria. Rupture of an arterial aneurysm with retroperitoneal or peritoneal hemorrhage is an uncommon but potentially lethal renal complication. Approximately one third of patients develop hypertension, which rarely reaches the malignant range. Red, tender inflammatory nodules are the most common cutaneous manifestation. Infarction, ulceration, and livedo reticularis may be present.

Arterial aneurysms may be detected by angiography in patients with PAN (Fig. 25.12). This is not a completely specific determination because any necrotizing arteritis that affects arteries large enough to be seen by angiography can produce this finding.

Pathology

Any artery in the kidney can be affected by PAN, from the main renal artery to the interlobular arteries, although the interlobar and arcuate arteries are affected most often.[16] Nodular inflammatory lesions and aneurysms (pseudoaneurysms) can be observed grossly when medium-sized arteries are involved. Inflammation in small arteries can be observed only by microscopy.

The characteristic acute lesion is segmental transmural fibrinoid necrosis of arteries, usually accompanied by infiltrating leukocytes with leukocytoclasia[3] (Fig. 25.13). The earliest lesions have numerous neutrophils, and later lesions have predominantly mononuclear leukocytes. Acute lesions may be complicated by thrombosis or hemorrhage. Older lesions develop fibrosis and endarterial remodeling. The aneurysms of necrotizing arteritis are not true aneurysms but rather inflammatory pseudoaneurysms. That is, the walls of the arteries are not dilated but rather have been eaten away by the necrotizing inflammation, which then erodes into the surrounding perivascular tissue to create an enlarged lumen at the site of inflammation. This explains the propensity for such lesions to induce thrombosis or undergo rupture.

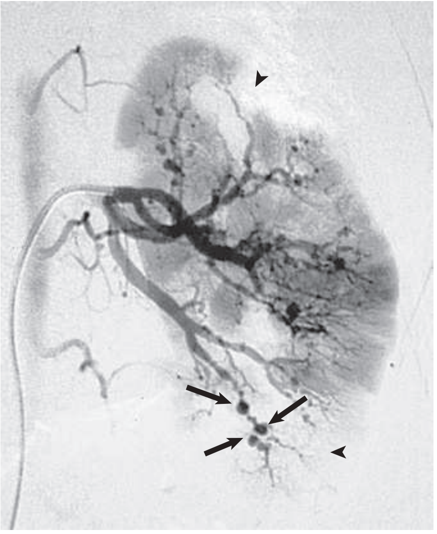

Fig. 25.12 Renal angiogram in polyarteritis nodosa. Angiogram shows patchy renal perfusion defects *(arrowheads)* and aneurysms *(arrows)*.

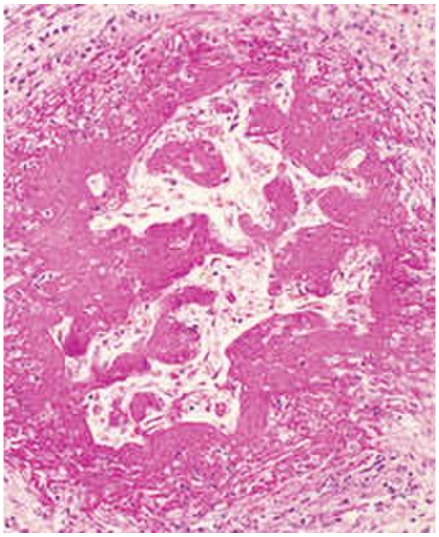

Fig. 25.13 Necrotizing arteritis in arcuate artery of patient with polyarteritis nodosa. The lumen is partially occluded by thrombotic material that is continuous with the fibrinoid material that has replaced the entire wall of the artery. (HE stain, ×50.)

The necrotizing arteritis of PAN cannot be distinguished by light microscopy from arteritis caused by other necrotizing vasculitides affecting arteries.[2,3] For example, necrotizing arteritis in a skeletal muscle biopsy specimen or a peripheral nerve biopsy specimen is histologically identical whether caused by PAN, MPA, GPA, or EGPA. For these vasculitides to be distinguished, additional clinical and serologic information is required.

Differential Diagnosis

Clinical features may assist in distinguishing PAN from other forms of vasculitis, especially other forms of necrotizing vasculitis that can affect arteries, such as MPA[2,3,23] (Table 25.5). A positive ANCA test result supports the diagnosis of one of the ANCA-associated small-vessel vasculitides rather than PAN. The presence of GN indicates some form of small-vessel vasculitis rather than PAN. Vasculitic pulmonary disease is

TABLE 25.5 Clinical Differences Between Polyarteritis Nodosa and Microscopic Polyangiitis

Clinical Feature	Polyarteritis Nodosa	Microscopic Polyangiitis
Microaneurysms by angiography	Yes	No (rare)
Rapidly progressive nephritis	No	Yes (very common)
Pulmonary hemorrhage	No	Yes
Renovascular hypertension	Yes (10%-33%)	No
Peripheral neuropathy	Yes (50%-80%)	Yes (10%-20%)
Positive hepatitis B serology	Uncommon	No
Positive ANCA	Rare	Frequent
Relapses	Rare	Frequent

Modified from reference 23.
ANCA, Antineutrophil cytoplasmic antibody.

rare in PAN but common in MPA, GPA, and EGPA. Peripheral neuropathy or muscle tenderness with arteritis in epineural or skeletal muscle arteries is not a useful differentiating feature because it often occurs in PAN, as well as in the ANCA-associated small-vessel vasculitides. Kawasaki disease causes necrotizing arteritis but is distinguished from PAN by the presence of the mucocutaneous lymph node syndrome.

Natural History

The natural history of PAN is difficult to determine because most of the early studies of outcome grouped MPA with PAN. PAN with multisystem involvement has a poor prognosis without therapy. [23] The 10-year survival with appropriate treatment is approximately 80%. Approximately 15% of patients who enter remission develop a relapse, which is much less frequent than with MPA. Relapse is more likely if treatment is delayed.

Treatment

PAN in patients with no evidence of HBV infection is treated with corticosteroids and cytotoxic drugs (usually cyclophosphamide) if there is life-threatening major organ involvement.[23,60,61] The regimens vary and include treatment approaches similar to those described earlier for MPA and GPA. However, in patients with no risk factors for poor outcome (e.g., age >50 years; cardiac, gut, or renal involvement), corticosteroids alone may be adequate and are less toxic therapy than corticosteroids combined with cytotoxic agents.[61]

Aggressive immunosuppressive therapy without initial antiviral therapy is contraindicated in patients with HBV-associated PAN because of potential adverse effects on the outcome of the HBV infection. Short-term corticosteroid treatment combined with antiviral agents and possibly plasma exchange should precede more extensive immunosuppression in such patients.

KAWASAKI DISEASE

Definition

Kawasaki disease is an acute febrile illness that usually occurs in young children, often under 1 year, and is characterized by the mucocutaneous lymph node (MCLN) syndrome (see later discussion).[2,4,62-64] Necrotizing arteritis is a complication of Kawasaki disease that is present in some but not all patients. Clinically significant renal involvement is very rare; therefore Kawasaki disease is rarely encountered by nephrologists. If untreated, approximately 20% to 25% of children develop coronary artery aneurysms that may cause myocardial infarction.[63] However, most patients who undergo autopsy examination after fatal myocardial infarction caused by coronary artery arteritis also have vasculitis in the renal arteries.[62]

Pathogenesis

The occasional occurrence of Kawasaki disease as an endemic or epidemic disease suggests that the cause may be an infectious agent or an environmental toxin.[2] Both cell-mediated and antibody-mediated mechanisms have been incriminated, as well as dysregulated innate immunity, possibly mediated by innate immune pathogen-associated molecular patterns.[64] At present, the etiology and pathogenesis of Kawasaki disease are unknown.

Epidemiology

Kawasaki disease usually occurs in children younger than 5 years and has a median age of 2 to 3 years.[63] It was first described in Japan, but it occurs worldwide. The disease is more common in Asians and Polynesians than in Whites and Blacks. In Japan, the incidence is 50 in 100,000 children younger than 5 years, with 50% of the children younger than 2.[20,63] Kawasaki disease occasionally occurs in an endemic or epidemic pattern but usually is sporadic. Kawasaki disease is not transmitted person to person and does not occur in clusters within households, schools, or nurseries.[64]

Clinical Manifestations

The MCLN syndrome is the characteristic clinical manifestation of Kawasaki disease.[4,63,64] This includes fever (temperature of usually 38° to 40° C), mucosal inflammation, swollen red tongue (strawberry tongue), polymorphous erythematous rash, indurative edema of the extremities, erythema of palms and soles, desquamation from the tips of digits, conjunctival injection, and enlarged lymph nodes. The frequency of active arteritic lesions peaks during the first week of the illness and is greatly reduced after 1 month. Arteritis most often is manifested as cardiac disease. Thrombosis of inflamed coronary arteries in patients with Kawasaki disease is the most common cause of childhood myocardial infarction. Clinically significant renal disease is uncommon. This is somewhat surprising because autopsy reveals arteritis in renal vessels in up to three fourths of patients.[62]

Pathology

The arteritis of Kawasaki disease involves small and medium-sized arteries. The acute histologic lesion is necrotizing inflammation with less fibrinoid necrosis and more vessel wall edema than usually observed with PAN[62] (Fig. 25.14). Aneurysm (pseudoaneurysm) formation and thrombosis may occur. The most frequent site of arteritis is the coronary arteries, followed by the renal arteries.[62] Arteritis most often affects interlobar arteries, occasionally arcuate arteries, and only rarely interlobular arteries.

Differential Diagnosis

Kawasaki disease has sometimes been misdiagnosed as childhood PAN. The differentiation of Kawasaki disease from PAN is important because corticosteroid treatment may increase the risk for coronary artery aneurysms in Kawasaki disease. Arteritis in a child younger than 5 years should always raise the possibility of Kawasaki disease. The presence or absence of the MCLN syndrome is the basis for distinguishing between Kawasaki disease and other forms of arteritis.[4]

Natural History

Kawasaki disease usually is self-limited, with an uneventful recovery if treated promptly with intravenous gamma globulins.[62,63] Recurrence occurs in less than 5% of patients.[63]

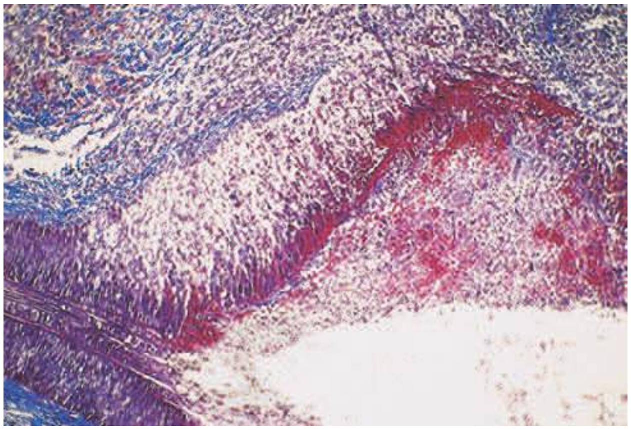

Fig. 25.14 Kawasaki disease arteritis affecting renal interlobar artery in a young child. The artery wall is intact on the *far left.* The remainder of the wall has extensive edema, infiltration by mononuclear leukocytes, and a band of fuchsinophilic *(red)* fibrinoid material roughly at the junction between the inflamed intima and muscularis. (Masson trichrome, ×25.)

Treatment

Aspirin and intravenous gamma globulin are the standard therapy for Kawasaki disease.[62,63] The role of corticosteroid treatment is controversial, but this may be beneficial in patients with severe disease that does not respond well to aspirin and intravenous immunoglobulin.

TAKAYASU ARTERITIS AND GIANT CELL ARTERITIS

Takayasu arteritis and giant cell arteritis affect the aorta and its major branches more often than other forms of vasculitis.[4,65,66] Giant cell arteritis has a predilection for the extracranial branches of the carotid artery but can affect arteries in almost any organ. Takayasu arteritis has a predilection for major arteries supplying the extremities. Both diseases cause chronic vascular inflammation, often with a granulomatous appearance that may include multinucleated giant cells. Giant cell arteritis, but not Takayasu arteritis, is associated with polymyalgia rheumatica. The relation of Takayasu arteritis and giant cell arteritis is not known. The striking demographic differences suggest, but do not prove, that they are distinct pathophysiologic entities.

Pathogenesis

The etiology and pathogenesis of giant cell arteritis and Takayasu arteritis are unknown.[2] Because of the histologic changes and the nature of the infiltrating leukocytes, cell-mediated immune mechanisms are incriminated. The inciting antigen or autoantigen has not been identified.

Epidemiology

Takayasu arteritis is seen most frequently in Asia. Giant cell arteritis occurs most often in individuals of northern European ancestry. Takayasu arteritis has a female-to-male ratio of approximately 9 : 1 and giant cell arteritis of 4 : 1. Takayasu arteritis usually is diagnosed in those between ages 10 and 20 years and is rare after age 50. Giant cell arteritis is rare before age 50. Takayasu arteritis has a uniform global incidence of 1 to 2 per million.[20] Race and ethnicity affect the vascular distribution of Takayasu arteritis, with the aortic arch and its branches affected mainly in Japanese patients, abdominal aorta and its branches affected mainly in Indian patients, lower abdominal aorta affected mainly in African populations, and renal involvement most common in Asian and African populations.[66]

Giant cell arteritis is probably the most common form of vasculitis, with an incidence that is highest in populations of Scandinavian descent, with an annual incidence of 15 to 35 per 100,000 over 50 years of age.[20]

Clinical Manifestations

In addition to nonspecific constitutional symptoms, such as fever, arthralgias, and weight loss, the major clinical manifestations of Takayasu arteritis and giant cell arteritis are caused by arterial narrowing and resultant ischemia.[2,65] The major clinical manifestations of Takayasu arteritis are reduced pulses (95% of patients), vascular bruits, claudication, and renovascular hypertension. Renovascular hypertension is a major cause of morbidity and mortality and results from renal ischemia caused by renal artery stenosis or aortic coarctation.[67] Reduced aortic elasticity and impairment of carotid artery baroreceptors also may play a role in some patients. The European League Against Rheumatism (EULAR) recommends thorough imaging assessment (see later discussion) of the entire major arterial tree when a diagnosis of Takayasu arteritis is suspected.[68]

Headache is the most common presenting symptom in patients with giant cell arteritis. Temporal artery tenderness, nodularity, or decreased pulsation is present in about half of patients. Additional common symptoms include blindness, deafness, jaw claudication, tongue dysfunction, extremity claudication, and reduced pulses. More than half of patients with giant cell arteritis have polymyalgia rheumatica, characterized by stiffness and aching in the neck and the proximal muscles of the shoulders and hips. Clinically significant renal disease is much rarer in giant cell arteritis than in Takayasu arteritis. There are case reports of necrotizing and crescentic GN associated with giant cell arteritis, but these may represent examples of GPA or MPA with temporal artery involvement.

Computerized tomography (CT), magnetic resonance angiography (MRA), fludeoxyglucose positron emission tomography-computerized tomography (FDG-PET/CT), and contrast-enhanced ultrasonography are used in diagnosis and to assess the activity of vascular inflammation in Takayasu arteritis and giant cell arteritis.[66] CT and MRA are used to identify structural changes (e.g., stenosis, aneurysms). FDG-PET/CT detects active inflammation even in vessels that show no overt structural changes by other imaging techniques.

Pathology

The aortitis and arteritis of Takayasu arteritis and giant cell arteritis cannot be confidently differentiated by pathologic examination.[4] Both are characterized in the active phase by inflammation with a predominance of mononuclear leukocytes, often with scattered multinucleated giant cells (Fig. 25.15). The chronic phase is characterized by progressive fibrosis that may cause severe narrowing of vessels, with resultant ischemia. Major renal arteries are often found to be involved at autopsy in both patients with Takayasu arteritis and those with giant cell arteritis. However, clinically significant renal disease is relatively common in Takayasu arteritis but rare in giant cell arteritis. A glomerular lesion characterized by nodular mesangial matrix expansion and mesangiolysis may occasionally be a component of Takayasu arteritis.[69]

Differential Diagnosis

There is a great deal of overlap between the clinical manifestations and pathologic features of Takayasu arteritis and giant cell arteritis. Patient age and presence or absence of polymyalgia rheumatica are the best factors for discriminating between these two vasculitides.[4] Giant cell arteritis also has been called “temporal arteritis,” but this is misleading because not all patients have temporal artery involvement and patients

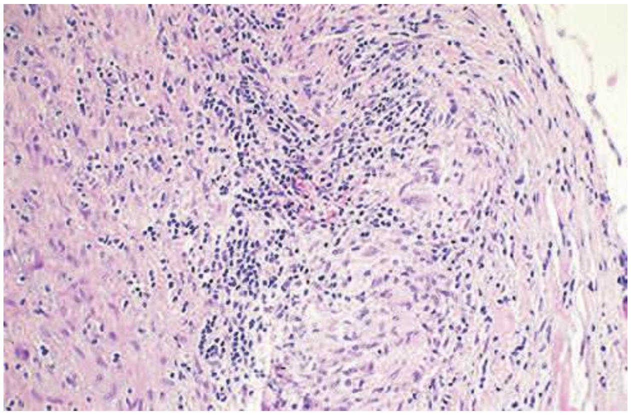

Fig. 25.15 **Severe giant cell arteritis affecting a main renal artery.** This caused marked renal atrophy and renovascular hypertension. (HE stain, ×50.)

with other types of vasculitis (PAN, GPA, MPA) can have involvement of the temporal arteries. Some of the reported examples of necrotizing GN associated with temporal arteritis probably represent GPA or MPA with temporal artery involvement.

Treatment

Corticosteroids are the usual treatment of giant cell arteritis and Takayasu arteritis.[68] EULAR recommends initial daily therapy with prednisolone 1 mg/kg for 1 month followed by tapering over several months.[68] More prolonged treatment may be dictated by persistent disease activity. Cytotoxic agents such as cyclophosphamide may be required in patients with recalcitrant disease. Patients with giant cell arteritis also should receive low-dose aspirin to protect against thrombotic vascular events.[68]

Management of renal disease is not an issue with typical giant cell arteritis, although rare patients have ischemic renal manifestations. Renovascular hypertension is the major renal problem caused by Takayasu arteritis.[66,67] When bilateral renal artery involvement occurs, angiotensin-converting enzyme inhibitors may precipitate renal failure in patients with Takayasu arteritis.[70] When medical management fails, the renovascular hypertension in patients with Takayasu arteritis may be controlled by vascular surgery or endovascular angioplasty.[66,67] Reconstructive vascular surgery should be performed during a quiescent phase of the disease.[68] The management of renovascular hypertension is covered in Chapter 41.

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SELF-ASSESSMENT QUESTIONS

1. In a patient who has systemic vasculitis affecting multiple organs, a renal biopsy showing a glomerulonephritis (GN) that is a component of the systemic vasculitis is definitive evidence that the systemic vasculitis is a:
   A. Large-vessel vasculitis
   B. Small-vessel vasculitis
   C. Medium-vessel vasculitis
   D. Variable-vessel vasculitis
2. If pathologic and serologic studies in a patient with crescentic GN are diagnostic for anti–glomerular basement membrane (GBM) disease, antineutrophil cytoplasmic antibody (ANCA) testing is:
   A. Unnecessary because it is unlikely to be positive
   B. Unnecessary because it would not change the prognosis if positive
   C. Necessary because it is positive in one fourth to one third of patients and changes the prognosis
   D. The disease is more like anti-GBM disease
3. Which of the following is most common in patients with polyarteritis nodosa (PAN)?
   A. Glomerulonephritis
   B. Pulmonary hemorrhage
   C. Polymyalgia rheumatica
   D. Hepatitis B infection
4. Which of the following is the most common clinical sign or symptom caused by Takayasu arteritis?
   A. Flank pain caused by renal infarction
   B. Acute renal failure
   C. Hematuria
   D. Hypertension
5. Is targeted B-cell therapy with rituximab an acceptable component of induction therapy for ANCA-associated vasculitis and glomerulonephritis?
   A. Yes, because induction with rituximab has fewer adverse events than induction with cyclophosphamide.
   B. Yes, because clinical trials have shown noninferiority between induction therapy with rituximab compared with cyclophosphamide.
   C. No, because clinical trials have shown that induction therapy with rituximab is inferior to induction with cyclophosphamide.
   D. No, because rituximab is not FDA approved for induction therapy.

26

Lupus Nephritis

Shikha Wadhwani, David Jayne, Brad H. Rovin

DEFINITION

Lupus nephritis (LN), the prototypical immune complex glomerulonephritis (GN), is common and serious in patients with systemic lupus erythematosus (SLE). SLE is defined by clinical and laboratory features as outlined in the 1997 American College of Rheumatology (ACR) criteria for the diagnosis of SLE (Box 26.1). The Systemic Lupus International Collaborating Clinics (SLICC) criteria introduced in 2012 (see Box 26.1) have shown greater diagnostic sensitivity and fewer misclassifications than the ACR criteria.[1,2] The SLICC criteria include biopsy-proven nephritis compatible with LN in the presence of either antinuclear antibody (ANA) or anti–double-stranded (ds)DNA antibody as sufficient evidence for the diagnosis of SLE, but eliminated dipstick-positive albuminuria as sufficient to confirm kidney involvement in LN. The SLICC criteria may influence the apparent incidence of LN.

EPIDEMIOLOGY

The incidence and prevalence of lupus and LN are influenced by age, gender, ethnicity, geographical region, diagnostic criteria used, and method of ascertainment, but across populations, clinically important kidney disease (Table 26.1) will occur in about 50% of patients with SLE.[3,4] The peak incidence of lupus is between the ages of 15 and 45 years, with women outnumbering men 8 to 15 : 1. Female predominance is less pronounced in children and older individuals. Among patients with lupus, LN affects both sexes equally, is more severe in children and men, and is less so in older adults. The incidence of LN is about 30% in White, 60% in Black and Hispanic, and 40% to 80% in Asian patients with SLE.[3,5] The higher frequency of LN in Black patients with lupus in the United States persists after adjusting for socioeconomic status.[6] Black and Hispanic patients with SLE develop LN earlier and have worse outcomes, including death and end-stage renal disease (ESRD), than White patients. The prevalence of LN in a U.S. Medicaid population was 31 in 100,000.[6]

Approximately 10% of patients with LN will develop ESRD[3]; however, this depends on histologic class. The risk for ESRD over 15 years was found to be as high as 44% in class 4 LN.[4]

SLE patients with LN die earlier than those without nephritis and have a standardized mortality ratio of 6 to 6.8 versus 2.4 in lupus without renal involvement.[7,8] This increases to 14 for those with chronic kidney disease and 63 for those with ESRD.[9] However, if LN remission is achieved through treatment, 10-year survival doubles to 95%.[10]

ETIOLOGY AND PATHOGENESIS

Genetics and Environment

A genetic predisposition to SLE is supported by disease clustering in families, twin concordance, racial differences in susceptibility, and the high frequency of autoantibodies and other autoimmune disorders in uninvolved family members of SLE patients.[11] A Taiwanese study found that the relative risk for lupus in families of those with SLE was 316 for twins, 24 for siblings, 11 for parents, 14 for children of patients, and 4.4 for nonrelated spouses, leading to estimates that heritability contributed 44% to the risk for SLE, shared environmental exposures contributed 26%, and nonshared environmental exposures 30%.[12]

Homozygous deficiency of early complement cascade components (C1q, C2, C4) carries a high risk for development of SLE; this is also true for certain Fc γ RIII receptor polymorphisms. Genome-wide association studies have identified over 100 loci associated with an increased risk for SLE, although the individual contribution of each gene to overall risk is low. Genetic risk scores are lowest in Europeans, higher in Asians, and highest in those of African ancestry.[13] Genes involved in lupus risk include those affecting B cell signaling, neutrophil function, interferon regulation, immune complex clearance, and Toll-like receptors.[11] A disproportionate number of transcription factors have been identified, suggesting an important contribution of gene dysregulation to lupus.[14] HLA genes are strongly associated with lupus risk, at least in European populations.[15] A meta-analysis of HLA class II alleles associated with SLE identified four DR allele families as conferring increased susceptibility or resistance to the development of LN when compared with healthy controls.[16] This study involved mostly White and Asian patients, and the findings may not be applicable to other patient groups. Independent of causation, other polymorphisms in genes such as MYH-9, ACE, TNIP-1, and APOL-1 (in Blacks) confer a worse prognosis for LN.

External environmental factors such as ultraviolet light exposure and smoking play a role in the onset and exacerbation of SLE and LN.[17] Viral infections may be triggers for lupus, but conclusive evidence for a viral pathogenesis of SLE or LN has yet to be produced. Exposure to certain medications (e.g., procainamide, hydralazine, quinidine, and anti-TNF biologics) has been linked to SLE or SLE-like syndromes, but LN occurs infrequently in such individuals. The internal environment also appears to be relevant given the strong female predominance of SLE, disease exacerbations during or shortly after pregnancy, and the effects of hormone treatment and ablation in animal models of LN.

Autoimmunity in Systemic Lupus Erythematosus

Patients with SLE typically develop multiple autoantibodies, many of which are directed against nucleic acids and proteins involved in transcription and translation, such as nucleosomes (DNA-histone), chromatin antigens, and small nuclear and cytoplasmic ribonuclear proteins.[18] In the early stages of disease, clearance of apoptotic cells is impaired and nuclear autoantigens released from these cells stimulate expression of interferon-α (IFN-α), which facilitates the generation of antigen-presenting cells, promotes the differentiation of autoreactive B cells into plasma cells, and fosters the development of T helper cells. Antigen

BOX 26.1 American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) Criteria for the Diagnosis of Lupus

ACR Criteria	SLICC ACR Criteria	
Presence (cumulative) of four or more of the following:	Presence (cumulative) of four or more of the following (with at least 1 clinical and 1 immunologic criteria) *OR* biopsy-proven lupus nephritis with positive ANA or anti-dsDNA	
	Clinical Criteria	**Immunologic Criteria**
1. Malar rash	1. Acute OR subacute cutaneous lupus	1. Positive ANA
2. Discoid rash	2. Chronic cutaneous lupus	2. Positive anti-dsDNA antibody
3. Photosensitivity	3. Nonscarring alopecia	3. Positive anti-Sm antibody
4. Oral or nasopharyngeal ulcers	4. Oral **OR** nasal ulcers	4. Positive antiphospholipid antibody (includes presence of a lupus anticoagulant, false-positive RPR, anticardiolipin antibody or anti-β_2 glycoprotein antibody)
5. Nonerosive arthritis (involving ≥2 joints, characterized by tenderness, swelling, or effusion)	5. Synovitis ≥2 joints (swelling or effusion) **OR** tenderness in 2 or more joints and ≥30 min of morning stiffness	5. Low complement (C3, C4, or CH50)
6. Pleuritis or pericarditis	6. Serositis	6. Direct Coombs test (in the absence of hemolytic anemia)
7. Renal disease (proteinuria >500 mg/day **OR** 3+ by dipstick **OR** cellular casts)	7. Renal disease (red blood cell casts **OR** proteinuria ≥500 mg/day on 24-hr urine collection **OR** spot ratio of urine protein to creatinine ratio ≥0.5)	
8. Neurologic disorder	8. Neurologic disorder	
9. Hematologic disorder	9. Hemolytic anemia	
10. Immunologic disorder (positive anti-dsDNA antibody **OR** positive anti-Sm antibody **OR** positive antiphospholipid antibody (includes presence of a lupus anticoagulant, false-positive treponemal test, positive anticardiolipin antibody)	10. Leukopenia **OR** lymphopenia	
11. Positive ANA	11. Thrombocytopenia	

ANA, Antinuclear antibody.

TABLE 26.1 Frequency of Kidney Manifestations in Lupus Patients With Renal Involvement

Manifestation	Prevalence (%)
Proteinuria	100
Nephrotic syndrome	45-65
Hematuria	
Microscopic	80
Gross	1-2
Red blood cell casts	10
Cellular casts	30
Reduced renal function	40-80
Rapidly progressive glomerulonephritis	10-20
Acute kidney injury	1-2
Hypertension	15-50
Hyperkalemia	15

mimicry, in which there is exposure to viral or bacterial peptides with sequences similar to those of native antigens, also may lead to induction of autoantibody-producing cell lines. Both autoreactive B and T cells clonally expand in lupus, facilitated by failure of apoptotic mechanisms to silence autoreactive cells (i.e., loss of tolerance as well as an increased expression of B cell trophic factors). The nature of antigen presentation also may be important, with certain nuclear antigens capable of triggering an immunogenic response through interactions with a variety of intracellular Toll-like receptors.

PATHOGENESIS OF LUPUS NEPHRITIS

Autoantibodies are crucial to the pathogenesis of LN, and the hallmark of LN is the accumulation of immune complexes in glomeruli.[19] Patients with LN have autoantibodies against dsDNA, Sm antigen, C1q, nucleosomes, and other antigens. There is direct binding of dsDNA antibodies to the glomerular basement membrane (GBM), and cross-linking of positively charged nucleosome components such as chromatin between autoantibodies and GBM.[19] In proliferative LN, immune complexes are found in the subendothelial space, whereas in membranous LN, immune complexes are found in the subepithelial space. The localization of immune complexes within glomeruli is influenced by size, charge, specificity, and avidity of the antigen and antibody, as well as by the clearance capacity of mesangium and local hemodynamics.

Glomerular immune complexes, especially in the subendothelial space, activate proinflammatory mechanisms, including the complement pathway, leukocyte Fc receptors, cytokines that regulate cell proliferation, and matrix formation and procoagulant factors.[19-21] Nucleosomes also can activate resident dendritic cells through binding to Toll-like receptors 2 and 9.[22] These activated pathways result in complement-mediated kidney damage, intraglomerular hypertension and coagulation, and Fc receptor–mediated leukocyte infiltration with release of proteolytic enzymes. Subepithelial immune complexes are associated with less inflammation but increased production of GBM components and more podocyte injury.

T cells contribute to the progression of LN by facilitating B cell differentiation and expansion. Additionally, T helper cell (Th1) cytokines are overexpressed in kidneys of patients with LN and promote intrarenal inflammation by activation of macrophages, complement, and the Fc receptor pathway. Kidney biopsies of LN patients also contain Th17 cells, which secrete interleukin-17 (IL-17), thought to sustain renal inflammation by driving T cells away from maturing into a regulatory phenotype ($CD4^{+}CD25^{hi}FoxP3^{+}$) capable of suppressing autoantibody production and attenuating the immune response.[23] CD8 T cells may gradually lose effector function and express inhibitory receptors under persistent antigen exposure, and in essence become "exhausted." Although exhaustion may, for example, result in an inability to clear a viral infection, it may be protective against relapse in autoimmune diseases. LN patients whose peripheral T cells displayed an exhausted phenotype had a nonrelapsing disease course.[24] It is unknown whether T cell exhaustion can be translated into a therapeutic approach for SLE.

In SLE and LN, neutrophils undergo a novel form of cell death called NETosis, in which a chromatin meshwork (or NET) is released.[22] These NETs are a source of autoantigens and are not properly degraded in lupus patients. In addition, lupus patients have an increased number of low-density granulocytes that are more susceptible to NETosis. NET material has been found in LN biopsy samples, and the subset of SLE patients with LN often do not degrade. The NETs induce production of IFN-α by plasmacytoid dendritic cells, which are also found in LN kidneys.[22]

Within the tubulointerstitial compartment, T and B cells are often found in close proximity to each other and appear to be interacting, in some cases even forming germinal centers.[25] Interstitial B cells aggregating with T cells may show clonal expansion and somatic hypermutation, suggesting the possibility of intrarenal autoantibody production against kidney-specific antigens, such as vimentin. Such interactions may contribute to interstitial inflammation in LN, and interstitial injury is a major determinant of long-term renal survival.[25]

CLINICAL MANIFESTATIONS

Immune complex kidney involvement (LN) is usually heralded by proteinuria and active urinary sediment with microhematuria, dysmorphic urine erythrocytes, and erythrocyte casts (see Table 26.1). More severe LN may present with the nephritic syndrome in association with proliferative GN, hypertension, and a decline in glomerular filtration rate (GFR). Less frequently, renal disease in lupus presents as a tubulointerstitial disorder such as renal tubular acidosis (Chapter 12), isolated interstitial nephritis, or as a thrombotic microangiopathy associated with or without a antiphospholipid antibody syndrome (see Chapter 28).

Extrarenal Manifestations

Patients with active SLE often present with nonspecific complaints of malaise, low-grade fever, poor appetite, and weight loss. Other common features include patchy alopecia, oral or nasal ulcerations, arthralgias, nondeforming arthritis, and a variety of skin findings, including photosensitivity, Raynaud's phenomenon, and a "butterfly" (malar) facial rash. Livedo reticularis is seen in up to 15% of cases and may be associated with miscarriage, thrombocytopenia, and antiphospholipid antibodies. Neuropsychiatric involvement presents with headache, nerve palsies, psychoses, or frank coma. Serositis, in the form of pleuritis or pericarditis, affects up to 40% of patients. Pulmonary hypertension can develop silently as a result of multiple pulmonary emboli or intravascular coagulation in association with antiphospholipid antibodies, or may be caused by nonthrombotic pulmonary arterial disease. Mitral valve prolapse, and less commonly Libman-Sacks endocarditis, are both seen in SLE. Splenomegaly and lymphadenopathy are present in about one fourth of patients, and hematologic abnormalities can affect all three cell lines. SLE-associated anemia can result from impaired erythropoiesis, autoimmune hemolysis, or bleeding. Thrombocytopenia and leukopenia may occur as part of the disease process or as complications of therapy. Thrombotic events are not uncommon and should prompt a search for antiphospholipid antibodies and other pro-coagulant abnormalities.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Although the diagnosis of lupus may be obvious in a young woman with classic manifestations and serologic markers, less typical presentations are common and often result in multiple physician consultations and diagnostic delay. This is in part a result of the varied features of the disease and because signs and symptoms evolve over time. The presence of four or more ACR criteria carries a 96% sensitivity and specificity for lupus (see Box 26.1). However, the ACR diagnostic criteria were developed for clinical studies and do not always prove useful in an individual patient. In the SLICC classification system (see Box 26.1), SLE can be diagnosed with biopsy-proven immune complex nephritis in the presence of ANA or anti-dsDNA, without other extrarenal disease manifestations.

Several autoimmune diseases mimic the extrarenal manifestations of SLE, and some are associated with kidney involvement and GN, including fibromyalgia, Sjögren syndrome, thrombotic microangiopathies, primary antiphospholipid syndrome, dermatomyositis, systemic sclerosis, and mixed connective tissue disease. Conversely, several common forms of GN must be distinguished from LN because of similar clinical features, including immunoglobulin A (IgA) vasculitis (Henoch-Schönlein purpura, see Chapter 23), antineutrophil cytoplasmic antibody (ANCA)–associated GN (see Chapter 25), bacterial endocarditis, and cryoglobulinemia. ANCAs of uncertain significance are detected in 20% of LN patients.

Immunologic Tests in Lupus

Antinuclear antibodies (ANAs) are found in more than 90% of untreated patients with lupus. Although highly sensitive, neither the presence nor pattern (e.g., diffuse, speckled) are specific for SLE. Autoantibodies against dsDNA are more specific, being present in 75% of untreated lupus patients, but are less sensitive than ANAs. Whereas high titers of anti-dsDNA antibodies correlate with the presence of SLE and are often used to follow the course of LN, antibodies to single-stranded DNA (ssDNA) are found in many rheumatologic conditions and do not correlate with the course of LN. Sm antibodies are strongly associated with the diagnosis of lupus and the presence of nephritis but are present in only about 25% to 30% of patients. Antibodies to C1q (anti-C1q) have been more closely associated with the activity of LN than anti-dsDNA antibodies and may have a prognostic role in the follow-up of patients with LN.[26]

Serum levels of total hemolytic complement and complement components C3 and C4 are often depressed in untreated SLE and especially in LN. In general, both C3 and C4 are depressed. Preferential C4 depression in lupus patients may reflect activation of the classic complement pathway. In some cases, low C4 with normal C3 in a patient with lupus may reflect genetic C4 deficiency or the presence of cryoglobulins. Preferential depression of C3 is observed in patients with postinfectious glomerulonephritis (PIGN) and the C3 glomerulopathies (see Chapters 22 and 55) rather than in SLE/LN.

TABLE 26.2 The ISN/RPS Classification of Lupus Nephritis and Associated Clinical Correlations

Class	Definition	Urine Findings	Clinical Findings
I: Minimal mesangial LN	Normal glomeruli by LM, but mesangial immune deposits by IF	Usually unremarkable	None relevant to kidney; excellent renal prognosis*
II: Mesangial proliferative LN	Mesangial hypercellularity and/or expansion with mesangial immune deposits	Microscopic hematuria; proteinuria, if present, is usually low-grade	Preserved renal function; hypertension infrequent; excellent renal prognosis*
III: Focal LN III (A): Purely active lesions: focal proliferative LN III (A/C): Active and chronic lesions: focal proliferative and sclerosing LN III (C): Chronic inactive lesions with glomerular scars: focal sclerosing LN	Segmental or global endocapillary or extracapillary glomerulonephritis affecting less than 50% of glomeruli with mesangial and subendothelial immune deposits	Microscopic hematuria; proteinuria	Hypertension possible; renal insufficiency and nephrotic syndrome not unusual; variable renal prognosis
IV: Diffuse LN IV-S (A) or IV-G (A): Purely active lesions: diffuse segmental (S) or global (G) proliferative LN IV-S (A/C) or IV-G (A/C): Active and chronic lesions: diffuse segmental or global proliferative and sclerosing LN IV-S (C) or IV-G (C): Inactive with glomerular scars: diffuse segmental or global sclerosing LN S: >50% of affected glomeruli have segmental lesions G: >50% of affected glomeruli have global lesions	Segmental (S) or global (G) endocapillary or extracapillary glomerulonephritis affecting 50% or more of glomeruli with mesangial and subendothelial immune deposits	Microscopic hematuria; proteinuria	Hypertension; renal insufficiency and nephrotic syndrome frequent; variable renal prognosis
V: Membranous LN	Glomerular basement membrane thickening with subepithelial and mesangial immune deposits	High-grade proteinuria; microscopic hematuria possible	Preserved renal function; nephrotic syndrome common; renal prognosis good* Anti-PLA2R antibody negative
VI: Advanced sclerosing LN	≥90% of glomeruli globally sclerosed without residual disease activity	Microscopic hematuria; proteinuria not unusual	Renal insufficiency/failure expected

IF, Immunofluoresence microscopy; *LM,* light microscopy; *LN,* lupus nephritis.
*As long as no transformation to a proliferative class.

RENAL BIOPSY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Although nephritis may be suspected based on clinical symptoms and laboratory markers, a renal biopsy is required for confirmation, subclassification, prognosis, and management decisions. Indications for biopsy include persistent proteinuria greater than 0.5 mg/mg (0.5 g/day), glomerular hematuria or leukocyturia without proteinuria, and/or unexplained fall in estimated GFR (eGFR). The risks for biopsy-related bleeding are increased when serologic features of the antiphospholipid syndrome are present. A repeat renal biopsy can be considered when there is deterioration or persistence in markers of renal disease with uncertainty as to future treatment.

PATHOLOGY

Although LN may affect all the structures of the kidney, glomerular involvement has been the best characterized. Often, the degree and type of glomerular involvement correlates with the clinical presentation and disease course and also influences treatment decisions. LN is currently classified by the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) system (Table 26.2), which is based on glomerular histology using light and immunofluorescence microscopy. Examples of the different histologic classes are shown in Figs. 26.1 through 26.5. Less common glomerular pathologies omitted from the ISN/RPS system include lupus podocytopathy (see later discussion) and pauci-immune crescentic GN (analogous to ANCA-associated renal vasculitis).

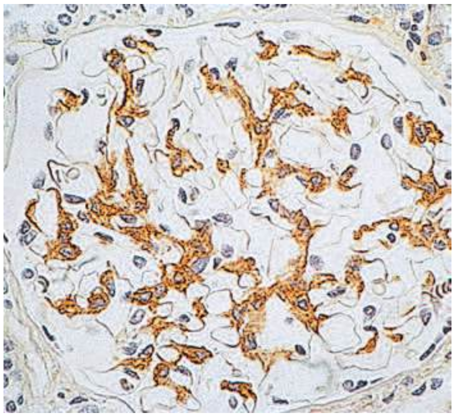

Fig. 26.1 ISN/RPS class I: minimal mesangial lupus nephritis. Light microscopy is normal, but immunoperoxidase shows C1q localization (associated with IgG and C3) throughout the mesangial area (magnification 400X).

Although IgG is generally the dominant glomerular immunoglobulin in LN, IgA and IgM along with the complement components C1q and C3 are often seen as well, giving the “full-house” pattern that is highly

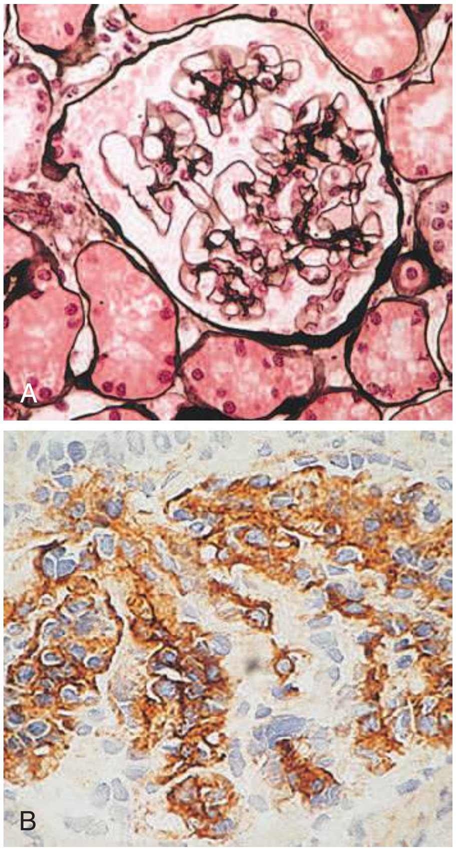

Fig. 26.2 ISN/RPS class II: lupus nephritis (mesangial disease). (A) Mesangial expansion but little increase in tuft cellularity (magnification 400X), and the peripheral capillary walls are normal. (Silver methenamine stain.) (B) Extensive mesangial IgG deposits shown by immunoperoxidase (magnification 400X); the aggregates are just beginning to invade peripheral capillary walls.

suggestive of LN. Strong glomerular C1q staining is also suggestive of LN. Fibrin staining, corresponding to active lesions, is often noted in the glomerular tuft, especially in crescents, if present.

On electron microscopy (EM), the distribution of immune deposits corresponds to immunoglobulin deposits identified by immunohistology. Some electron-dense immune deposits have an organized substructure known as *fingerprinting,* corresponding to the presence of curvilinear microtubular or fibrillar structures in the deposits. Tubuloreticular inclusions, which are tubular structures located in the endoplasmic reticulum of renal endothelial cells, are often found in biopsy specimens of LN patients and are thought to reflect a high interferon milieu.

Tubulointerstitial and Vascular Disease

A deficit of the ISN/RPS classification system is that it does not assess the tubulointerstitial or vascular compartments of the kidney, even though interstitial and vascular damage predicts kidney outcomes.[27] About 50% of patients with LN, predominantly those with proliferative glomerular lesions, have immune aggregates along tubular basement membranes. Interstitial inflammatory cell infiltrates, including T cells, B cells, and monocytes are frequently found, and tubulitis can be seen in active disease (Fig. 26.6). In chronic disease, the interstitium is often expanded by fibrosis and sparser infiltrates. Infrequently, tubulointerstitial nephritis is seen in the absence of glomerular disease and may result in acute kidney injury or renal tubular acidosis.

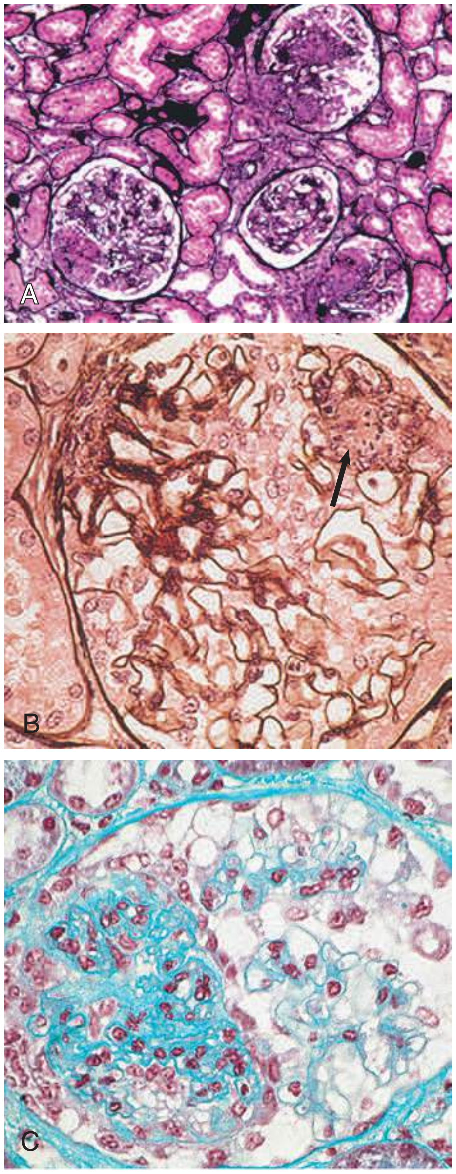

Fig. 26.3 ISN/RPS class III: focal proliferative lupus nephritis. (A) Low-power magnification shows focal and segmental proliferative lesion–active (class IIIA) with less than 50% of glomeruli affected (magnification 100X). (Hematoxylin-eosin [HE] stain.) (B) Area of focal necrosis containing cellular debris, karyorrhexis *(arrow),* is surrounded by an area of cellular proliferation (magnification 400X). (Silver methenamine/HE.) (C) Major focal and segmental proliferative lesion is affecting almost half the glomerular capillary tuft (magnification 400X). (Hematoxylin/lissamine green.)

True vasculitis is rare in LN, but several other vascular lesions can be seen (Fig. 26.7). For example, fibrinoid vessel necrosis or thrombotic microangiopathy may be found in severe proliferative LN.

Transformation of Histologic Appearance and "Silent" Lupus Nephritis

The ISN/RPS class found at diagnostic kidney biopsy for LN is not fixed for an individual's entire clinical course. Those successfully treated for proliferative (class III/IV) LN may transform to a less serious histology, such as class II, or have resolution of inflammatory lesions with scarring and move from an active to a chronic histologic pattern. Conversely, patients initially diagnosed with class II or V LN may transform to proliferative LN, usually class IVG (global).

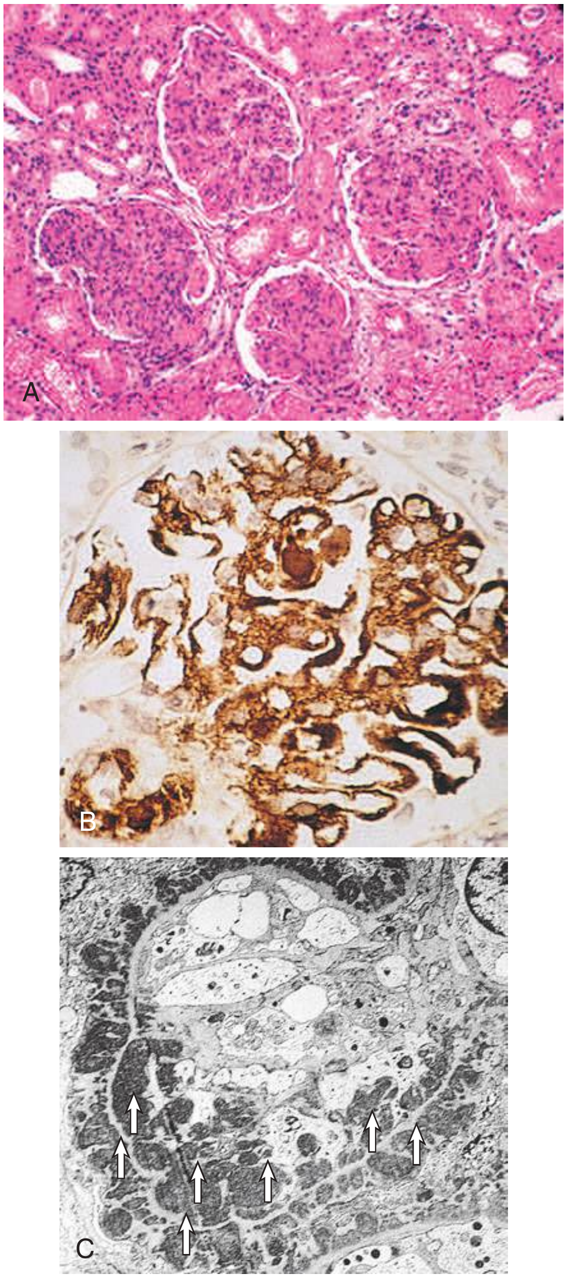

Fig. 26.4 **ISN/RPS class IV: lupus nephritis.** (A) Active, diffuse proliferative lupus nephritis (magnification 100X). (B) Immunoperoxidase staining shows dense, irregular aggregates of IgG along the peripheral capillary walls (magnification 400X). (C) Electron microscopy reveals the immune aggregates as electron-dense deposits *(arrows)*, predominantly in the subendothelial location.

This class switch is often heralded by increasing proteinuria and activity of the urine sediment.[28] Switching between class IVS (segmental) and G subtypes is not seen and may reflect different pathogenic mechanisms.

The concept of silent LN has been proposed based on kidney biopsies done in patients with SLE but no clinically obvious kidney involvement.[29] A few hundred such patients have been reported, with normal kidney function and no hematuria or proteinuria but with immune complexes in their glomeruli and a histologic pattern most often consistent with class I/II LN. A few such patients even display class III, IV, or V LN. Silent LN may represent a preclinical stage in the evolution of LN.

Clinical, Laboratory, and Histopathologic Correlations and Outcomes

Given the highly variable clinical presentations of LN and the overlap in the clinical features of patients with different types of glomerular injury, kidney biopsy remains the gold standard for diagnosis and subsequent management of LN. Table 26.2 summarizes the typical clinicopathologic correlations of LN. Lupus membranous nephropathy may be distinguished from idiopathic membranous nephropathy by the absence of anti-PLA2r autoantibodies in the circulation and by the presence of all IgG isotypes in the immune deposits, although restriction to the IgG4 isotype has been rarely observed in LN patients.

The importance of the kidney biopsy is underscored by the significant number of patients with SLE and kidney injury who do not have classic LN. For example, up to 24% of patients may have a renal thrombotic microangiopathy, either alone or associated with LN.[30] A small (1.3%) but important subset of patients with SLE present with nephrotic syndrome, with or without acute kidney injury, but their kidney biopsies appear normal on light microscopy, mimicking minimal change disease (MCD), or show segmental sclerosis, mimicking focal segmental glomerulosclerosis (FSGS).[31] EM shows diffuse podocyte effacement, without immune complexes. These patients, although not classified by ISN/RPS, have lupus podocytopathy and like MCD or FSGS, often respond to corticosteroids alone. A recent Chinese study showed that remission in response to corticosteroids for 12 weeks occurred in 75% of patients with podocytopathy and more than 90% when those with FSGS-like lesions were excluded.[32] The risk for relapse exceeded 50%, and at repeat kidney biopsy half of the relapsed patients had transformed to class IV or V LN. Although these results may not be generalizable to a non-Asian population, they underscore the importance of histology-driven treatment decision analysis.

Long-Term Prognosis and Kidney Histology

Features of reversible (active) or irreversible (chronic) damage on kidney biopsy are captured by the National Institutes of Health (NIH) activity and chronicity indices (Table 26.3). Similar to other types of GN, long-term kidney prognosis is poor if the biopsy sample shows extensive glomerulosclerosis or interstitial fibrosis and tubular atrophy. In patients with less extensive scarring the activity and chronicity indices at diagnostic biopsy may not correlate with the course of LN.[28] In contrast, after treatment, persistent activity (activity index >2) on repeat kidney biopsy is associated with a worse long-term renal prognosis; high chronicity (chronicity index >6) at repeat biopsy shows a similar trend.[28]

TREATMENT

It is useful to divide the treatment of patients with active proliferative LN into initial and maintenance phases. The *initial or induction phase* addresses acute life- or organ-threatening disease. The *maintenance phase* focuses on consolidating remissions, preventing relapses and the long-term management of chronic, more indolent disease.

The ISN/RPS biopsy classification should guide initial therapy (see Table 26.2). In general, the immunosuppressive treatment of extrarenal lupus manifestations is sufficient for class I and II LN. The combination of high-dose corticosteroids plus an immunosuppressive agent is mainly used for patients with active focal proliferative LN (classes IIIA and IIIA/C), active diffuse proliferative LN (classes IVA and IVA/C), and membranous lupus (class V).

Although the goal of initial therapy is to induce a complete renal remission, this occurs in only 30% to 40% of LN patients by 12 months.[33] Most studies define complete renal response as a reduction in proteinuria

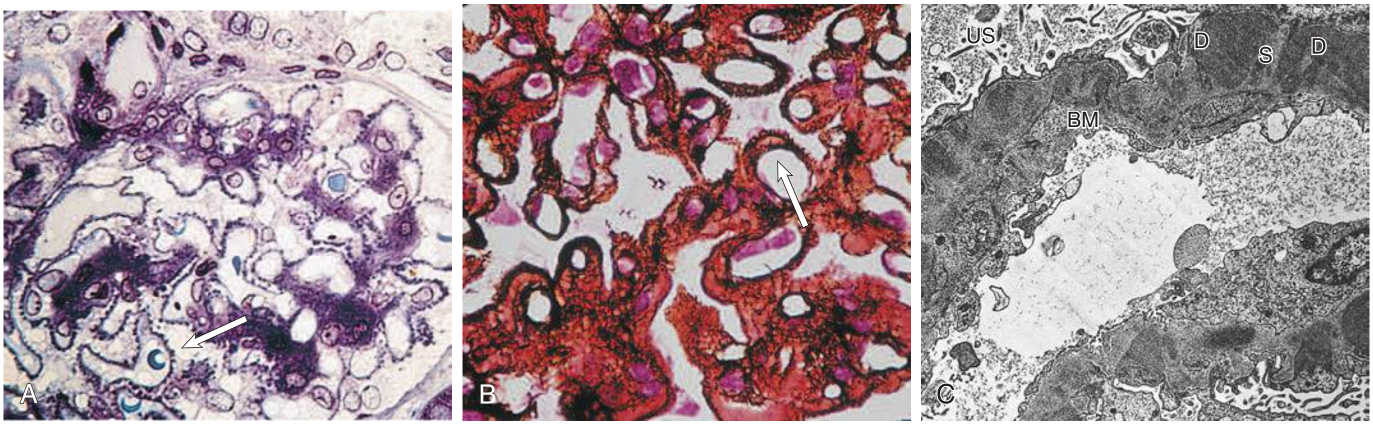

Fig. 26.5 **ISN/RPS class V: membranous lupus.** (A) Thick (~0.5 mm) araldite-embedded section stained with toluidine blue shows not only the extramembranous material in dark blue *(arrow)* but also the presence of mesangial deposits, which are common in lupus membranous nephropathy (magnification 400X). (B) Silver methenamine–stained section shows some double contouring of the silver-positive basement membrane *(arrow)* and subendothelium-deposited material, as well as the characteristic silver-positive spikes of basement membrane–like material (magnification 400X). (C) Electron micrograph shows the predominantly subepithelial electron-dense deposits *(D)* separated by protrusions of basement membrane material (spikes, *S*). *BM*, Basement membrane; *US*, urinary space.

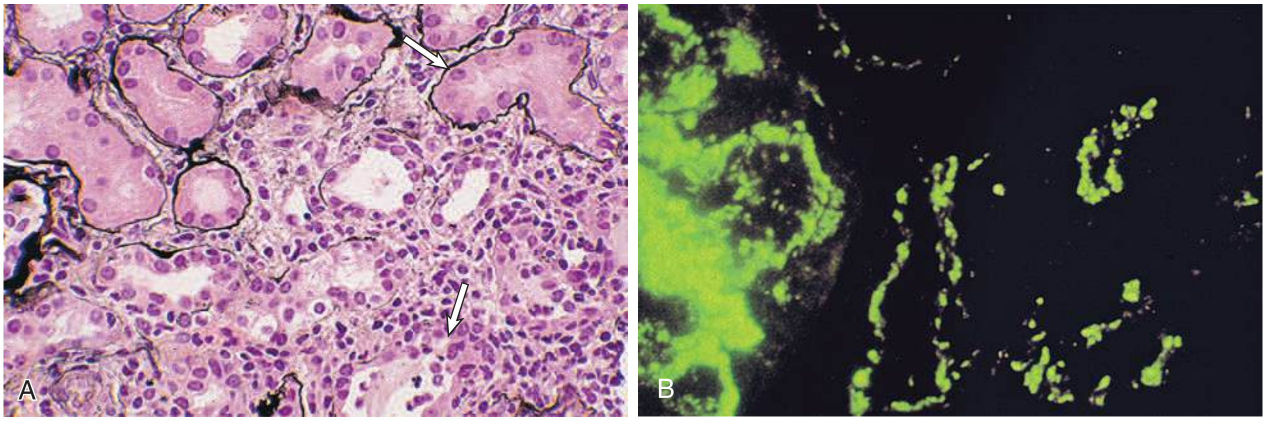

Fig. 26.6 **Interstitial lupus nephritis.** (A) Interstitial infiltrate invading and destroying tubules (tubulitis). Tubular basement membranes, which stain black with silver, are digested in the areas of tubulitis *(arrow)* (magnification 400X). (B) Immunofluorescence shows aggregates of C3 in the tubular basement membrane *(right)* as well as within the glomerulus *(left)*. Such tubular basement membrane aggregates are common in lupus nephritis, being found in 60% to 65% of biopsy specimens overall and with increasing frequency from class II (20%) to class IV (75%).

TABLE 26.3 **The Point System Used to Calculate Lupus Nephritis Biopsy Activity and Chronicity Indices***

	LESIONS CONTRIBUTING TO ACTIVITY INDEX						LESIONS CONTRIBUTING TO CHRONICITY INDEX			
Semiquantitative Lesion Score*	**Cellular Crescents**	**Glomerular Necrosis: Karyorrhexis**	**Glomerular Neutrophils**	**Endocapillary Proliferation**	**Large Subendothelial Immune Deposits**	**Interstitial Inflammation**	**Glomerular Sclerosis**	**Fibrous Crescent**	**Tubular Atrophy**	**Interstitial Fibrosis**
None	0	0	0	0	0	0	0	0	0	0
Mild	2	2	1	1	1	1	1	1	1	1
Moderate	4	4	2	2	2	2	2	2	2	2
Severe	6	6	3	3	3	3	3	3	3	3

*Maximum activity index is 24; maximum chronicity index is 12.

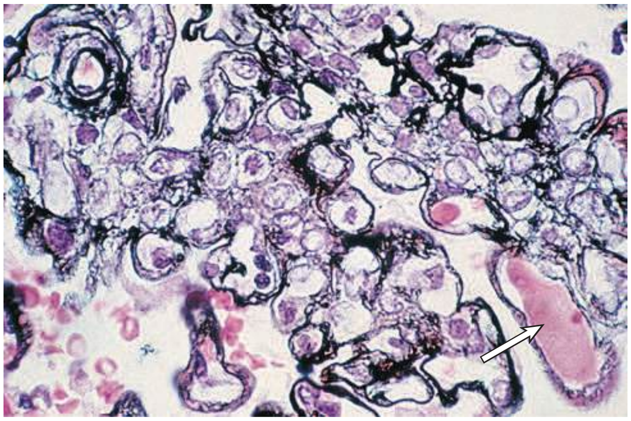

Fig. 26.7 Vascular damage in lupus nephritis. Thrombus *(arrow)* occludes a glomerular capillary loop in this class IV biopsy specimen. Such a thrombus contains platelets and cross-linked fibrin as well as immunoglobulins and thus has some characteristics of true thrombus (magnification 400X). (Silver methenamine/hematoxylin stain.)

to less than 0.5 or a ratio of urine protein to creatinine of less than 0.5 absence of glomerular hematuria or red blood cell (RBC) casts, and normalization or stabilization of GFR. The predictive value of glomerular hematuria in the definition of remission has recently been questioned.[34] It may be best to view induction as the first step of controlling renal inflammation to allow healing of kidney injury, which translates clinically into stabilization or improvement of renal function, attenuation of proteinuria, and reduction in urine sediment activity. However, all of these kidney parameters may not normalize by the end of induction. The term *partial response* has required a 50% reduction in proteinuria to subnephrotic levels and stability or improvement in GFR and is usually achieved before complete response criteria are met.

Evidence in support of specific therapeutic agents and regimens should be treated with caution because of small study sizes, uncontrolled or nonblinded methods, and heterogeneity in both LN presentations and responses to therapy. Therapeutic toxicity is a major contributing factor to morbidity and mortality, so claims of efficacy must be balanced against adverse events. Other factors, such as ethnicity, referral practice, center experience, and use of concomitant medications vary across studies and over time, reducing the generalizability of some study results.

In addition to the immunosuppressive regimens discussed next, the kidney protective measures outlined in Chapter 79 should be used as appropriate. Furthermore, unless contraindicated, all patients with LN should be treated with an antimalarial agent because this was associated with a lower risk for developing LN and ESRD and improved responses to LN treatment.[35]

Proliferative Lupus Nephritis: Induction

Corticosteroids

High-dose corticosteroids are used in all current induction regimens and are considered the standard of care. Prednisone (or prednisolone) is most often started at 0.5 to 1 mg/kg/day ideal body weight (no more than 80 mg/day) and then reduced to approximately 10 mg/day or less by 3 to 6 months. There is variation in the use of intravenous methylprednisolone infusions (0.5 to 1 g daily for 1 to 3 days) either as a routine component of induction therapy followed by lower oral corticosteroid dosing or for nephritis perceived to be severe. Adverse effects of corticosteroids have led to attempts to minimize prolonged courses of high-dose corticosteroid therapy in lupus patients. A study comparing cyclophosphamide alone to cyclophosphamide plus high-dose corticosteroids as initial therapy in a White population with mild-moderate disease showed comparable complete and partial remission rates at 2 years.[36] An observational study (RITUXILUP) used anti–B cell therapy (rituximab) plus 2 doses of intravenous methylprednisolone followed by maintenance with mycophenolate mofetil (MMF) in the absence of oral steroids.[37] The overall complete plus partial renal response rate was 88%, with a median time to remission of 9 months. During the follow-up period 19 LN flares occurred at a median of 24 months after remission and 79% were managed without oral steroids.

Immunosuppressive Agents

Although corticosteroids effectively control proliferative LN, long-term kidney function was better preserved with fewer LN relapses at 3 to 5 years if corticosteroids were combined with cyclophosphamide during initial therapy.[38] These data highlight the need for long-term follow-up in assessing initial LN therapies. Both daily oral and intravenous pulses of cyclophosphamide are effective in LN, although intravenous cyclophosphamide given as 6-monthly pulses of 0.5 to 1 g/m^2 (NIH protocol) has been the standard of care for several years. The Euro-Lupus Nephritis Trial compared lower dose (500 mg) cyclophosphamide intravenously every 2 weeks for 3 months (total of 3 g) followed by azathioprine maintenance to the NIH protocol, and similar efficacy with less toxicity and fewer infections short term[39] and after 5 to 10 years.[40] Although the Euro-Lupus cyclophosphamide regimen was initially tested in a mainly White population, similar rates of remission induction are achieved with low-dose cyclophosphamide in Black, Hispanic, and Southeast Asian patients.[41,42]

Several randomized clinical trials involving multiethnic cohorts have shown that oral MMF plus corticosteroids for 6 months followed by maintenance therapy is at least as effective as 6-monthly pulses of cyclophosphamide (NIH protocol) plus corticosteroids followed by maintenance therapy.[33] MMF also showed similar treatment response rates to the Euro-Lupus regimen at 24 weeks.[42] Cyclophosphamide has been favored in patients presenting with marked renal impairment or severe class IV LN on biopsy, but there are no convincing differences in outcome between MMF and cyclophosphamide induction for such patients.[43] No improvement in overall mortality or severe infections has been seen with MMF; gastrointestinal disturbances are more frequent, but the risk for amenorrhea is lower than with cyclophosphamide.

Optimal MMF dosing and adjustment for different patient subgroups remains unclear. A dosing range of 2 to 3 g/day has been recommended as a target with dose reduction for intolerance and in certain ethnic subgroups. The MMF metabolite mycophenolic acid (MPA) has been pharmacokinetically monitored as the area under the concentration-time curve (AUC) in patients receiving MMF for LN induction or maintenance. However, monitoring yields highly variable AUCs after empiric MMF dosing with no correlation between AUCs and trough drug levels, and as yet there is no consensus on a target MPA AUC and no correlation of adverse events with AUC.[44]

Long-term follow-up of patients who participated in clinical trials of MMF versus cyclophosphamide found no differences in renal outcome, although one study reported a non-significant increase in renal flares in patients induced with MMF.[45] Differences in response between ethnic and geographical subgroups have been suggested but not confirmed.[46] However, a retrospective analysis of a Korean cohort showed similar remission rates for MMF and cyclophosphamide, but more relapses and a higher incidence of ESRD in the MMF group.[47] A meta-analysis showed a reduction in the 10- and 15-year risk of ESRD from LN between 1970 and the mid-1990s, coincident with the use of cyclophosphamide as standard-of-care induction therapy. It is of some concern that from the mid-1990s until the late 2000s ESRD plateaued, but then increased slightly, coincident with the era of MMF induction.[4]

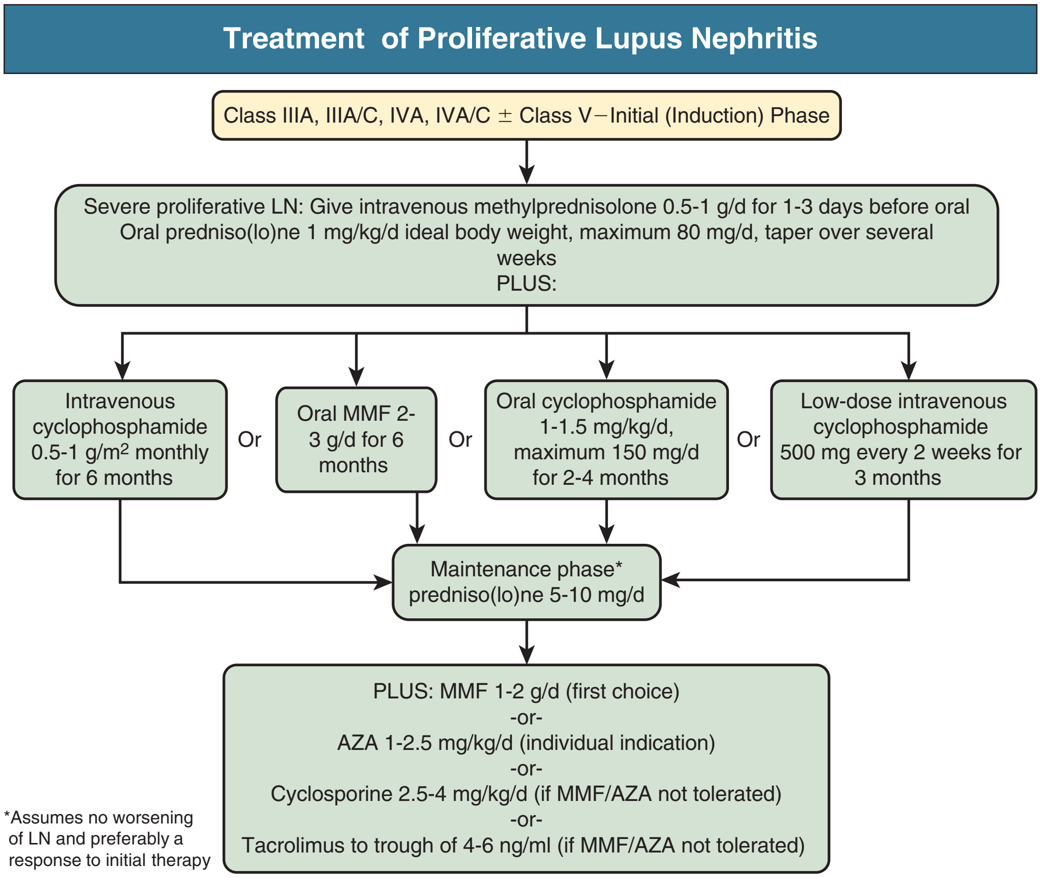
Treatment of Proliferative Lupus Nephritis
Class IIIA, IIIA/C, IVA, IVA/C ± Class V–Initial (Induction) Phase
Severe proliferative LN: Give intravenous methylprednisolone 0.5-1 g/d for 1-3 days before oral
Oral predniso(lo)ne 1 mg/kg/d ideal body weight, maximum 80 mg/d, taper over several weeks
PLUS:
Intravenous cyclophosphamide 0.5-1 g/m2 monthly for 6 months
Or
Oral MMF 2-3 g/d for 6 months
Or
Oral cyclophosphamide 1-1.5 mg/kg/d, maximum 150 mg/d for 2-4 months
Or
Low-dose intravenous cyclophosphamide 500 mg every 2 weeks for 3 months
Maintenance phase* predniso(lo)ne 5-10 mg/d
PLUS: MMF 1-2 g/d (first choice)
-or-
AZA 1-2.5 mg/kg/d (individual indication)
-or-
Cyclosporine 2.5-4 mg/kg/d (if MMF/AZA not tolerated)
-or-
Tacrolimus to trough of 4-6 ng/ml (if MMF/AZA not tolerated)
*Assumes no worsening of LN and preferably a response to initial therapy

Fig. 26.8 Approach to the induction and maintenance treatment of proliferative lupus nephritis (LN). *AZA,* Azathioprine; *MMF,* mycophenolate mofetil.

The ACR, the Kidney Disease: Improving Global Outcomes (KDIGO), and the European League Against Rheumatology/European Renal Association (EULAR/ERA) have independently developed evidence-based guidelines for LN therapy. These are synthesized in the treatment algorithm presented in Fig. 26.8.[48-50]

Other Immunosuppressive Strategies

Azathioprine (AZA) has been used in combination with corticosteroids for the induction of remission in proliferative LN. A randomized trial comparing AZA with cyclophosphamide found no difference in eventual outcome but more relapses, doubling of serum creatinine concentration, and more chronicity on repeat biopsy in the AZA group.[51] Although AZA is not recommended as first-line therapy by the major LN guidelines, it remains an option when MMF or cyclophosphamide are unavailable, undesirable, or contraindicated.

The calcineurin inhibitors (CNIs) tacrolimus and cyclosporine have been tested as LN induction therapies and compared favorably in the short term.[33] A trial from Hong Kong randomized 150 patients to tacrolimus or MMF for 6 months, with responders receiving AZA for maintenance.[52] Complete remission rates were approximately 60% in each group, although there was a trend toward more renal flares at 5-year follow-up in the tacrolimus group. Additionally, the primary proteinuria end-point was less than 1 g/day, which may have inflated the complete response rate. Another Asian study took a multitargeted approach, randomizing patients to tacrolimus plus MMF and corticosteroids or the NIH protocol of cyclophosphamide plus corticosteroids. The multitarget induction regimen was associated with a higher remission rate than cyclophosphamide but more patients in the multitarget group withdrew because of adverse events at 6 months, despite lower rates of leukopenia and upper gastrointestinal symptoms in this group.[53] Although short-term, a preliminary report indicated a higher 6-month complete renal response rate (33% vs. 19%) in a multiethnic LN cohort treated with the CNI voclosporin plus corticosteroids and MMF compared with corticosteroids and MMF alone.[54] In future studies, it will be important to verify preservation of long-term kidney function and improvements in histology in CNI-treated LN patients. Furthermore, it is not clear that proteinuria is an appropriate renal remission end-point for comparing a CNI-based regimen to other drugs because of the known nonimmune antiproteinuric effects of CNIs.

Biologic Agents

Rituximab, an anti-CD20 monoclonal antibody that depletes B cells, has led to improved disease control in patients with LN with relapsing or refractory disease in retrospective and nonrandomized trials. However, in a large randomized, prospective trial, when used in combination with MMF and corticosteroids for induction, rituximab did no better at 1 year than placebo.[55] The role of rituximab in LN is therefore currently uncertain, but it may be considered when other therapies have failed.

Abatacept, a fusion protein of CTLA4 and the immunoglobulin heavy chain, blocks T and B cell co-stimulation. In two large randomized controlled trials of proliferative LN, abatacept proved no better than placebo on a background of MMF and corticosteroids[56] or a background of low-dose cyclophosphamide and corticosteroids.[41] However, a retrospective analysis of data from the first trial using different definitions of remission suggested that abatacept may have been effective with somewhat less stringent response criteria.

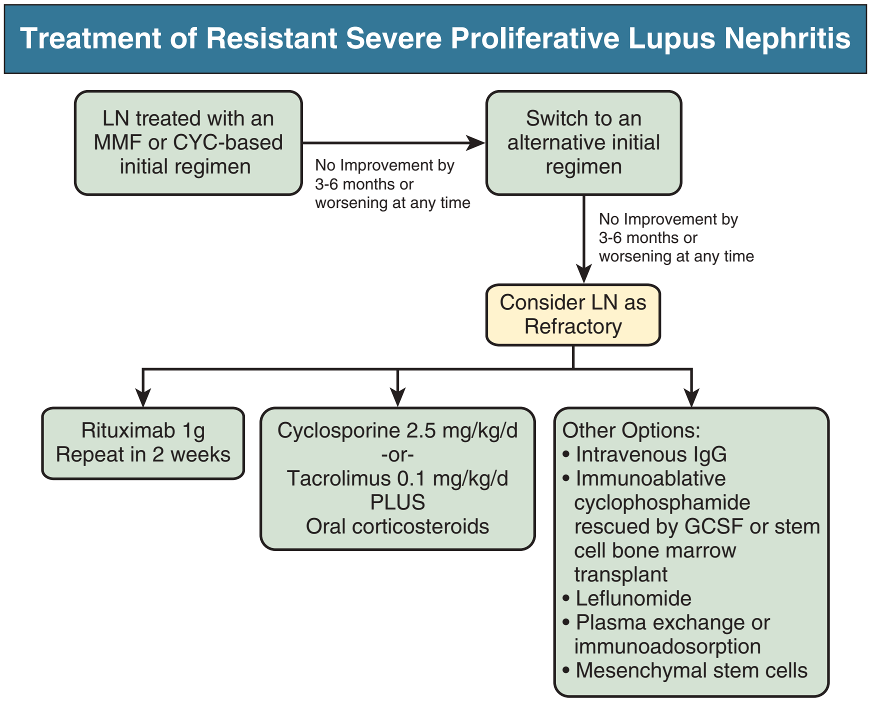
Treatment of Resistant Severe Proliferative Lupus Nephritis
LN treated with an MMF or CYC-based initial regimen
No Improvement by 3-6 months or worsening at any time
Switch to an alternative initial regimen
No Improvement by 3-6 months or worsening at any time
Consider LN as Refractory
Rituximab 1g Repeat in 2 weeks
Cyclosporine 2.5 mg/kg/d -or- Tacrolimus 0.1 mg/kg/d PLUS Oral corticosteroids
Other Options:
• Intravenous IgG
• Immunoablative cyclophosphamide rescued by GCSF or stem cell bone marrow transplant
• Leflunomide
• Plasma exchange or immunoadosorption
• Mesenchymal stem cells

Fig. 26.9 Treatment of resistant proliferative lupus nephritis (LN). *CYC,* Cyclophosphamide; *GCSF,* granulocyte colony-stimulating factor; *IgG,* immunoglobulin G; *MMF,* mycophenolate mofetil.

Other pathogenic mediators currently being targeted in SLE or LN with monoclonal antibodies are the B cell–stimulating cytokine BAFF and the type 1 interferon, IFN-α. Studies using an anti–IL-6 antibody and an anti-TWEAK antibody failed to show efficacy in proliferative LN.[57,58]

Resistant Proliferative Lupus Nephritis

There is no uniformly accepted definition of resistant or refractory LN. Up to one third of proteinuric nonresponders to induction therapy have inactive histologic findings on repeat biopsy. Fig. 26.9 outlines therapies that have been attempted for refractory disease. Most of these therapies were investigated in small, uncontrolled, and retrospective studies.

Rituximab has had some success in patients with refractory disease, benefitting about 30% of nonresponders.[59] In a registry, three different rituximab regimens often in combination with other immunosuppressives were tried in 68 patients, and after 12 months 31% were in complete renal remission.[60] Although no benefit was seen with the addition of plasma exchange to immunosuppressive therapy for remission induction in LN, the removal of circulating antibodies and other immune reactants may be considered for patients with high serologic activity and progressive refractory nephritis or thrombotic microangiopathy.[61] Intravenous immunoglobulin and CNIs have shown benefit in small series of patients with resistant LN.[62,63] Infusion of allogeneic mesenchymal stem cells derived from umbilical cord or bone marrow has been tested in a cohort of patients with refractory LN.[64] At 12 months, about 23% of patients had a complete renal response, but 40% of patients were considered to have treatment failures. Finally, for patients with life-threatening resistant disease, small pilot studies have tested total lymphoid irradiation and immunoablation by high-dose cyclophosphamide and antithymocyte globulin, with or without autologous stem cell reconstitution. These approaches have led to sustained treatment-free remissions, but toxicity and treatment-related mortality needs to be carefully weighed against potential benefit.[65]

Renal Response to Initial Therapy

Achieving complete remission of LN predicts a good long-term outcome with more than 90% 5-year patient and renal survival rates compared with only 69% and 45% for the group not achieving remission.[10] Partial remissions are also associated with improved outcomes. Complete and partial renal responses to MMF or cyclophosphamide range from 18% to 85% at 6 months and 32% to 85% at 12 months, and about half of treated LN patients achieve a complete or partial response by 1 year, with an additional 25% by 2 years.[66] Predictors of remission at the start of treatment have traditionally included lower baseline serum creatinine concentration, lower baseline urinary protein excretion, favorable renal histologic class, lower chronicity index, stable GFR after 4 weeks of therapy, and White race.

A post-hoc analysis of the Euro-Lupus low-dose cyclophosphamide trial found an absolute level of proteinuria less than 0.8 g/day 1 year after starting induction treatment was the single best predictor of good renal outcome after at least 7 years of follow-up.[34] The other 12-month predictors examined were serum creatinine concentration below 1 mg/dl (88 μmol/l) and fewer than 5 urine RBCs per high-power field. In another study after induction with low-dose cyclophosphamide, an absolute level of proteinuria less than 0.7 g/day 1 year after starting induction treatment again was the single best predictor of good renal outcome after at least 7 years of follow-up .[67] However, the negative predictive value of proteinuria alone was low in both analyses, and many patients who did not achieve proteinuria less than 0.7 to 0.8 g/day at 1 year still maintained good kidney function over time. Additionally, most of these patients were White.

Proliferative Lupus Nephritis: Maintenance Therapy

Because it generally takes months for proteinuria and serum creatinine concentrations to decrease to baseline levels after beginning LN treatment,[68] one important aspect of maintenance immunosuppression is to consolidate renal responses into complete and partial remissions using drugs with a lower side effect profile than induction drugs. Additionally, maintenance therapy should ideally prevent renal flares and attenuate or abrogate the development of chronic kidney disease. Current strategies for LN maintenance therapy are presented in Fig. 26.8.

Early investigations showed maintenance cyclophosphamide was superior to corticosteroids alone.[38,69] Subsequent work demonstrated that less intense maintenance immunosuppression with AZA or MMF was as effective as maintenance cyclophosphamide and was associated with improved patient morbidity and survival.[70]

Corticosteroids, tapered from the initial treatment period, are generally continued during the maintenance period, but at low dose (see Fig. 26.8). Both daily and alternate-day corticosteroid regimens have been used, but there is no consensus as to the optimal duration of corticosteroid therapy.

Two randomized clinical trials compared AZA 2 mg/kg/day and MMF 2 g/day for LN maintenance. In multiethnic patients who received induction with cyclophosphamide or MMF, MMF maintenance therapy was better than AZA at preventing renal flares, preserving renal function over 3 years, and delaying progression to ESRD.[45] In a study of mainly European White patients (MAINTAIN Nephritis trial), AZA and MMF were equally effective at preventing renal flares over 4 years after initial treatment with low-dose cyclophosphamide.[71] Although MMF appears to be the maintenance drug of choice for most LN patients, therapy should be individualized. In some patients, AZA may be preferred, such as for patients in complete remission who want to become pregnant. Finally, two randomized trials compared the CNIs tacrolimus and cyclosporine to AZA for maintenance.[72,73] Although both trials were underpowered and the tacrolimus trial had only 6 months of follow-up, both demonstrated that CNIs were as effective as AZA in preventing renal flares. Given fewer data for tacrolimus and cyclosporine, and concerns over long-term nephrotoxicity, CNIs are best reserved for patients who are unable to take MMF or AZA.

The duration of maintenance therapy, and whether maintenance can ever be stopped in patients with LN remain open questions. In general, LN patients are placed on maintenance immunosuppression for several years. Withdrawal of maintenance therapy is the subject of an ongoing RCT (NCT01946880). Therapy reduction was examined retrospectively in European LN patients who had achieved complete remission with normal kidney function, proteinuria of 0.5 g/day or less, inactive urine sediment, and no extrarenal SLE signs or symptoms.[74] The cohort started with 73 patients, 20 of whom experienced flare when prednisone was tapered to a very low dose. Therapy was completely stopped in the other 52 patients, a median of 73 months after beginning induction therapy. These patients were then followed for a median of 172 months, and 61% never relapsed. There were 15 cases of LN and 5 nonrenal flares that occurred at a median of 37 months after stopping maintenance. Risk factors for LN flare after withdrawal of therapy in this cohort included shorter duration of overall treatment, decreased use of antimalarials, and lack of maintenance cytotoxic drug use.

Membranous Lupus Nephropathy

Membranous nephropathy is often diagnosed in association with proliferative forms of LN. In these patients, treatment is directed at the proliferative component. Alternatively, the combination of low doses of corticosteroids, MMF, and a CNI, the so-called multitarget regimen, has shown considerable success in an Asian cohort of mixed membranous and proliferative LN.[75]

The optimal treatment of pure class V LN remains unclear, but a reasonable treatment algorithm is presented in Fig. 26.10. KDIGO

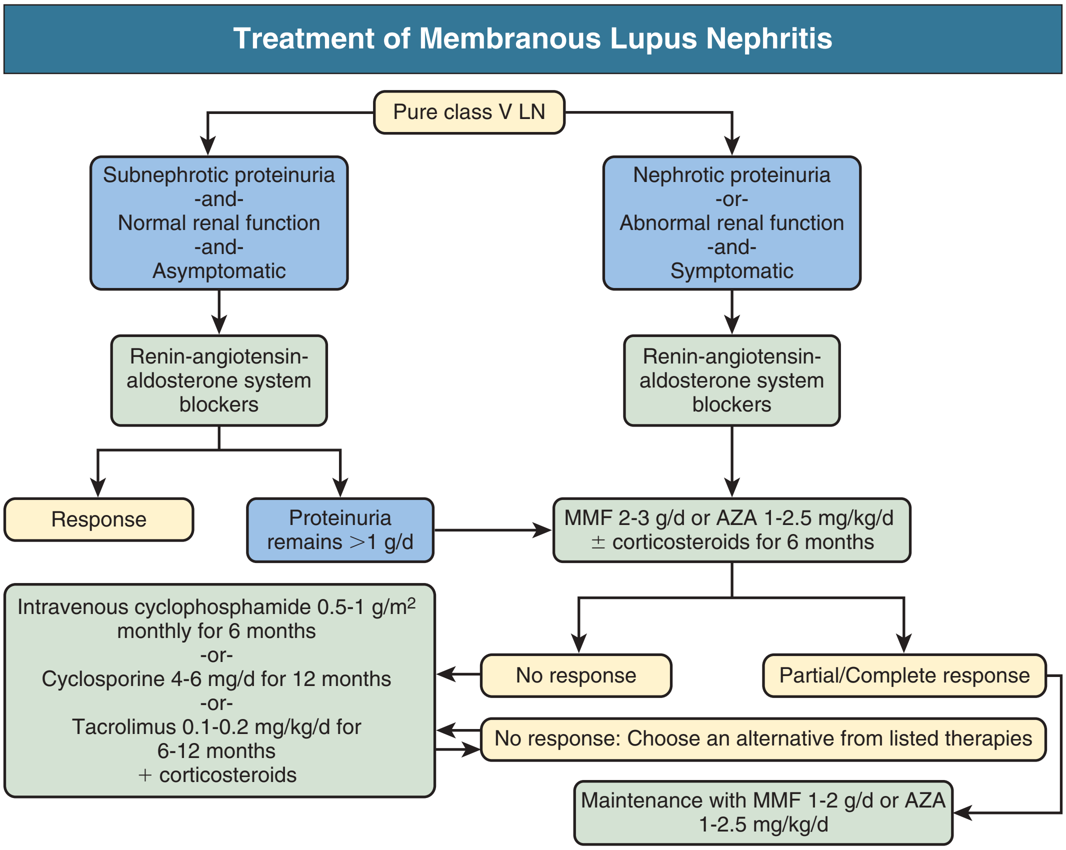
Treatment of Membranous Lupus Nephritis
Pure class V LN
Subnephrotic proteinuria -and- Normal renal function -and- Asymptomatic
Nephrotic proteinuria -or- Abnormal renal function -and- Symptomatic
Renin-angiotensin-aldosterone system blockers
Renin-angiotensin-aldosterone system blockers
Response
Proteinuria remains >1 g/d
MMF 2-3 g/d or AZA 1-2.5 mg/kg/d ± corticosteroids for 6 months
Intravenous cyclophosphamide 0.5-1 g/m2 monthly for 6 months -or- Cyclosporine 4-6 mg/d for 12 months -or- Tacrolimus 0.1-0.2 mg/kg/d for 6-12 months + corticosteroids
No response
Partial/Complete response
No response: Choose an alternative from listed therapies
Maintenance with MMF 1-2 g/d or AZA 1-2.5 mg/kg/d

Fig. 26.10 Treatment of membranous lupus nephritis. *AZA,* Azathioprine; *MMF,* mycophenolate mofetil.

guidelines suggest renoprotective and antiproteinuric therapies for patients with subnephrotic proteinuria and no renal impairment, with immunosuppression reserved for patients with nephrotic syndrome and/or renal impairment.[48] The only small RCT in patients with class V LN compared cyclophosphamide or cyclosporine to corticosteroids alone.[76] The patients studied had preserved kidney function and a mean proteinuria of almost 6 g/day. Complete and partial remissions were more frequent in the cyclophosphamide and cyclosporine-treated patients. Cyclosporine induced remission more rapidly than the other drugs, but LN relapses were fewer in the cyclophosphamide group. Two trials of MMF versus cyclophosphamide as initial therapy of LN included 84 patients with pure membranous nephropathy among the 510 patients enrolled.[77] Remissions, relapses, and courses were similar in the class V patients treated with MMF and cyclophosphamide. Azathioprine plus corticosteroids also has been successful in patients with membranous LN, but these studies have been observational or retrospective.[78]

Long-Term Monitoring of Lupus Nephritis Patients

The relapse (flare) rate for LN ranges from 35% to 60%, depending on the population studied, the criteria for relapse, and the maintenance therapy used,[78-80] suggesting that LN patients in remission be closely followed. We recommend quarterly monitoring (including blood pressure, kidney function, proteinuria, urinary sediment, serum C3 and C4) with anti-dsDNA measured at least biannually.[50] Although changes in serology alone do not warrant therapeutic action, they may serve as an early warning that autoimmune activity is increasing and patients should be watched even more closely for flare.

Repeat kidney biopsies should be considered during long-term management of LN.[66] At LN flare, a repeat biopsy should be considered if a change in histologic class is suspected. Patients with proliferative LN tend to remain proliferative at flare, but patients with class II and V not infrequently develop a proliferative component. Evaluation of persistent proteinuria and declining kidney function in LN also may benefit from a repeat biopsy. Several studies have shown considerable discordance between histologic activity and clinical activity. Persistent proteinuria may be due to persistent inflammatory disease activity and require further immunosuppression or may be due to chronic damage and nephron loss, in which immunosuppression will not be beneficial. When considering reduction or withdrawal of maintenance therapy a repeat biopsy may help because even patients with sustained clinical inactivity still may have histologic activity.[66]

ANTIPHOSPHOLIPID ANTIBODY SYNDROME, ATHEROSCLEROSIS, AND PREGNANCY IN LUPUS NEPHRITIS

Intrarenal thrombosis caused by the antiphospholipid antibody syndrome is found in 30% of patients with SLE and may occur in the presence or absence of LN (see Chapter 28). The mainstay of treatment for antiphospholipid nephropathy has been anticoagulation plus chloroquine or hydroxychloroquine, although immunosuppressive agents also have been used.

Patients with lupus have increased risk for atherosclerotic complications and greater atherosclerotic plaque burden compared with age-matched controls, and these factors contribute to morbidity and mortality in SLE.[74] The risk for heart attack in a young woman with SLE is 50 times greater than that of a healthy woman, and even older women with SLE have 2.5 to 4 times the risk for myocardial infarction of age-matched controls. After adjustment for all traditional cardiovascular risk factors, patients with SLE have a 7- to 10-fold higher risk for nonfatal and a 17-fold higher risk for fatal myocardial infarctions. Chronic kidney disease, a frequent outcome of LN, is also a cardiovascular risk factor. Reduction of atherosclerotic risk should focus on blood pressure control (goal of 130/80 mm Hg), use of statins and hydroxychloroquine to correct lipid abnormalities,[81] and reduction of inflammatory disease activity.

The effects of SLE and LN on pregnancy and fetal outcomes, and the effects of pregnancy on LN activity, are discussed in Chapter 43.

END-STAGE RENAL DISEASE AND RENAL TRANSPLANTATION

Although approximately 10% of all lupus patients develop ESRD, the overall proportion of patients with ESRD attributable to lupus is 1% to 2%.[3,82] Patients of African ancestry are at higher risk for ESRD. Extrarenal lupus is often quiescent by the time patients reach ESRD, but those with active extrarenal disease may require immunosuppression while receiving renal replacement therapy. It has been suggested that patients with LN defer transplantation for 3 to 6 months to allow SLE to become inactive; however, recent data suggest that there is an increased risk for allograft failure if LN patients wait more than 3 months before transplantation.[83] Interestingly, the correlation between longer wait times and increased allograft failure was not seen in African American patients. Survival of lupus patients on dialysis or after kidney transplantation is similar to those of patients with other renal diseases.[82] Thrombotic events are increased in LN recipients, especially if they are positive for antiphospholipid antibody, but this does not appear to correlate to a diminished allograft survival.[82] Recurrent LN after kidney transplantation is rare, occurring in only about 1% of patients.[84]

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SELF-ASSESSMENT QUESTIONS

1. A 21-year-old African American woman presents for initial therapy of lupus nephritis (LN). She was diagnosed with systemic lupus erythromatosus (SLE) 1 year ago, when she was found to have alopecia, malar rash, and arthralgias with antinuclear antibodies (ANA) and double-stranded DNA (dsDNS) antibodies. At that time, urine sediment was unremarkable, serum creatinine was 0.6 mg/dl, and she had no proteinuria. She was treated with low-dose corticosteroids and hydroxychloroquine, with resolution of her symptoms. Over the past month, she noticed foamy urine and mild ankle swelling. Evaluation showed blood on her urine dipstick, 24-hour urine with 4 g protein, serum creatinine of 1 mg/dl, and a rising dsDNA titer with both C3 and C4 now newly decreased. A kidney biopsy revealed ISN class IVA lupus nephritis, with 25% cellular crescents and areas of glomerular capillary necrosis. The patient is young and may want children in the future. Considering options for initial therapy for this patient's lupus nephritis, which of the following statements is correct?
   A. She should be treated with intravenous rituximab for initial therapy.
   B. She should be treated with high-dose corticosteroids and azathioprine for initial therapy.
   C. Mycophenolate mofetil (MMF) or cyclophosphamide is an appropriate choice. Ovarian protection or cryopreservation of eggs should be considered if cyclophosphamide is to be used.
   D. She should not receive MMF because she wants to get pregnant in the future.
2. A 24-year-old African American female has been treated for the last 6 months with MMF (2 to 3 g/day) and a tapering dose of corticosteroids for active focal proliferative lupus nephritis (ISN class IIIA). Her initial proteinuria decreased from 3.4 g daily to 1.2 g daily, urine sediment is inactive, and serum creatinine decreased from 1.6 to 0.9 mg/dl over the 6 months of therapy while anti-dsDNA titer declined and serum complement values returned to normal. What is the optimal therapy for this patient at this time?
   A. Continue the current dose of MMF for an additional 6 months and then taper slowly over 1 year.
   B. Given the persistent proteinuria, change to intravenous cyclophosphamide at 500 mg every 2 weeks for 6 doses and then administer azathioprine at 2 mg/kg daily.
   C. Reduce the MMF to 1000 mg bid and plan to continue for 3 years unless otherwise indicated.
   D. Change to azathioprine at 2 mg/kg/day, and plan to continue for 4 years unless otherwise indicated.
3. A 32-year-old White woman with a history of LN in the past wants to become pregnant and is concerned about flares during the pregnancy. In considering medications that have been used successfully in SLE patients during pregnancy, you discuss use of which of the following medications?
   A. Corticosteroids
   B. Intravenous cyclophosphamide, but not oral cyclophosphamide
   C. Rituximab
   D. Mycophenolate mofetil
4. A 28-year-old White female patient presents with nephrotic syndrome and is found to have class V membranous lupus on renal biopsy. Based on randomized controlled trials, which of the following medications has *not* been shown to be effective in treating this pattern of lupus nephritis?
   A. Intravenous cyclophosphamide
   B. Intravenous rituximab
   C. Oral cyclosporine
   D. Oral MMF

27

Renal Amyloidosis and Glomerular Diseases With Monoclonal Immunoglobulin Deposition

Pierre Ronco, Pierre Aucouturier, Bruno Moulin

The glomerular capillaries are a favorite site for the deposition of abnormal, misfolded, or aggregated proteins. In most patients, the resulting diseases are caused by a monoclonal immunoglobulin or subunit thereof and can be classified into two categories by electron microscopy (EM) (Table 27.1). The first category includes diseases with fibril formation, mainly amyloidosis, and diseases with microtubule formation, including cryoglobulinemic glomerulonephritis (see Chapter 21) and immunotactoid glomerulonephritis (GN). The second disease category is characterized by nonorganized electron-dense granular deposits. These deposits are localized along basement membranes in most tissues, especially in the kidney, and define a disease termed *monoclonal immunoglobulin deposition disease* (MIDD). In other rare cases, termed *proliferative glomerulonephritis with monoclonal immunoglobulin deposition* (PGNMID), monotypic immune complex–like deposits are observed.

RENAL AMYLOIDOSIS

General Characteristics of Amyloidosis

Definition

Amyloidosis is a generic term for a family of diseases defined by morphologic criteria. The diseases are characterized by the deposition in extracellular spaces of a proteinaceous material. Amyloid deposits are composed of a felt-like array of 7.5- to 10-nm-wide rigid, linear, nonbranching, aggregated fibrils of indefinite length. One amyloid fibril is made of two twisted 3-nm-wide filaments, each displaying the typical "cross-β"structure, where antiparallel β-sheets are perpendicular to the filament axis.

Amyloid Precursor–Based Classification

Amyloidoses are classified according to the nature of the precursor protein that composes the main component of fibrils[1] (Table 27.2). The amyloidogenic propensity is related to the ability of this precursor to form intermolecular β-sheets, and is enhanced by overproduction or impaired clearance of the precursor.

Renal amyloidoses mostly include immunoglobulin light-chain (AL) and systemic secondary (AA) amyloidoses. Other precursors, such as transthyretin, fibrinogen, apolipoprotein A-I, and lysozyme, are responsible for rare familial cases.

Other Components of All Amyloid Fibrils

Glycosaminoglycans (GAGs) are found tightly associated with amyloid fibrils extracted from involved tissues. GAGs are polysaccharide chains made of repeating hyaluronic acid–hexosamine units normally linked to a protein core, thus forming proteoglycans. Proteoglycans, mostly of the heparan sulfate type, appear to induce and stabilize the β-pleated amyloid structure.

Another constituent of all amyloid deposits is serum amyloid P component (SAP). SAP is resistant to proteolytic digestion, and coating of amyloid fibrils with SAP could result in their protection from catabolism. The high affinity of SAP toward amyloid has been exploited for scintigraphy with [^{123}I]-SAP. CPHPC (R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid) is a proline-derived small compound that specifically binds to SAP and allows rapid decreases in serum SAP levels. The combination of CPHPC with an anti-SAP antibody targets amyloid deposits and enables their elimination by recruiting phagocytic cells in a mouse model of AA amyloidosis.[2] A phase-1 human clinical trial in 15 patients using CPHPC followed by infusion of an anti-SAP antibody confirmed their potential in clearing amyloid deposits.[3]

General Mechanisms of Fibrillogenesis

Amyloidogenesis involves a nucleation-dependent polymerization process. Formation of an ordered nucleus is the initial and thermodynamically limiting step, followed by addition of monomers and elongation of the fibrils. Fibrillogenesis may involve several mechanisms of processing of the amyloid precursor, including partial proteolysis and conformational modifications. Macrophages seem to favor AA amyloidosis through C-terminal proteolysis of the precursor SAA and may be involved in other steps of the pathogenesis. In AL amyloidosis, the variable domain of the light chain (V_L) seems to be the main component of the fibrils. Light chains are internalized at caveolae of mesangial cells followed by trafficking to the lysosomal compartment where fibrils are formed.[4]

Pathology

On light microscopy, the deposits are extracellular, eosinophilic, and metachromatic, inducing a change in the color of dyes. After Congo red staining, the deposits appear faintly red (Fig. 27.1A) and show characteristic apple-green birefringence under polarized light (see Fig. 27.1B). Metachromasia is also observed with crystal violet, which stains the deposits red.

The earliest lesions are located in the mesangium (see Fig. 27.1A), along the glomerular basement membrane (GBM), and in the blood vessels. Mesangial deposits may be sparse or more diffuse, sometimes featuring a lobular distribution. Amyloid deposits also may infiltrate the GBM or may be localized on both of its sides, forming spikes. Advanced amyloid typically produces a nonproliferative, noninflammatory glomerulopathy with marked enlargement of the kidney. When glomeruli become massively sclerotic, the deposits may be difficult to demonstrate by Congo red staining. In this case, EM may be helpful; EM is also helpful in the very early stages in nephrotic patients (Fig. 27.2).

Except for fibrinogen amyloidosis, the media of the blood vessels is prominently involved at early stages. Vascular involvement may

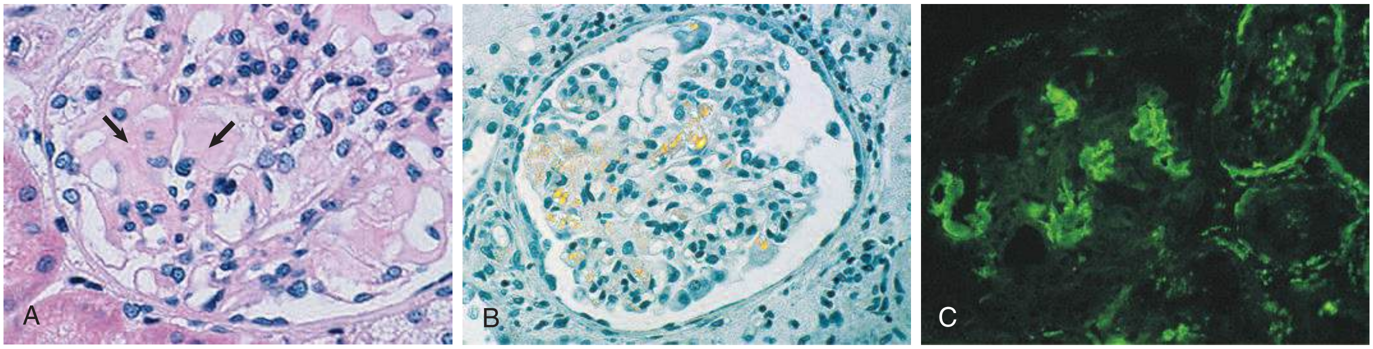

Fig. 27.1 **Amyloidosis.** (A) Amyloid deposits *(arrows)* in a glomerulus. (Hematoxylin-eosin [HE] stain; magnification ×312.) (B) Congo red staining. Apple-green birefringence under polarized light. (×312.) (C) Immunofluorescence with anti-κ antibody. Note glomerular and tubular deposits. (×312.) (Courtesy Dr. Béatrice Mougenot, Paris.)

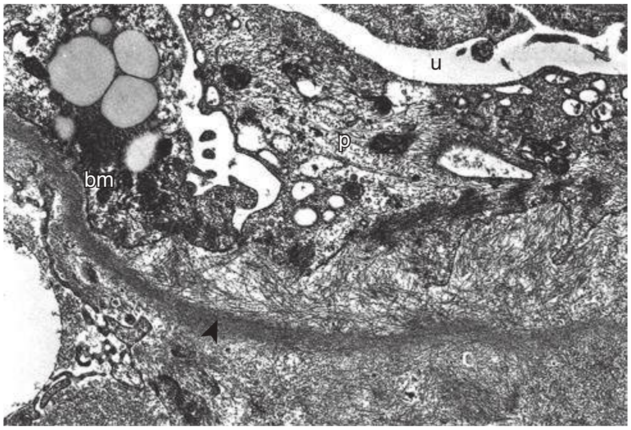

Fig. 27.2 **Electron micrograph of amyloid deposits invading glomerular basement membrane.** Randomly oriented fibrils are located on both sides of the basement membrane *(bm)*, and the lamina densa is attenuated *(arrowhead)*. *p,* Podocyte; *u,* urinary space. (×10,000.) (Courtesy Dr. Béatrice Mougenot, Paris.)

TABLE 27.1 Glomerular Diseases With Tissue Deposition or Precipitation of Monoclonal Immunoglobulin Components

Immunoglobulin Deposits	Glomerular Disease
Organized	
Fibrillar	Amyloidosis (AL, AH); fibrillary glomerulonephritis
Microtubular	Cryoglobulinemia; immunotactoid glomerulonephritis
Nonorganized: Granular	Monoclonal immunoglobulin deposition disease (MIDD): light-chain (LCDD), heavy-chain (HCDD), and light- plus heavy-chain deposition (LHCDD) diseases Proliferative glomerulonephritis with monoclonal immunoglobulin deposition

predominate and occasionally occurs alone, particularly in AL amyloidosis. Deposits also may affect the tubules and interstitium.

Given the diversity of amyloidosis types, immunohistology should be routinely performed (see Fig. 27.1C). Immunohistology with antibodies specific for immunoglobulin chains may be difficult to interpret, because of the absence or inaccessibility of light-chain epitopes. Alternative techniques such as immuno-EM[5] and mass spectrometry–based proteomic analysis of deposits after laser microdissection or extraction from the whole sample, at highly specialized centers, can correctly classify more than 99% of patients with systemic amyloidosis.[6] A genetic cause should be sought by DNA sequencing in all patients with amyloidosis in whom confirmation of the amyloid precursor cannot be obtained by other techniques.[7]

Immunoglobulin-Associated Amyloidosis (AL Amyloidosis)

Free immunoglobulin subunits, mostly light chains, secreted by a single clone of B cells, are the cause of the most frequent and severe amyloidosis affecting the kidney. The involvement of an immunoglobulin heavy chain (AH and AHL amyloidosis) is rare.[8]

Pathogenesis

Determinant factors are borne by the precursor light chain, as demonstrated by transfer into experimental animals. Studies on the mechanisms of AL amyloidogenesis are made particularly difficult by the unique structural heterogeneity of the precursor. There is a striking overrepresentation of the lambda (λ) isotype, which is twofold to fourfold more common than the kappa (κ) isotype. A rarely expressed homology family of light-chain variable regions, the $V_{\lambda VI}$ variability subgroup, is found only in amyloid-associated monoclonal immunoglobulin light chains.

Amyloidogenicity is associated with physicochemical features that include low-molecular-mass light-chain fragments in the urine, abnormal disulfide bonding of light chains, and low isoelectric point (pI). An analysis of almost 200 light-chain sequences identified 12 positions in κ chains and 12 in λ chains where certain residues were associated with amyloidosis. Because of their high dimerization constant, light chains from patients with AL amyloidosis may display antibody-like binding properties toward extracellular structures that could favor a nucleation process.

The tropism of organ involvement is influenced both by the germline gene used for the light-chain variable region (V_L) and by somatic mutations occurring in the secreting clone. Patients expressing a monoclonal light chain of the $V_{\lambda VI}$ subgroup are more likely to present with dominant renal involvement and less frequent cardiac and multisystem disease, whereas those expressing monoclonal κ light chains of the $V_{\kappa I}$ subgroup are more likely to have dominant hepatic involvement. In addition, organ-specific environmental factors are also involved.

Amyloid light chains may contribute directly to the pathogenesis, independently of extracellular fibril deposition. In the heart and the kidney at least, the infiltration alone does not correlate well with clinical

TABLE 27.2 Characteristics of the Common Types of Amyloidosis

				ORGAN INVOLVEMENT						
	Acquired or Hereditary	**Underlying Disorder**	**Precursor Protein**	**Heart**	**Kidneys**	**Liver**	**PN (AN)**	**Other**	**Treatment**	**Treatment Target**
AL	Acquired	Plasma cell dyscrasia	Monoclonal immunoglobulin light chain	+++	+++	++	+(+)	Soft tissue gastrointestinal	Chemotherapy or ASCT	dFLC <40 mg/l
AA	Acquired	Inflammatory disorders (RA, JIA, IVDU, FPS)	SAA	–/+ (late)	+++	+ (late)	–	Gastrointestinal (late)	Suppression of inflammation	SAA <4 mg/l
ATTR	Acquired	—	Wild-type *TTR*	+++	–	–	–	Carpal tunnel syndrome	Supportive	Optimum control of heart failure
	Hereditary	Mutations in *TTR* gene	Abnormal *TTR*	++	–	–	+++ (+++)	–	Liver transplant (younger patients with V30M-related ATTR), diflunisal, (doxycycline/ TUDCA) Supportive	Optimum control of congestive heart failure and symptoms of PN/AN
AFib	Hereditary	Mutations in fibrinogen α-chain gene	Abnormal fibrinogen	–	+++	–/+	–	–	Supportive, organ transplant	Preserve renal function
ALect2	Acquired	Uncertain	Lect2	–	+++	++	–	–	Supportive	Preserve renal function
AApoA1	Hereditary	Mutations in apolipoprotein A1 gene	Abnormal *ApoA1*	+	++	++	+/– (–)	Testis	Supportive, organ transplant	Preserve renal function
ALys	Hereditary	Mutations in lysozyme gene	Abnormal lysozyme	–	+	++	–	Gastrointestinal or skin	Supportive	
AGel	Hereditary	Mutations in gelsolin gene	Abnormal gelsolin	–	–/+	–	++ (–) cranial	–	Supportive	
Aβ2M	Acquired or hereditary	Long-term dialysis	Aβ2M	–	–	–	– (+*)	Carpal tunnel syndrome, arthropathy	Supportive, renal transplant	

Modified from reference 53.

*AN only in familial Aβ2M amyloidosis.

+, Relative frequency; +++, very common; ++, common; +, less common; –/+, rare; –, not applicable or does not occur in this condition.

(drug), Undergoing clinical trials. *AA,* Amyloid A; *AApoA1,* apolipoprotein A1 amyloid; Aβ2M, β2-microglobulin-related; *AFib,* fibrinogen A α-chain; *AGel,* gelsolin amyloid; *AL,* amyloid light chain; *ALect2,* leukocyte cell–derived chemotaxin 2; *ALys,* lysozyme amyloid; *AN,* autonomic neuropathy; *ASCT,* autologous stem cell transplant; *ATTR,* amyloid transthyretin; *dFLC,* difference between involved and uninvolved free light chain; *FPS,* familial periodic fever syndromes; *IVDU,* intravenous drug abuse; *JIA,* juvenile inflammatory arthritis; *PN,* peripheral neuropathy; *RA,* rheumatoid arthritis; *SAA,* serum amyloid A; *TTR,* transthyretin; *TUDCA,* tauro-ursodeoxycholic acid; *UK-NAC,* UK National Amyloidosis Centre.

manifestations. Light chains from amyloid patients incubated with mesangial cells induce a macrophage-like phenotype, whereas those from light-chain deposition disease patients induce a myofibroblast-like phenotype.

Epidemiology

The incidence of AL amyloidosis is 9 cases per 1 million population per year. Fewer than one in four patients with AL amyloidosis have an overt immunoproliferative disease, most frequently multiple myeloma. The apparent prevalence of myeloma depends on the diagnostic criteria used. Demographic characteristics of *primary* amyloidosis, that is, amyloidosis without overt immunoproliferative disease, which is now part of the new entity called *monoclonal gammopathy of renal significance* (MGRS), are not different from those of myeloma.[9] The median age at diagnosis is 64 years, with a slight predominance of male patients, and about 10% are less than 50 years old.[10] Conversely, amyloid deposits are found in approximately 10% of all patients with myeloma and in 20% of those with light chain only myeloma.

Clinical Manifestations

The clinical presentation of AL amyloidosis depends on the pattern and severity of organ involvement, and almost any organ system may be affected by amyloid deposits. Except for the combination of macroglossia and periorbital purpura, which is pathognomonic of AL amyloidosis and occurs in less than a third of cases, clinical features are rarely specific and mimic other more common conditions of the elderly, particularly weakness and weight loss (Table 27.3). Except for bone pain, the initial symptoms in patients with and without myeloma are similar. However, nephrotic syndrome, orthostatic hypotension, and peripheral neuropathy are more frequent in patients with AL amyloidosis without myeloma.

TABLE 27.3 Clinical and Laboratory Features at Presentation in 474 Patients With Proven Light-Chain (AL) Amyloidosis

Features	Percentage
Initial Symptoms	
Fatigue	62
Weight loss	52
Pain	5
Purpura	15
Gross bleeding	3
Physical Findings	
Hepatomegaly	24
Palpable spleen	5
Lymphadenopathy	3
Macroglossia	9
Laboratory Findings	
Increased plasma cells (bone marrow >6%)	56*
Anemia (hemoglobin <10 g/dl)	11
Elevated serum creatinine (1.3 mg/dl) (>113 μmol/l)	45
Elevated alkaline phosphatase	26
Hypercalcemia (>11 mg/dl) (>2.75 mmol/l)	2
Proteinuria (>1.0 g/24 h)	55
Urine light chain	73†
κ chain	23
λ chain	50

From reference 10.
*15% of patients having myeloma.
†Of 429 patients.

Kidneys are the organs most commonly involved in AL amyloidosis, with a high risk for progression to end-stage renal disease (ESRD). In a study of 145 patients with AL amyloidosis, 42% of the patients who presented with renal manifestations required renal replacement therapy versus 5% of those who did not.[11] Renal impairment (serum creatinine >1.2 mg/dl [106 μmol/l]) is found in nearly half of the patients, with full nephrotic syndrome in 68%. Rare forms of vascular limited AL amyloidosis present with renal impairment but little (<1 g/day) or no proteinuria. There is a poor correlation between the extent of amyloid deposits seen on a kidney biopsy specimen and the extent of proteinuria. Renal manifestations also may include renal tubular acidosis (mostly as a part of Fanconi syndrome; see Chapter 48) and nephrogenic diabetes insipidus (resulting from urinary concentration defect), when amyloid deposits occur around proximal tubules and the loops of Henle or collecting ducts, respectively.

Restrictive cardiomyopathy is found at presentation in up to one third of patients and causes death in about half. Infiltration of the ventricular walls and the septum may be recognized by echocardiography and cardiac magnetic resonance imaging, which has high specificity for diagnosis of cardiac amyloidosis. Amyloid may induce arrhythmias and sick sinus syndrome. Amyloid deposits in the coronary arteries may result in angina and myocardial infarction. Cardiac troponins and N-terminal pro–brain natriuretic peptide (NT-proBNP) are sensitive markers of myocardial dysfunction and powerful predictors of overall survival in patients with AL amyloidosis.

Involvement of the gastrointestinal (GI) tract is common and can cause motility disturbances, malabsorption, hemorrhage, or obstruction. Macroglossia may interfere with eating and obstruct airways (Fig. 27.3). Abnormalities of hepatic function are usually mild. Splenomegaly may be associated with spleen dysfunction, predisposing to fatal bacterial infections. Peripheral nerve involvement may result in a painful sensory polyneuropathy, followed by motor deficits. Autonomic neuropathy causing orthostatic hypotension (one of the more disabling complications of AL amyloidosis), lack of sweating, GI disturbances, bladder dysfunction, and impotence may occur alone or together with peripheral neuropathy. Skin involvement may take the form of purpura, characteristically around the eyes (Fig. 27.4), and ecchymoses, papules, nodules, and plaques, occurring usually on the face and upper trunk. AL amyloidosis may infiltrate articular structures and mimic rheumatoid or an asymmetric seronegative synovitis. Infiltration of the shoulders may produce severe pain and swelling (shoulder pad sign). A rare but

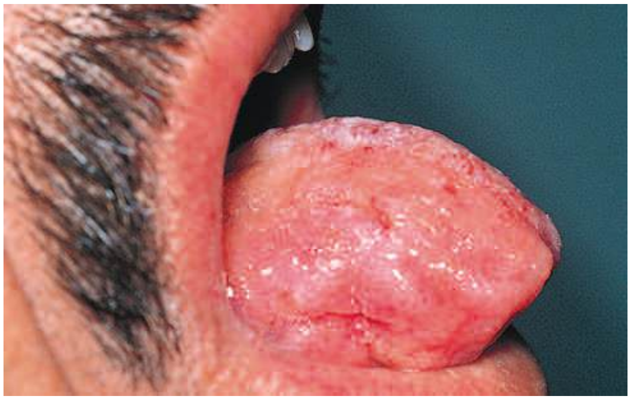

Fig. 27.3 Macroglossia in patient with AL amyloidosis. (Courtesy Dr. S. Aractingi, Paris.)

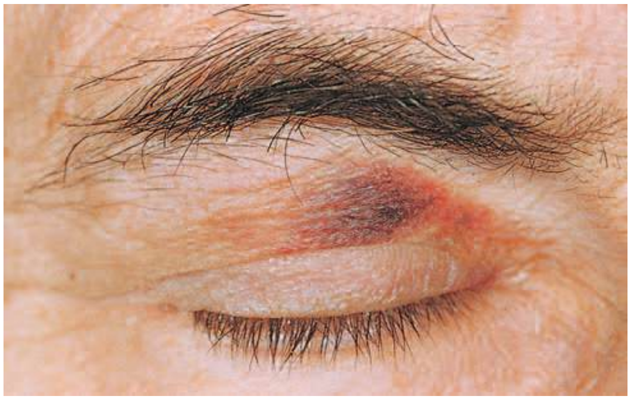

Fig. 27.4 Skin involvement in AL amyloidosis. Noninfiltrated purpuric macule of the superior eyebrow, typical of AL amyloidosis. (Courtesy Dr. S. Aractinji, Paris.)

potentially serious manifestation of AL amyloidosis is an acquired bleeding diathesis that may be associated with deficiency of factor X or factor IX or with increased fibrinolysis. It should be screened by prothrombin time and activated partial thromboplastin time before any biopsy of a deep organ. Widespread vascular deposits also may be responsible for bleeding.

A monoclonal immunoglobulin is found in the serum or the urine in almost 90% of patients. Immunochemical techniques combined with serum free light-chain (FLC) assays detect an abnormal result in 99% of patients.[12] The λ isotype is twice as frequent as the κ, contrasting with the 1:2 ratio of λ to κ observed in myeloma alone. Abnormal serum FLC may precede by many years the clinical onset of AL amyloidosis.

Renal AH and AHL amyloidosis account for 7.3% of cases of renal immunoglobulin-related amyloidosis and affect older patients with a median age at biopsy of 63 years.[8] Compared with patients with renal AL amyloidosis, those with renal AH and AHL amyloidosis present with less cardiac involvement, probably explaining their better survival. Renal biopsy is needed to diagnose renal AH/AHL because other sites usually are not affected. Most of the patients with renal AH/AHL amyloidosis have a circulating intact monoclonal immunoglobulin.

Immunoglobulin M (IgM)-related amyloidosis is a relatively uncommon variant of immunoglobulin-related amyloidosis, accounting for 6% of AL amyloidosis patients. It is characterized by less cardiac involvement but more frequent lymph nodes and neuropathic involvement. Non-Hodgkin lymphoma is the predominant underlying clonal disorder found in 54% of the patients, but plasma cell infiltration is still reported in 6% of the cases. Up to 74% of patients have an abnormal FLC ratio. Independent factors that have an impact on survival are Mayo stage according to revised classification including cardiac biomarkers (NT-proBNP and troponin),[13] age older than 67 years, neuropathy (peripheral and autonomic nervous system), and liver involvement, leading to a new staging system for IgM AL amyloidosis.[14]

Diagnosis

Diagnostic procedures in AL amyloidosis follow a stepwise approach to confirm the presence of amyloid deposition and identify the type of fibril and then assess the underlying plasma cell/B cell clone and evaluate the extent and severity of organ involvement. Because the disease is diagnosed more than 1 year after the onset of symptoms in almost 40% of cases, AL amyloidosis should be considered in any patient who presents with nephrotic-range proteinuria with or without renal impairment, nondilated cardiomyopathy, peripheral neuropathy, hepatomegaly, or autonomic neuropathy (Fig. 27.5). Particular vigilance should be maintained in patients with multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS), especially of the λ isotype.

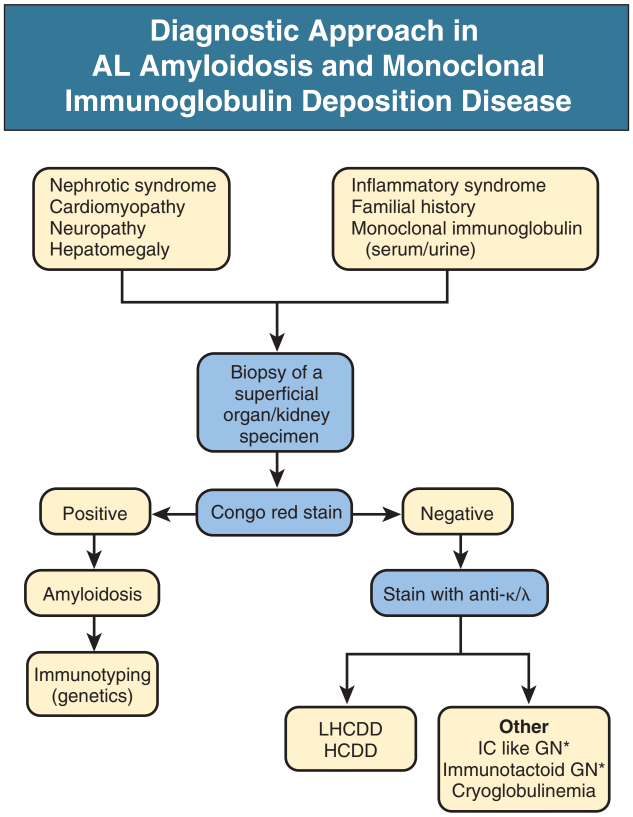

Fig. 27.5 Algorithm of diagnostic procedures in light-chain (AL) amyloidosis and monoclonal immunoglobulin deposition disease (MIDD). *No extrarenal manifestation. *GN*, Glomerulonephritis; *HCDD*, heavy- chain deposition disease; *IC*, immune complex; *LHCDD*, light- and heavy-chain deposition disease.

All patients require immunofixation of serum and urine in an attempt to demonstrate the presence of a monoclonal light chain and quantitation of serum FLC. In most cases, the absolute difference between serum levels of free κ and λ (dFLC) will be a key parameter for the follow-up. In patients with chronic kidney disease (CKD), both types of polyclonal FLC increase with decreasing GFR, and one should look at the κ/λ ratio. A bone marrow specimen may be important at diagnosis because 10% of patients will not have a demonstrable monoclonal light chain by immunofixation, and a clone of plasma cells detected in the bone marrow by immunohistochemistry is a strong evidence of AL amyloidosis.

Biopsy of an affected organ is usually diagnostic, but less invasive alternatives should be preferred first. Biopsies of salivary glands or of subcutaneous abdominal fat yield positive results in 80% to 90% of cases. Rectal biopsy is diagnostic in more than 80%, provided the biopsy specimen contains submucosal vessels. Bone marrow biopsy specimens should be stained with Congo red for the presence of amyloid, and involvement of the bone marrow (observed in about 50% of patients) is strongly suggestive of the AL type.

It is not always easy to be certain that amyloidosis is of the AL type because immunohistochemical staining for immunoglobulin light chains may not be diagnostic,[15] and the presence of a monoclonal component is strong but not conclusive evidence. Caution is especially required when patients have an entire monoclonal immunoglobulin in the serum without evidence of FLC in the serum and urine. In those cases, hereditary forms of amyloidosis should be considered because they may produce clinical syndromes indistinguishable from AL and may coexist with MGUS.[7] In cases of doubt, DNA analysis and amyloid fibril sequencing by mass spectrometry are necessary.

Several criteria have been established to define organ involvement. Particularly, elevation of NT-proBNP and cardiac troponin (cTnT) are markers of myocardial dysfunction in AL amyloidosis that strongly correlate with prognosis and are therefore used for the risk assessment staging according to the Mayo risk stratification systems.[13] However, a limitation of the NT-proBNP based staging system is the influence of renal failure on the concentration of this biomarker that can be partly overcome by using brain natriuretic peptide (BNP) in patients with an eGFR less than 30 ml/min/1.73 m^2.[16] Patients presenting with a standard Mayo Clinic stage III and very high concentrations of NT-proBNP (>8500 ng/l) or systolic hypotension (<100 mm Hg) have a poor prognosis, most of them dying within a few weeks from diagnosis.[17] At variance with cardiac involvement, the effect of kidney involvement on survival is not major but may limit the access to effective treatments. A recent staging system for renal involvement is used to predict the risk for dialysis and relies on the measurement of eGFR and proteinuria.[18] Proteinuria greater than 5 g/24 h and eGFR less than 50 ml/min/1.73 m^2 are predictive of a high risk for progression to dialysis, respectively 60% and 85% at 3 years.

Treatment and Outcome

Treatment of systemic AL amyloidosis relies mainly on chemotherapy to suppress the underlying clonal plasma cell. Consensus criteria to define hematologic and organ responses to treatment have been validated to identify early refractory patients.[19] These criteria should be assessed at least every 2 cycles or 3 months. "Partial response" is defined by a 50% or greater reduction in the difference between serum levels of free κ and λ (dFLC), "very good partial response" by a dFLC below 40 mg/l, and "complete response" by the absence of a detectable monoclonal immunoglobulin with normal serum FLC and κ/λ ratio (in the absence of renal impairment). Because organ response is highly correlated with the hematologic response and is predictive of overall survival, the treatment aim is to achieve at least a very good partial response. In the responders, gradual regression of AL amyloid deposits is possible. Clinical improvement does not parallel regression of amyloid load. Scintigraphy after injection of [^{123}I]-SAP component may be helpful for monitoring the extent of systemic amyloidosis, but this imaging technique is not readily available.

Patients with AL amyloidosis can be classified as at low, intermediate, or high risk. Only low-risk patients are potential candidates for high-dose melphalan followed by autologous stem cell transplantation (ASCT). These patients represent about 15% to 20% of all cases and are characterized by age younger than 65 years; an excellent performance status; levels of NT-proBNP and cTnT lower than 5000 ng/ml and 0.06 ng/ml, respectively; preserved renal function; and the absence of autonomic neuropathy or amyloid-related GI bleeding. The other patients, and more particularly those with cardiac cTnT levels higher than 0.06 ng/ml or NT-proBNP levels higher than 5000 ng/l, should not be considered candidates for ASCT because of unacceptable transplant-related mortality. Most patients are at intermediate risk (ineligible for ASCT, stages I to IIIa) and are treated with combination chemotherapy regimens, such as melphalan-dexamethasone (MDex), cyclophosphamide-bortezomib-dexamethasone (CyBorD), bortezomib-melphalan-dexamethasone (BMDex), or cyclophosphamide-thalidomide-dexamethasone (CTD).[20] Most of the studies evaluating these regimens are retrospective and not randomized, limiting the comparison of their efficacy and making selection of the best treatment difficult. Immune-modulatory drugs such as thalidomide, lenalidomide, and pomalidomide are used as rescue treatment for patients refractory to first-line regimens or those who relapse but cannot repeat front-line therapy. High-risk patients (stage IIIb) should be treated with low-dose chemotherapy under very close monitoring because of the risk to destabilize organ function with high doses of dexamethasone and bortezomib. Bortezomib may be preferred because of its rapidity of action.

Supportive therapy is aimed at sustaining organ function with specific modalities such as salt restriction and diuretics for edema, adequate nutritional support, octreotide to control diarrhea, pacemaker implantation in patients with recurrent arrhythmic syncope, fitted elastic leotards and midodrine for hypotension, or gabapentin or pregabalin for neuropathic pain. Angiotensin-converting enzyme inhibitors are generally poorly tolerated because of hypotension.

Except for those with advanced cardiac disease who may benefit from urgent heart transplantation, survival of patients with AL amyloidosis has improved in the last decade, with 4-year overall survival ranging from 40% to 60%. In patients eligible for ASCT, the hematologic response rate exceeds 70% (with 35% of complete response) and the overall median survival is 7.6 years.[21] About half of these patients in complete response are projected to be alive at 14 years, raising the hope that they might be cured. Intermediate-risk patients treated with MDex have comparable results to that observed with ASCT, with hematologic response rate of 76% (31% of patients obtaining complete response) and a median overall survival of 7.3 years. The use of bortezomib is associated with higher hematologic response rate but fails to demonstrate an overall survival advantage.

Emerging therapies are flourishing and include daratumumab, a monoclonal antibody that targets plasma cell antigen CD38, passive immunotherapies with antibodies directed against conformational epitopes of both light chains or against human AL amyloid deposits with the aim of fostering their reabsorption, stabilizers of λ dimers, and small compounds that activate the unfolded protein response.[22]

DIALYSIS AND TRANSPLANTATION

Most studies of the clinical course and outcome of dialysis patients include both AL and AA amyloidosis. Patient survival is about 70% at 1 year and decreases to 30% to 44% at 5 to 6 years. Median survival is shorter in patients with AL amyloidosis (26 to 39 months) than with AA amyloidosis; sepsis and cardiac deaths are the main causes of mortality.[23] Cardiac amyloid is the most important predictor of mortality in dialysis patients with AL amyloidosis.[23]

The management of patients with AL amyloid on hemodialysis is often complicated by persistent hypotension, GI hemorrhage, chronic diarrhea, and difficulties in the creation and maintenance of vascular access. Survival of AL and AA amyloidosis patients treated with peritoneal dialysis (PD) is similar to that of patients receiving hemodialysis.

Kidney transplantation is limited by the severity of heart involvement and the recurrence of deposits in the transplanted kidney. It may be offered to select patients who have achieved persistent hematologic remission, at least for 1 year. When solid-organ transplantation is considered (heart, liver, kidney), it should be preceded or followed by chemotherapy to avoid systemic progression and amyloid recurrence on the transplanted organ.[24] Patient survival was 9 years in those who had achieved at least a partial clonal response after kidney transplantation, versus 5 years in those who had no response.[25]

Inflammatory (Secondary) Amyloidosis (AA Amyloidosis)

Epidemiology

AA amyloidosis develops in 5% of patients with sustained elevation of serum amyloid A protein (SAA). Patients at risk are those with a long duration of chronic inflammatory disease (median 17 years), high magnitude of acute-phase SAA response, homozygosity for SAA1 genotype, familial Mediterranean fever (FMF) trait (heterozygosity for variant pyrin), or other family history of AA amyloidosis.[26]

An important epidemiologic aspect of AA amyloidosis is the changing spectrum of underlying disease. Pyogenic and granulomatous infections, especially tuberculosis, account for far fewer cases (now only 15%) than previously.[26] In these patients, antibiotic treatment efficiently prevents AA amyloidosis by suppressing its cause. In contrast, the relative proportion of chronic inflammatory arthritis has increased by 60%.[26] However, it may be expected that effective disease-modifying treatments of these conditions will induce a decline in the incidence of AA amyloidosis. AA amyloidosis can be observed in a variety of other diseases, such as inflammatory bowel disease, non-ANCA systemic vasculitis, neoplasia, and immunodeficiency states. Hereditary AA amyloidoses associated with familial recurrent fever syndromes account for an increasing proportion of cases, about 10% in recent series.

Clinical Manifestations

Table 27.4 provides clinical features of AA amyloidosis.[26] The main target organ is the kidney, which is affected in almost all patients with AA amyloidosis. Presentation may be acute with nephrotic syndrome or very insidious. Proteinuria is absent in about 5% of cases. GI disturbances (e.g., diarrhea, constipation, malabsorption) and hepatosplenomegaly are the next most common manifestations. In contrast to AL amyloidosis, congestive heart failure (CHF), peripheral neuropathy, macroglossia, and carpal tunnel syndrome occur infrequently.

TABLE 27.4 Characteristics at Presentation of 374 Patients With Systemic Secondary (AA) Amyloidosis

Age, yr (range)	50 (9-87)
Male gender	210 (56%)
Race or Ethnic Group	
White	307 (82%)
South Asian	27 (7%)
Other	40 (11%)
Duration of Inflammatory Disease at Diagnosis (yr)	
Median	17
Range	0-68
Renal Dysfunction	
Proteinuria >500 mg/day or serum creatinine >133 μmol/l	363 (97%)
End-stage renal disease	41 (11%)
Proteinuria, g/day median (range)	3.9 (0-26.0)
Liver Involvement	
Hepatomegaly, no. (%)	35 (9%)
Deposits on SAP scintigraphy	85 (23%)
Splenic Involvement	
Deposits on SAP scintigraphy	370 (99%)
Cardiac Involvement	
Cardiac failure, no.	1
Cardiac infiltration, no.	2

From reference 26.

Diagnosis

Because only half of the patients in whom amyloid was found on renal tissue at autopsy are reported to have proteinuria before death, some recommend a systematic search for amyloidosis in patients with active, long-lasting inflammatory arthritis, even in the absence of proteinuria and CKD. The identification of even asymptomatic amyloid deposits should prompt more effective control of inflammation. Although findings on kidney biopsy are positive in almost 100% of symptomatic patients, less invasive biopsy procedures should be attempted first. Biopsies of accessory salivary glands and abdominal fat yield positive results in more than 80% of patients. Immunohistochemical staining using antibodies to SAA is required to confirm that Congo red–positive amyloid deposits are of the AA type. SAP scintigraphy shows that bones are not affected (unlike AL amyloidosis).

Natural History and Treatment

Average survival time of patients with AA amyloidosis is 133 months, much longer than with AL amyloidosis.[26] Main causes of death are infections and dialysis-related complications but not cardiac complications. Amyloid load and clinical outcome relate to circulating concentrations of SAA. The relative risk for death among patients with an SAA concentration below 4 mg/l is almost 18 times lower than in those with an SAA concentration of 155 mg/l or greater. Even a very modest elevation in the SAA concentration of 4 to 9 mg/l is associated with a risk for death increased by a factor of 4. These data emphasize the importance of vigorous treatment of the underlying inflammatory disease. SAA (preferable to C-reactive protein) serum levels should be monitored monthly and maintained at a target value of less than 4 mg/l.[26]

Amyloid deposits regress in 60% of patients who have a median SAA concentration below 10 mg/l, and survival in these patients is superior to survival when amyloid deposits do not regress. Other factors associated with increased mortality are older age and ESRD.

Eprodisate, a member of a newer class of compounds interfering with interactions between amyloidogenic proteins and GAGs, thus inhibiting polymerization of amyloid fibrils, slowed decline of renal function in patients with AA amyloidosis.[27] However, eprodisate had no beneficial effect on proteinuria, ESRD, amyloid content of abdominal fat, or mortality risk. The combination of CPHPC and anti-SAP antibody, as well as new biologics, are currently under evaluation.[22] Emphasis should remain on treatment of the underlying inflammatory disorder.

Most patients receiving renal transplantation in AA amyloidosis are those with rheumatic diseases. Amyloid deposits recur in about 10% of the grafts. Infections and cardiovascular events are the main causes of early death and require careful management.[28]

Familial Mediterranean Fever and Other Hereditary Recurrent Fever Syndromes

FMF represents a particular type of AA amyloidosis and is the most frequent cause of familial amyloidosis. FMF is usually transmitted as an autosomal recessive disorder and occurs most often in Sephardic Jews and Armenians. It is caused by mutations of the *MEFV* gene encoding a protein called pyrin, or marenostrin. Clinically, there are two independent phenotypes. In the first, brief episodic, febrile attacks of peritonitis, pleuritis, or synovitis occur in childhood or adolescence and precede the renal manifestations. In the second phenotype, renal symptoms precede and may long be the only manifestation of the disease. The attacks are accompanied by dramatic elevations of acute phase reactants, including SAA. Amyloid deposits are responsible for severe renal lesions with prominent glomerular involvement, leading to ESRD at a young age, and for early death.

Colchicine can prevent the development of proteinuria, may occasionally reverse nephrotic syndrome, and may prevent eGFR decline in patients with non-nephrotic proteinuria. It is less effective in preventing progression in patients with nephrotic syndrome or renal impairment. The minimum daily dose of colchicine for prevention of amyloidosis is 1 mg, and patients with clinical evidence of amyloidotic kidney disease should receive daily doses of 1.5 to 2 mg. However, about 10% of patients are unresponsive to colchicine and others are intolerant. Interleukin-1 receptor (IL-1R) antagonists are second-line agents in those patients.

The recent identification of genes responsible for syndromes of periodic fever with amyloidosis has led to a molecular diagnosis of hereditary AA amyloidosis. These syndromes include TNF-α receptor–associated periodic fever syndrome, Muckle-Wells syndrome, and familial cold autoinflammatory syndrome. Only a few cases of systemic AA amyloidosis have been reported in the hyperimmunoglobulinemia D with periodic fever syndrome. Most of these conditions can be controlled by means of anti–IL-1 or anti-TNF-α agents.

MONOCLONAL IMMUNOGLOBULIN DEPOSITION DISEASE

History and Definition

It was known from the late 1950s that nonamyloidotic forms of glomerular disease "resembling the lesion of diabetic glomerulosclerosis" could occur in multiple myeloma. Subsequently, monoclonal light chains were detected in these lesions.[29]

In clinical and pathologic terms, light-chain, light- and heavy-chain, and heavy-chain deposition disease (LCDD, LHCDD, and HCDD, respectively) are similar and therefore may be referred to as monoclonal immunoglobulin deposition disease (MIDD). These forms differ from amyloidosis in that the deposits lack affinity for Congo red and do not have a fibrillar organization. The distinction also relates to different molecular mechanisms of amyloid, which implicates one-dimensional elongation of a pseudocrystalline structure, and MIDD, which rather involves a one-step precipitation of immunoglobulin chains.

Epidemiology

MIDD is a rare disease that may occur in a wide range of ages (<30 to >90 years), with a male preponderance.[30] In MIDD, only 60 patients with HCDD have been described thus far[31] but the disease most likely remains underdiagnosed. MIDD is the second most frequent glomerulopathy in plasma cell dyscrasias, found in about 5% of patients with multiple myeloma at autopsy, approximately half the incidence of AL amyloidosis.[32] Conversely, the prevalence of multiple myeloma is higher than in patients with AL amyloidosis, being found in approximately 50% of patients with LCDD or LHCDD and 20% of those with HCDD. MIDD occasionally may occur with Waldenström macroglobulinemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma. The remaining patients can be classified as having MGRS.[9]

Pathogenesis

The pathogenesis of MIDD involves the kidney deposition of monoclonal immunoglobulin subunits inducing a dramatic accumulation of extracellular matrix. However, light-chain deposition does not mean pathogenicity and singular properties of light chains or heavy chains are most likely required for completion of the pathogenetic process that leads to kidney fibrosis. The same light chain can form granular aggregates or amyloid fibrils, depending on the environment, and different, partially folded intermediates of the light chain may be responsible for amorphous or fibrillar aggregation pathways.

HCDD also may be associated with unique heavy chains. A deletion of the first constant domain C_H1 was found in deposited or circulating heavy chains in patients with γ-HCDD.[31,33] In the blood, the deleted heavy chain either was associated with light chains or circulated in small amounts as a free unassembled subunit. It is likely that the C_H1 deletion facilitates the secretion of free heavy chains that are rapidly cleared from the circulation by organ deposition.[34] Partial or complete deletion of the variable V_H domain in heavy-chain disease without HC deposition suggests that this domain is required for tissue precipitation in HCDD.

A striking feature of light-chain deposition disease (LCDD) and HCDD is extracellular matrix accumulation. Nodules are made of normal matrix constituents. In cultured mesangial cells, LCDD light chains enhance the production of tenascin-C and profibrotic cytokines, such as transforming growth factor β and platelet-derived growth factor. It has been suggested that light chains bind an as-yet unidentified common caveolae-associated receptor on mesangial cells and induce their phenotypic transformation into myofibroblasts with increased synthesis of extracellular matrix constituents and reduced secretion of matrix metalloproteinases.

Clinical Manifestations

MIDD is a systemic disease with immunoglobulin-chain deposition in a variety of organs, although visceral immunoglobin-chain deposits may be totally asymptomatic. MIDD typically presents in the sixth decade.

Renal Manifestations

Renal involvement is an almost constant feature of MIDD, and renal symptoms, mostly proteinuria and CKD, often dominate the clinical presentation.[35] In 18% to 53% of patients with LCDD, albuminuria is associated with nephrotic syndrome. In about one fourth, however, albuminuria is less than 1 g/day and these patients have clinical features suggesting tubulointerstitial disease.[36] Hematuria is more common than would be expected for a nephropathy in which cell proliferation is usually modest. Patients with HCDD appear to have a higher prevalence of hypertension, hematuria, and nephrotic-range proteinuria, reaching 70% at diagnosis, associated with nodular glomerulosclerosis.[31]

The high prevalence of greater than 80%, early appearance, and severity of CKD are other salient features of MIDD. In most cases, GFR declines rapidly, which is a main reason for referral. CKD occurs with comparable frequency in patients with either low or high protein excretion and may manifest in the form of subacute tubulointerstitial nephritis or rapidly progressive glomerulonephritis (RPGN), respectively.

Extrarenal Manifestations

Liver and cardiac manifestations occur in about 25% of patients with LCDD and LHCDD. Liver deposits are constant. They are either discrete and confined to the sinusoids and basement membranes of biliary ductules without associated parenchymal lesions or massive with marked dilation and multiple ruptures of sinusoids, resembling peliosis. Hepatomegaly with mild alterations of liver function test results is the most common symptom, but patients also may develop life-threatening hepatic insufficiency and portal hypertension.

Cardiac involvement may be responsible for cardiomegaly and severe heart failure. Arrhythmias, conduction disturbances, and CHF are seen, with diastolic dysfunction and reduction in myocardial compliance similar to that found in cardiac amyloidosis.

Deposits may occur along the nerve fibers and in the choroid plexus, as well as in the lymph nodes, bone marrow, spleen, pancreas, thyroid gland, submandibular glands, adrenal glands, GI tract, abdominal vessels, lungs, and skin. They may be responsible for peripheral neuropathy

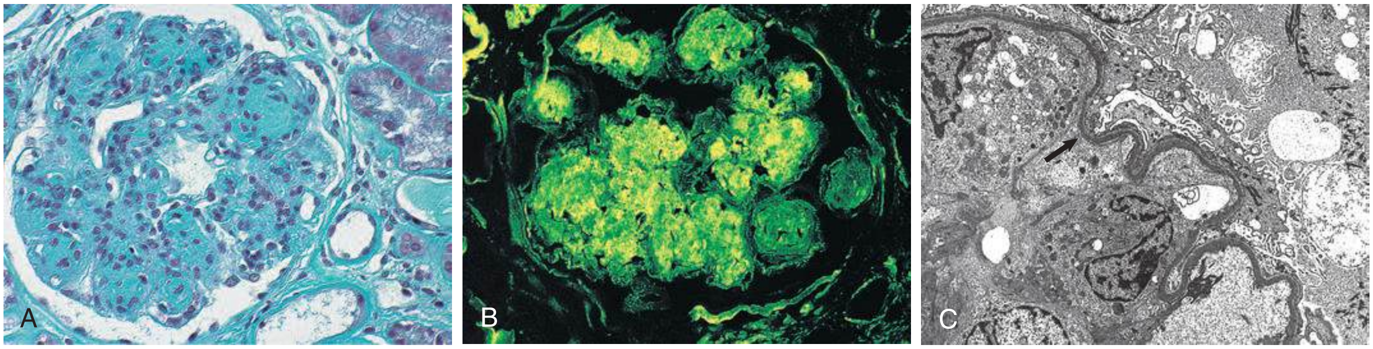

Fig. 27.6 Light-chain deposition disease. (A) Nodular glomerulosclerosis with mesangial matrix accumulation. (Masson trichrome stain; ×312.) (B) Staining of mesangial nodules and tubular basement membranes with anti-κ antibody. (Immunofluorescence; ×312.) (C) Electron micrograph showing a layer of dense granular deposits *(arrow)* under the endothelium along the glomerular basement membrane. (×2500.) (Courtesy Dr. Béatrice Mougenot, Paris.)

(20% of the reported cases), GI disturbances, pulmonary nodules, amyloid-like arthropathy, and sicca syndrome. Extrarenal deposits seem to be less common in patients with HCDD.

Pathology

Light Microscopy

Tubular lesions are characterized by the deposition of a refractile, eosinophilic, periodic acid–Schiff (PAS)-positive, ribbon-like material along the outer part of the tubular basement membranes. The deposits predominate around the distal tubules, the loops of Henle, and, in some instances, the collecting ducts, whose epithelium is flattened and atrophied. Typical myeloma casts are only occasionally seen in pure forms of MIDD. In advanced stages, a marked interstitial fibrosis including refractile deposits is frequently associated with tubular lesions.

Glomerular lesions are heterogeneous. Nodular glomerulosclerosis is found in about two thirds of patients with LCDD (Fig. 27.6A), and in almost all patients with HCDD, being a characteristic feature of this disease. Mesangial nodules are composed of PAS-positive, membrane-like material and are often accompanied by mild mesangial hypercellularity. Lesions resemble diabetic nodular glomerulosclerosis, with distinctive characteristics; the distribution of the nodules is fairly regular in a given glomerulus, the nodules are often poorly argyrophilic, and exudative lesions (e.g., fibrin caps and extensive hyalinosis of efferent arterioles) are not observed. In occasional cases with prominent endocapillary cellularity and mesangial interposition, the glomerular features mimic membranoproliferative glomerulonephritis (MPGN). Crescents are very uncommon except in α-HCDD.[31] Milder forms of LCDD show increased mesangial matrix or cells and modest GBM thickening, with abnormal brightness and rigidity. Glomerular lesions may be detectable only by immunostaining or ultrastructural examination in early stages.

Arteries, arterioles, and peritubular capillaries all may contain PAS-positive deposits in close contact with their basement membrane. Deposits do not show the staining characteristics of amyloid, but Congo red–positive amyloid deposits co-occur in approximately 10% of patients.[35]

Immunohistology

Immunohistology is central in the diagnosis of the various forms of MIDD. A criterion required for the diagnosis of MIDD is monotypic light-chain (mainly κ; Fig. 27.6B) or heavy-chain fixation along tubular basement membranes. The tubular deposits stain strongly and predominate along the loops of Henle and the distal tubules, but also often are detected along the proximal tubules. In contrast, glomerular immunohistology patterns display marked heterogeneity. In patients with nodular glomerulosclerosis, deposits of monotypic immunoglobulin chains are usually found along the peripheral GBM and to a lesser extent in the nodules themselves (see Fig. 27.6B). A linear staining usually decorates the Bowman capsule. Deposits are common in vascular walls and interstitium.

In patients with HCDD, immunohistology with anti–light-chain antibodies is negative despite typical nodular glomerulosclerosis. Monotypic deposits of γ, α, or μ chains may be identified. Any γ subclass may be observed. If immunofluorescence fails to detect light chains or γ-, α-, or μ heavy chains, IgD HCDD should be suspected and may require the use of laser microdissection and mass spectrometry.[37] Analysis of the kidney biopsy specimen with monoclonal antibodies specific for the constant domains of the γ heavy chain allowed identification of a deletion of the C_H1 domain in all tested cases. In most cases of γ1 or γ3 HCDD, complement components including C1 could be demonstrated in a granular or pseudolinear pattern. Complement deposits are often associated with signs of complement activation in serum.

Eculizumab treatment of dense deposit disease was shown to induce an HCDD-like pathology, although the clinical significance of this is not completely known.[38]

Electron Microscopy

The most characteristic ultrastructural features on EM are finely to coarsely granular electron-dense deposits along the outer (interstitial) aspect of the tubular basement membranes. In the glomerulus, the deposits are predominantly in a subendothelial position along the GBM and are located mainly along and in the lamina rara interna (see Fig. 27.6C). Deposits also can be found in mesangial nodules, the Bowman capsule, and the wall of small arteries between the myocytes.

Diagnosis

The diagnosis of MIDD must be suspected in any patient with nephrotic syndrome or rapidly progressive tubulointerstitial nephritis or with echocardiographic findings indicating diastolic dysfunction and the presence of a monoclonal immunoglobulin component in the serum or the urine (see Fig. 27.5). Sensitive techniques such as immunofixation fail to identify a monoclonal immunoglobulin component in 10% to 20% of patients with MIDD, although the serum FLC ratio is consistently abnormal.[30] The kidney biopsy thus plays an essential role in the diagnosis of MIDD and the associated dysproteinemia.

The diagnosis of plasma cell dyscrasia relies on bone marrow aspiration and bone marrow biopsy with cell morphologic evaluation and, if necessary, immunophenotyping with anti-κ and anti-λ antisera to demonstrate monoclonality.

Treatment and Outcome

The outcome of MIDD remains uncertain, mainly because extrarenal deposits of light chains can be totally asymptomatic or cause severe organ damage leading to death. As in AL amyloidosis, treatment of patients with MIDD should be aimed at reducing immunoglobulin production.[39] Monitoring of light-chain production should rely on serum FLC assay, particularly when a blood or urine monoclonal component cannot be detected by conventional methods.

Most patients treated with high-dose melphalan and stem cell transplant achieve a hematologic and organ response with very low treatment-related mortality.[39] However, the role of stem cell transplantation is now challenged by highly effective new drugs, such as bortezomib. In 49 patients treated with a combination of bortezomib and dexamethasone, with or without cyclophosphamide, the overall hematologic response rate was 91% after a median follow-up of 54 months and a renal response rate was achieved in 26 patients, with a 35% increase in median eGFR and an 86% decrease in median 24-hour proteinuria.[40] To reduce the risk for disease recurrence in the graft, only patients who achieve a complete hematologic response should be candidates for renal transplantation.[41]

The outcome of patients with MIDD has improved with a reduction in the rate of ESRD and mortality, respectively, at 20% and 10%.[40] Such improvement is explained by earlier diagnosis and more potent chemotherapeutic regimens. Predictors of renal survival include a lower initial serum creatinine level and post-treatment difference between involved and uninvolved serum-FLCs under 40 mg/l (defining a very good partial hematologic response). Several variables have been independently associated with worse patient survival: older age, associated multiple myeloma, extrarenal LC deposition, and lytic bone lesions.[30] Nodular mesangial lesions and light-chain deposits may be reversible after effective chemotherapy.

Renal Diseases Associated With Monoclonal Immunoglobulin Deposition Disease

Myeloma cast nephropathy is found in about a third of patients with MIDD.[35] Clinical features and outcomes of MIDD and minimal change disease (MCN) more closely resemble those in MCN than pure MIDD. Nodular glomerulopathy is uncommon (<10%), some ribbon-like tubular basement membranes are seen in less than half the patients, and a third of the patients do not have granular dense deposits on EM. Renal and patient survival is significantly worse.

Amyloid deposits are found in one or more organs in about 7% of LCDD patients. Because amyloid deposits are focal, their true incidence may be greatly underestimated. It is possible that the coexisting diseases are induced by different variant clones.

NONAMYLOID FIBRILLARY AND IMMUNOTACTOID GLOMERULOPATHIES

Fibrillary and immunotactoid glomerulopathies are characterized, respectively, by fibrillar and microtubular deposits in the mesangium and the glomerular capillary loops (Table 27.5). These deposits do not have an amyloid-like cross-β structure and are readily distinguishable from amyloid on EM by the larger thickness of fibrils and lack of Congo red staining.

Epidemiology

The incidence of glomerulopathy with nonamyloid deposition of fibrillar or microtubular material in a nontransplant adult biopsy population is estimated at around 1%. It is most likely underestimated because of the insufficient attention given to atypical reactions with histochemical amyloid stains and the frequent lack of immune-ultrastructural studies. Only immunotactoid glomerulopathy has a significant association with underlying dysproteinemia, whereas fibrillary glomerulonephritis (FGN) has a wide spectrum of etiologies.[43] At variance with immunotactoid

TABLE 27.5 Immunologic and Clinical Characteristics of Fibrillary and Immunotactoid Glomerulopathies

Characteristics	Amyloidosis (AL Type)	Fibrillary Glomerulopathy	Immunotactoid Glomerulopathy
Congo red staining	Yes	No	No
Composition	Fibrils	Fibrils	Microtubules
Fibril or microtubule size	8-15 nm	12-22 nm	>30 nm*
Organization in tissues	Random (β-pleated sheet)	Random	Parallel arrays
Immunoglobulin deposition	Monoclonal LC (mostly λ)	Usually polyclonal (mostly IgG4), occasionally monoclonal (IgG1, IgG4)	Usually monoclonal (IgGκ or IgGλ)
Glomerular lesions	Deposits spreading from mesangium	MPGN, CGN, MP	Atypical MN, MPGN
Renal presentation	Severe NS, absence of hypertension and hematuria	NS with hematuria, hypertension; RPGN	NS with microhematuria and hypertension
Extrarenal manifestations (fibrillar deposits)	Systemic deposition disease	Pulmonary hemorrhage	Microtubular inclusions in leukemic lymphocytes
Association with LPD	Yes (myeloma)	Uncommon	Common (CLL, NHL, MGUS)
Treatment	Melphalan + dexamethasone; intensive therapy with blood stem cell autograft	Corticosteroids ± cyclophosphamide (crescentic GN)	Treatment of the associated LPD

*Mean diameter of the substructures did not differ between fibrillary glomerulonephritis (15.8 ± 3.5 nm) and immunotactoid glomerulopathy (15.2 ± 7.3 nm) in the series of Bridoux and colleagues.[42]

CGN, Crescentic glomerulonephritis; *CLL,* chronic lymphocytic leukemia; *GN,* glomerulonephritis; *LC,* light chain; *LPD,* lymphoproliferative disorder; *MGUS,* monoclonal gammopathy of undetermined significance; *MN,* membranous nephropathy; *MP,* mesangial proliferation; *MPGN,* membranoproliferative glomerulonephritis; *NHL,* non-Hodgkin lymphoma; *NS,* nephrotic syndrome; *RPGN,* rapidly progressive glomerulonephritis.

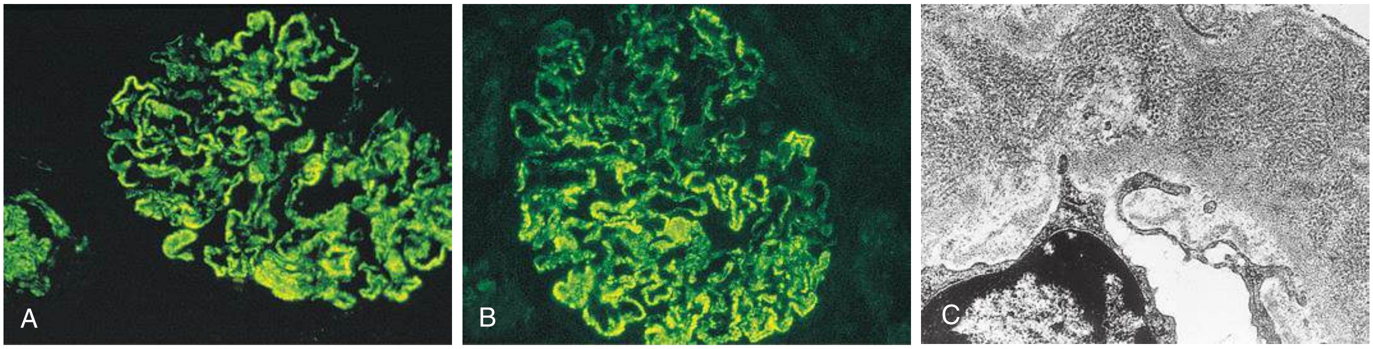

Fig. 27.7 **Immunotactoid glomerulopathy.** Atypical membranous nephropathy showing exclusive staining of the deposits with (A) anti-γ antibodies, and (B) anti-κ antibodies. (Immunofluorescence; ×312.) (C) Electron micrograph of glomerular basement membrane shows microtubular structure of the subepithelial deposits. (Uranyl acetate and lead citrate; ×20,000.) (Courtesy Dr. Béatrice Mougenot, Paris.)

glomerulopathy in which immunoglobulin deposits are usually monoclonal (IgGκ or IgGλ), those described in FGN are usually polyclonal (mostly IgG4).[42] Hematologic malignancy can be present in up to 38% of patients with immunotactoid glomerulopathy, including chronic lymphocytic leukemia in 19%, lymphoplasmacytic lymphoma in 13%, and multiple myeloma in 13%.[44]

Clinical Manifestations

The characteristics of fibrillary and immunotactoid glomerulopathies are described in Table 27.5 in comparison to AL amyloidosis. Patients with immunotactoid and fibrillary glomerulopathies have a mean age of 55 to 60 years (extreme: 19 to 86 years). They usually present with nephrotic syndrome, microscopic hematuria, and mild to severe CKD. Recent series show no significant difference at presentation between patients with immunotactoid and fibrillary glomerulopathy in serum creatinine level, incidence of nephrotic syndrome, microscopic hematuria, hypertension, or CKD. Extrarenal manifestations are uncommon and may involve the lung, skin, and peripheral nervous system.

Pathology

Immunotactoid Glomerulopathy

Renal biopsy shows membranous nephropathy (often associated with segmental mesangial proliferation; Fig. 27.7) or lobular MPGN. Granular deposits of IgG and C3 are observed along capillary basement membranes and in mesangial areas.[44] On EM, the distinguishing morphologic features of immunotactoid glomerulopathy are organized deposits of large, thick-walled microtubules (typically greater than 30 nm in diameter), at times arranged in parallel arrays (see Fig. 27.7C). Intracytoplasmic crystal-like immunoglobulin inclusions can be found in circulating B-lymphocytes of patients with CLL and related lymphoma.[42]

Fibrillary Glomerulopathy

Mesangial proliferation and aspects of MPGN are predominantly reported in series of fibrillary glomerulopathy. Glomerular crescents are present in about 30% of the biopsy specimens. Immunofluorescence studies mainly show IgG deposits mostly of the IgG4 subclass with a predominant mesangial localization. Monotypic deposits containing mostly IgGκ are detected in no more than 15% of patients.[45] On EM, fibrils are randomly arranged and their diameter varies between 12 and 22 nm. The fibril size alone is not sufficient to distinguish nonamyloidotic FGN from amyloid.[42]

One of the most abundant proteins by mass spectrometry is DnaJ heat shock protein family B member 9 (DNAJB9). It remains to be determined whether this protein serves as an autoantigen or whether it accumulates in fibrils because of still unknown unusual physicochemical properties.[42a, 42b, 42c]

Diagnosis

Diagnosis of immunotactoid and fibrillary glomerulopathies relies on EM, which must be performed in patients with atypical membranous nephropathy or MPGN, as well as in those with monotypic deposits in glomeruli. Diagnosis also relies on the detection by immunohistochemistry in glomeruli of DNAJB9 which seems to be a specific marker for fibrillary glomerulopathy (Nasr S, Vrana JA, Dasari S, et al, Kidney int Reports, 2018, accepted). All renal biopsy specimens should be routinely examined with anti-κ and anti-λ light-chain antibodies. In patients with immunotactoid glomerulopathy, lymphoproliferative disease should be sought. Association of immunotactoid and fibrillary glomerulopathy with hepatitis C virus or HIV infection also has been reported.

Outcome and Treatment

Patients with fibrillary glomerulopathy usually respond poorly to corticosteroids and cytotoxic drugs, with an incidence of ESRD of about 50%.[42,44,45] Several reports suggest that they may respond to rituximab.[45] The prognosis of immunotactoid glomerulopathy appears to be better than that of FGN. Therapy directed against the underlying hematologic malignancy usually leads to remission of the nephrotic syndrome.[42,45] Renal transplantation has been performed in a few patients. Disease recurred in several, especially in those with a persistent monoclonal gammopathy.

GLOMERULAR LESIONS ASSOCIATED WITH WALDENSTRÖM MACROGLOBULINEMIA AND OTHER MONOCLONAL IMMUNOGLOBULIN M-SECRETING B CELL LYMPHOPROLIFERATIVE DISORDERS

Symptomatic renal disease is much less common in patients with Waldenström macroglobulinemia than in those with multiple myeloma. Glomerulonephritis with intracapillary thrombi of aggregated IgM (intracapillary monoclonal deposit disease, ICMDD) is the most characteristic entity, which also may occur with other IgM-secreting monoclonal proliferations.[46] On immunohistology, thrombi and deposits stain with anti-μ and with anti-κ. The deposits are electron dense and granular without microtubular organization. Some of these patients have strong activation of the classic complement pathway with or without cryoglobulinemia. The frequency of ICMDD has decreased over time mostly because of improved treatment of Waldenström macroglobulinemia, whereas AL amyloidosis, cryoglobulinemic glomerulonephritis, and MPGN are increasingly encountered.[47] Lymphomatous infiltration of the renal interstitium is present in half of the cases.

Treatment should target the IgM-secreting clone. Renal manifestations usually improve with chemotherapy including rituximab.[47,48]

OTHER TYPES OF GLOMERULONEPHRITIS

In some patients, glomerular deposition of monoclonal IgG can produce a proliferative GN that mimics immune complex GN on light and EM.[49] Proper recognition of this entity, now termed *proliferative glomerulonephritis with monoclonal immunoglobulin deposits* (PGNMID), requires confirmation of monoisotypy by immunostaining for the γ heavy-chain subclasses. The IgG3κ isotype is strikingly overrepresented in PGNMID deposits. Tissue fixation of complement was observed in 90% of cases, and hypocomplementemia was found in 40% of the patients, all of whom had either IgG1 or IgG3 deposits. Clinical presentation included CKD in 80%, proteinuria in 100%, nephrotic syndrome in 44%, and microhematuria in 60%. Minute amounts of a monoclonal serum protein with the same heavy- and light-chain isotype as that of the glomerular deposits was identified in 50% of cases. Only one patient had multiple myeloma at presentation, and none developed hematologic malignancy over the course of follow-up. Proliferative GN with monoclonal IgG deposits may recur in the allograft.

A monoclonal IgM also can be found in PGNMID with an MPGN pattern. Few cases of "proliferative" GN with monoclonal immunoglobulin deposits with a membranous pattern have been reported. The majority of these patients have IgG1 deposits instead of IgG3.[50] A circulating monoclonal IgG could be detected in only one fourth of these patients.

Because PGNMID is a newly described entity and most patients have no overt malignancy, optimal treatment remains to be established. Every effort should be made to identify the type of clonal proliferation (plasmacytic or lymphocytic), which has an impact on the choice of therapy and the expected response.[51] Cyclophosphamide and bortezomib in association with dexamethasone are the drugs of choice in patients with bone marrow plasma cell infiltration or without detectable cell clone, whereas rituximab-based therapy is recommended in patients with a lymphocytic cell clone.

An increasing number of cases of C3 glomerulonephritis (C3GN) and monoclonal gammopathy have been reported. This association is encountered in about 60% of patients with C3GN above 60 years of age.[52] Such association may be related to complement activation through an autoantibody activity of the monoclonal IgG against a complement alternative pathway regulatory protein. In some cases of C3GN, masked monoisotypic IgGκ deposits may be demonstrated on antigen retrieval by pronase digestion.

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SELF-ASSESSMENT QUESTIONS

1. Does AL (light-chain) amyloidosis involve the heart?
   - **A.** A contraindication to cardiac transplantation
   - **B.** Less common than in AA amyloidosis
   - **C.** Primarily responsible for valve dysfunction
   - **D.** A contraindication to hemodialysis
   - **E.** Best evaluated by assessment of brain natriuretic peptide (BNP) in patients with glomerular filtration rate (GFR) <30 ml/min/1.73 m^2
2. Does monoclonal immunoglobulin deposition disease (MIDD) involve the kidney?
   - **A.** A contraindication to kidney transplantation
   - **B.** Characterized by crescent formation
   - **C.** Frequently responsible for nondiabetic glomerulosclerosis
   - **D.** Characterized by microtubular deposits
   - **E.** Caused by deposition of cryoglobulin
3. Which of the following is the key investigation for the diagnosis of immunotactoid glomerulopathy?
   - **A.** Immunofixation of serum proteins
   - **B.** Immunofixation of urinary proteins
   - **C.** Bone marrow aspiration
   - **D.** Immunofluorescence examination of kidney biopsy sample
   - **E.** Electron microscopy
4. Which of the following is the most common clinical sign or symptom caused by MIDD?
   - **A.** Renal failure
   - **B.** Hematuria
   - **C.** Hypertension
   - **D.** Jaundice
   - **E.** Heart failure

28

Rare Glomerular Disorders

Richard J. Glassock

This chapter describes several rather uncommon, often rare, disorders or clinical syndromes that have glomerular disease as a major part of the clinical manifestations and tend to affect mainly adults. These disorders are not necessarily related to each other, and each must be recognized and differentiated from other, far more common, glomerular disorders to determine whether a familial disorder is present, to estimate the prognosis to plan appropriate therapy, or to determine the risk for a recurrence in the transplanted kidney. In addition, the chapter describes the primary and secondary antiphospholipid antibody syndromes in detail.

MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS WITHOUT IgA DEPOSITS

Mesangial proliferative glomerulonephritis (MesPGN) encompasses a heterogeneous collection of disorders having diverse clinical features and a largely unknown etiology and pathogenesis. The common feature of these disorders is a histologic pattern of glomerular injury on light microscopy characterized by diffuse mesangial proliferation[1-4] (Fig. 28.1). Thus MesPGN is noted for a diffuse and global increase in mesangial cells, often accompanied by an increase in mesangial matrix. Other cells (e.g., neutrophils and monocytes) also may contribute to the hypercellularity. Thus MesPGN is a glomerular lesion, *not a specific disease entity.*

For the purpose of this discussion, other forms of cellular proliferation that occur within the mesangial zones but are more focally and segmentally distributed are not included. These focal and segmental forms of proliferative glomerulonephritis (GN), often accompanied by areas of segmental necrosis of the glomerular tufts and very localized crescents, may accompany the evolution of pure MesPGN, but they often signify the presence of systemic disease, including systemic lupus, IgA-vasculitis (Henoch-Schönlein purpura) and IgA nephropathy, infective endocarditis, microscopic polyangiitis, granulomatous polyangiitis, Goodpasture disease, rheumatoid vasculitis, and mixed connective tissue disease. On occasion, focal and segmental proliferative GN is discovered in the absence of any recognizable multisystem disease process and in the absence of IgA deposits (i.e., idiopathic focal and segmental proliferative GN). Such patients have a clinical presentation, course, and response to treatment that are similar to those described for pure MesPGN, but they are not discussed further in this section.

In "pure" MesPGN, the peripheral capillary walls are thin and delicate, without obvious deposits, reduplication, focal disruptions, or cellular necrosis. The visceral and parietal epithelial cells, although occasionally enlarged, have not undergone proliferation. Crescents and segmental sclerosis should be absent in the pure form of the disorder. In addition, large deposits staining with periodic acid–Schiff (PAS) or fuchsin in the mesangium should be absent, because these deposits suggest IgA nephropathy (see Chapter 23), lupus nephritis (LN; see Chapter 26), or C3 glomerulonephritis (see Chapter 22), which may commonly manifest as a mesangial proliferative lesion. Postinfectious glomerulonephritis (as a result of streptococcal or nonstreptococcal microbial infections) also may cause a lesion of MesPGN. The tubulointerstitium and vasculature are usually normal, unless reduced renal function or hypertension is present or the patient is of advanced age.

On immunofluorescence (IF) microscopy, a wide variety of patterns of immunoglobulin and complement deposition are observed (Table 28.1). Most often, diffuse and global IgM and C3 deposits are found scattered throughout the mesangium in a granular pattern (so-called IgM nephropathy, see later discussion), but isolated C3, C1q, or even IgG deposits may also be seen.[5-7] If IgA is the predominant immunoglobulin deposited, the diagnosis is IgA nephropathy. In some cases, no immunoglobulin deposits are found. Prominent C3 deposition in the absence of immunoglobulin deposition should suggest C3 glomerulopathy (see Chapter 22).[7] Extensive C1q deposits, with or without immunoglobulin deposits should suggest C1q nephropathy (see later discussion).[8] On electron microscopy (EM), the number of mesangial cells is increased, with an occasional leukocyte. The amount of mesangial matrix is frequently but not invariably diffusely increased. Electron-dense deposits within the mesangium often can be seen. Very large mesangial or paramesangial electron-dense deposits suggest IgA nephropathy even if IF microscopy is not available. Subendothelial, intramembranous, or subepithelial deposits are not seen. If present, these suggest a postinfectious etiology or an underlying disease such as LN or C3 glomerulopathy. Deposits of multiple immunoglobulin classes identified by immunohistology and large numbers of tubuloreticular inclusions on EM suggest underlying LN.

The clinical presentation of MesPGN is quite varied, although persistent or recurring microscopic or macroscopic hematuria with mild proteinuria is most common. It commonly affects young adults,[1,2] with a slight male predominance. Nephrotic syndrome with heavy proteinuria is a less frequent initial presentation but is seen more often in association with diffuse mesangial IgM deposits (IgM nephropathy; see later discussion),[3] C1q deposits (C1q nephropathy)[4] or C3 glomerulonephritis.[5] Pure MesPGN is a rather uncommon lesion (<5%) in patients diagnosed with idiopathic nephrotic syndrome. In some countries, such as India and China, MesPGN is found in 10% to 15% of renal biopsy samples, but the frequency is much less in well-developed countries. Lesions of MesPGN have been observed in acute parvovirus B19 disease and in association with Castleman disease.

Renal function and blood pressure are usually normal, at least initially. Serologic studies are generally unrewarding. Serum C3 and C4

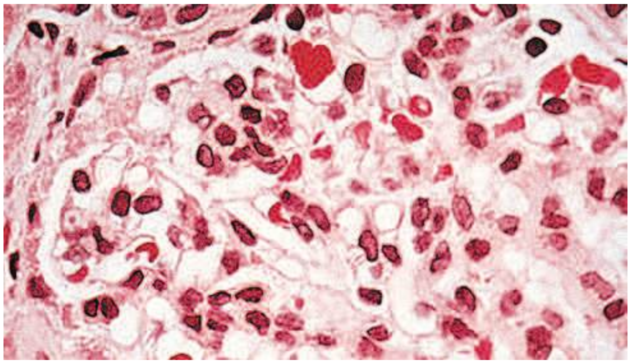

Fig. 28.1 Pure mesangial proliferative glomerulonephritis (MesPGN). Note the increase in mesangial cellularity, the delicate peripheral capillary walls, and the absence of sclerosis or parietal epithelial cell proliferation. (Hematoxylin-eosin stain; magnification ×410.) (Modified from Churg J, Berstein J, Glassock R. *Renal Disease: Classification and Atlas of Glomerular Disease.* New York: Igaku-Shoin; 1995.)

TABLE 28.1 Immunofluorescence Microscopy Patterns in Mesangial Proliferative Glomerulonephritis

Pattern	Associated Disorders
Predominantly mesangial IgA deposits (± IgM, C3)	IgA nephropathy
Predominantly mesangial IgG deposits (± IgM, C1q, C3)	Often associated with lupus nephritis
Predominantly mesangial IgM deposits (± C3)	IgM nephropathy
Mesangial C1q deposits (± IgG, IgM, C3)	C1q nephropathy
Isolated mesangial C3 deposits	Often associated with resolving poststreptococcal GN or C3 GN
Negative for immunoglobulin or complement deposits	Idiopathic MesPGN

GN, Glomerulonephritis; *IgA, Immunoglobulin; MesPGN,* Mesangial proliferative glomerulonephritis.

complement components and hemolytic complement activity (CH50) are typically normal. A low C3 and normal C4 level suggests C3 glomerulopathy or poststreptococcal GN. Antinuclear antibody (ANA), antineutrophil cytoplasmic autoantibody (ANCA), anti–glomerular basement membrane (anti-GBM) autoantibody, and cryoimmunoglobulins are negative. Nevertheless, these studies should be performed in most patients to exclude known causes. MesPGN also can be found in resolving postinfectious (poststreptococcal) GN, often with isolated C3 deposits with scanty, subendothelial or subepithelial (hump-like) deposits on EM. Urinary protein biomarkers may help determine prognosis.[6] MesPGN also can be seen in non-poststreptococcal GN.

The prognosis of non-IgA MesPGN is quite variable depending on the underlying IF findings (see later discussion of IgM and C1q nephropathy), but it is often benign. The 30-year renal survival has been estimated to be 50%.[2] Severe and persistent nephrotic syndrome is a sign of a poor prognosis, particularly in males.[2] Patients with nephrotic syndrome may evolve to typical focal and segmental glomerulosclerosis over time.

The treatment of pure MesPGN, unaccompanied by other underlying diseases or lesions such as systemic lupus erythematosus (SLE), minimal change disease (MCD) lesion, or IgA nephropathy, is not well defined.[1,2] No randomized controlled trials (RCTs) have been performed because of the uncommon nature of the disorder. The prognosis for patients with isolated hematuria or hematuria combined with mild proteinuria (<500 mg/day) is generally benign, and thus no treatment other than management of hypertension is needed, unless a distinct change in the course is observed. Repeat renal biopsy may be indicated in such circumstances. For patients with nephrotic syndrome (with or without impaired renal function), a more aggressive approach is often recommended, especially in the presence of diffuse IgM deposits, as discussed later (IgM nephropathy), because many such patients will eventually progress to focal segmental glomerulosclerosis (FSGS). Even in the absence of RCTs, an initial course of corticosteroid therapy may be justified in most patients with nephrotic-range proteinuria, such as prednisone, 60 mg/day or 120 mg every other day for 2 to 3 months, followed by lowered doses on alternate-day regimen for 2 to 3 additional months. About 30% to 50% of these patients experience a decrease in proteinuria to subnephrotic levels, and complete remissions may occur. Relapses of proteinuria are common when steroids are tapered or discontinued. Such relapsing, partially corticosteroid-responsive patients might benefit from the addition of cyclophosphamide, chlorambucil, cyclosporine, mycophenolate mofetil (MMF), or rituximab to the regimen, although information on the efficacy and safety of these agents in pure MesPGN is limited.

Patients with persistent treatment-unresponsive nephrotic syndrome will almost invariably progress to ESRD, accompanied by a conversion to a lesion of FSGS over several years. Whereas transplantation is not contraindicated, patients who do progress to ESRD rapidly and develop superimposed FSGS may have a high risk for recurrence of proteinuria and FSGS in the transplanted kidney (see Chapters 18 and 108).

Immunoglobulin M Nephropathy

IgM nephropathy is characterized by diffuse and generalized glomerular deposits of IgM often accompanied by C3.[3,7] Mesangial electron-dense deposits are also observed. On light microscopy, a picture of pure MesPGN is usually observed, sometimes with superimposed FSGS.[7] Crescentic disease is very uncommon but may occur. A consensus definition of IgM nephropathy proposed (1) dominant mesangial staining for IgM by IF, (2) mesangial electron-dense deposits by EM, and (3) absence of any identifiable systemic disease.[7] Patients with only IgM deposits by IF but MCD by light microscopy and EM do not have IgM nephropathy, according to this definition. Patients may present with recurring macrohematuria and proteinuria, the latter in the nephrotic range in as many as 40% to 50% of patients.[7] Middle-aged adults are most commonly affected, and there is a slight male predominance.[7]

Glomerulosclerosis (but not the extent of mesangial proliferation), persisting nephrotic syndrome, and a poor response to corticosteroids or immunosuppressive therapy are often seen and connote a poor prognosis. As many as 80% of patients with IgM nephropathy and nephrotic syndrome will eventually progress to typical FSGS and, if unresponsive to corticosteroids, will slowly develop chronic kidney disease (CKD) and end-stage renal disease (ESRD). Patients with IgM deposition accompanying MesPGN but without nephrotic syndrome tend to have a benign course.

Treatment of IgM nephropathy with nephrotic syndrome is highly uncertain, although steroid therapy may be associated with a complete or partial remission in as many as 50% of patients. Anecdotal reports of success with rituximab have appeared. The etiology and pathogenesis are unknown, but IgM deposition itself is believed to be an important pathogenic factor acting to augment complement-mediated injury.

C1q Nephropathy

C1q nephropathy is characterized by IF microscopy showing diffuse marked deposition of C1q, often accompanied by IgG, IgM, or both.[4,8] C3 deposits are observed much less frequently. These immunopathologic

BOX 28.1 Rheumatic Diseases Associated with Glomerular Lesions

Glomerulonephritis With Rheumatic Disease

- Systemic lupus erythematosus (SLE; see Chapter 26)
- Rheumatoid arthritis
- Mixed connective tissue disease
- Rheumatic fever
- Ankylosing spondylitis
- Reiter syndrome
- Dermatomyositis/polymyositis
- Scleroderma
- Relapsing polychondritis
- Systemic or renal-limited polyangiitis (see Chapter 25)

BOX 28.2 Renal Disease in Rheumatoid Arthritis

Glomerular Lesions That May Be Direct Complications of the Disease

- Membranous nephropathy (MN)
- MesPGN (± IgA or IgM deposits)
- Diffuse proliferative GN
- Necrotizing and crescentic GN (rheumatoid vasculitis)
- Amyloidosis (AA type)

Glomerular Lesions Associated With Agents Used in Treatment of Rheumatoid Arthritis

- Gold: MN, MCD, acute tubular necrosis
- Penicillamine: MN, crescentic GN, MCD
- NSAIDs: Acute tubulointerstitial nephritis (TIN) with MCD, acute tubular necrosis, MCD without TIN
- Cyclosporine: Chronic vasculopathy and TIN, focal and segmental glomerulosclerosis (?)
- Azathioprine/6-mercaptopurine: TIN
- Pamidronate: Focal segmental glomerulosclerosis
- TNF-α inhibitors: Lupus-like lesions, crescentic GN

MCD, Minimal change disease; *MesPGN,* mesangial proliferative glomerulonephritis; *NSAIDs,* nonsteroidal antiinflammatory agents; *TIN,* tubulointerstitial nephritis.

features resemble those seen in LN; however, these patients have none of the clinical features of SLE and usually do not develop SLE even after prolonged follow-up. Anti-C1q vasculitis (also known as hypocomplementemic urticarial vasculitis or McDuffie syndrome) can resemble C1q nephropathy, although urticarial lesions and systemic symptoms are more common in anti-C1q vasculitis. These patients also have low levels of serum C1q and elevated anti-C1q auto-antibodies,

The light microscopic lesions of C1q nephropathy are heterogeneous. In addition to MesPGN, other morphologic lesions, including MCD and FSGS, are typically observed by light microscopy. Electron-dense deposits are seen in mesangium, subepithelial, and subendothelial locations as well. Nephrotic-range proteinuria occurs, often with hematuria. Males predominate and African Americans are often affected. Serum C3 components, ANA, and anti–double-stranded DNA (anti-dsDNA) antibodies are consistently normal or negative. The response to treatment is poor, and progression to ESRD may occur, particularly when nephrotic syndrome is present and FSGS lesions are seen by light microscopy. Anecdotal reports of success with immunosuppressive agents, including rituximab, have appeared. Patients with C1q deposits and MCD appear to respond well to conventional steroid therapy.

Mesangial Proliferative Glomerulonephritis Associated With Minimal Change Disease

MesPGN also may be a part of the spectrum of MCD-FSGS lesions (see Chapters 17 to 19). Distinct mesangial hypercellularity superimposed on a lesion of MCD (diffuse foot process effacement seen on EM) may point to a greater likelihood for corticosteroid unresponsiveness and an eventual evolution to the FSGS lesion.

GLOMERULONEPHRITIS WITH RHEUMATIC DISEASE

Several collagen vascular diseases other than SLE may be complicated by GN[9] (Box 28.1), including rheumatoid arthritis (RA), mixed connective tissue disease, polymyositis and dermatomyositis, acute rheumatic fever, scleroderma, and relapsing polychondritis. IgA nephropathy also may be seen in association with the seronegative spondyloarthropathies. Toxic or hypersensitivity reactions to nonsteroidal antiinflammatory drugs (NSAIDs) can contribute to glomerular disease.[10]

Rheumatoid Arthritis

A wide variety of glomerular, tubulointerstitial, and vascular lesions of the kidney may complicate RA (Box 28.2).[9] Clinical abnormalities, including abnormal urinalysis (hematuria, leukocyturia, proteinuria), and reduced renal function are common in patients with severe or long-standing disease RA. Membranous nephropathy (MN) (see Chapter 20) is the most common glomerular lesion, possibly because of the underlying disease itself or in the past as a result of therapy (parenteral or oral gold or penicillamine). The presence of human leukocyte antigen (HLA)-DR3 increases the risk for development of MN in a patient with RA. The lesion is not associated with anti–phospholipase A_2 receptor (anti-PLA$_2$R) autoantibodies.

MN that is associated with RA but not due to medication exposure has a course that is similar to that of the idiopathic disease, although spontaneous remissions are less likely to occur. By comparison, MN associated with drugs used to treat RA is most likely to remit after discontinuance of the drug therapy. Of patients with RA with drug-induced MN, 60% to 80% will remit within 1 year of stopping treatment.

Secondary (AA) amyloidosis (see Chapter 27) is found in 5% to 20% of patients with RA undergoing renal biopsy. Nephrotic syndrome and progressive renal failure are common.

NSAIDs also may produce tubulointerstitial nephritis, MCD, or both simultaneously (see also Chapters 17 and 60). A severe, necrotizing polyangiitis may complicate the course of long-standing RA (rheumatoid vasculitis). These patients may have profound reduction in C3 levels, striking elevation of rheumatoid factors, and marked polyclonal hypergammaglobulinemia. Renal involvement in rheumatoid vasculitis is now relatively uncommon for poorly understood reasons. The use of TNF-α inhibitors for treatment of RA can evoke a picture resembling LN (see Chapter 26).

Mixed Connective Tissue Disease

Mixed connective tissue disease is characterized by features that overlap with those of SLE, scleroderma, and polymyositis. Typically, the serum of such patients contains high-titer autoantibodies to extractable nuclear antigens (ribonucleoprotein-extractable nuclear antigen, U1 ribonucleoprotein antigen). Low titers of anti-dsDNA antibody also may be found. Renal disease, originally thought to be quite rare, is found in 10% to 50% of patients, most frequently MN and MesPGN. Treatment with steroids is generally effective, but some patients exhibit progressive

CKD. Patients with severe GN may respond to treatment regimens similar to those used in the treatment of LN (see Chapter 26).

Polymyositis and Dermatomyositis

The related collagen vascular diseases polymyositis and dermatomyositis are characterized by inflammatory lesions in muscle and variable skin lesions and often include Raynaud phenomenon. On occasion, patients have proteinuria and hematuria secondary to MesPGN with IgM deposits. Acute kidney injury (AKI) may rarely supervene when severe muscle injury and myoglobinuria are present. Treatment with steroids may ameliorate the renal manifestations and improve the muscle and skin manifestations.

Acute Rheumatic Fever

Acute rheumatic fever secondary to a pharyngeal (but not cutaneous) infection with a rheumatogenic strain of group A β-hemolytic streptococci is seldom accompanied by renal disease (see Chapter 55). Poststreptococcal GN and acute rheumatic fever almost never coexist because of the distinct difference between nephritogenic and rheumatogenic strains of streptococci. In addition, cutaneous streptococcal infections are never associated with acute rheumatic fever sequelae. Nevertheless, on rare occasions, MesPGN has been associated with acute rheumatic fever. MesPGN usually manifests with hematuria with scant proteinuria and often resolves with appropriate treatment and control of acute rheumatic fever.

Ankylosing Spondylitis and Reiter Syndrome (Seronegative Spondyloarthropathies)

The seronegative spondyloarthropathies and oligoarticular arthropathies may be associated with mesangial IgA deposition or MesPGN in some patients. Clinical manifestations are usually mild and nonprogressive. AA amyloidosis may complicate long-standing ankylosing spondylitis.

Scleroderma (Systemic Sclerosis)

Scleroderma is a heterogeneous disorder of unknown etiology characterized by uncontrolled expansion of connective tissue in the skin and other visceral organs,[11] as well as vascular thickening and narrowing. Clinical manifestations vary from increased connective tissue in localized patches of skin (morphea) to diffuse and generalized disease (systemic sclerosis). The latter leads to thickening of the skin of the face and hands, telangiectasia, Raynaud phenomenon, tendon friction rubs, and sclerodactyly. A characteristic pattern of blood vessel abnormalities is seen in the nail beds. Visceral involvement causes interstitial pulmonary fibrosis, loss of esophageal and other gastrointestinal motility, restrictive cardiomyopathy, and renal disease. Limited forms of the disease (CREST syndrome: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) occur but are seldom associated with renal disease. The disorder is more frequent in females, with an onset usually in young adults. Approximately 90% of patients will have a speckled pattern of fluorescent ANA, and 30% will have detectable antibody to topoisomerase I (Scl-70). Anticentromere antibody is strongly associated with the CREST syndrome. Anti–NA polymerase III, antitopoisomerase, and anticentromere antibodies are associated with more systemic and renal involvement and a poor prognosis. Rarely, the visceral abnormalities occur without cutaneous lesions (systemic sclerosis *sine* scleroderma).

Renal involvement in scleroderma ranges from low-grade proteinuria and slight impairment of glomerular filtration rate, to a more marked reduction in renal blood flow leading to a greatly elevated filtration fraction secondary to mild MesPGN, to severe AKI.[12,13] The last is referred to as scleroderma renal crisis (SRC) and consists of severe (hyperreninemic) hypertension, encephalopathy, systolic and diastolic congestive heart failure, and AKI. Rare cases of SCR may be seen without cutaneous features and even with relatively normal blood pressure. These patients are often positive for anti RNA polymerase II antibody, and complement activation can be observed.[14] There is often an accompanying microangiopathic hemolytic anemia with schistocytes and elevated serum lactate dehydrogenase. AKI results from primary involvement of the arcuate and interlobular arteries (Fig. 28.2). It may be superimposed on lesions of hypertensive emergencies (e.g., fibrinoid necrosis of the afferent arterioles) and ischemic glomerular changes (e.g., wrinkling of the capillary wall and thickening of the basal lamina).

The prognosis of patients with SRC has remarkably improved with the use of angiotensin-converting enzyme (ACE) inhibitors.[12,13] In one study, ACE inhibitor treatment was associated with better patient survival at 1 year (75% vs. 15%) and with significant preservation or recovery

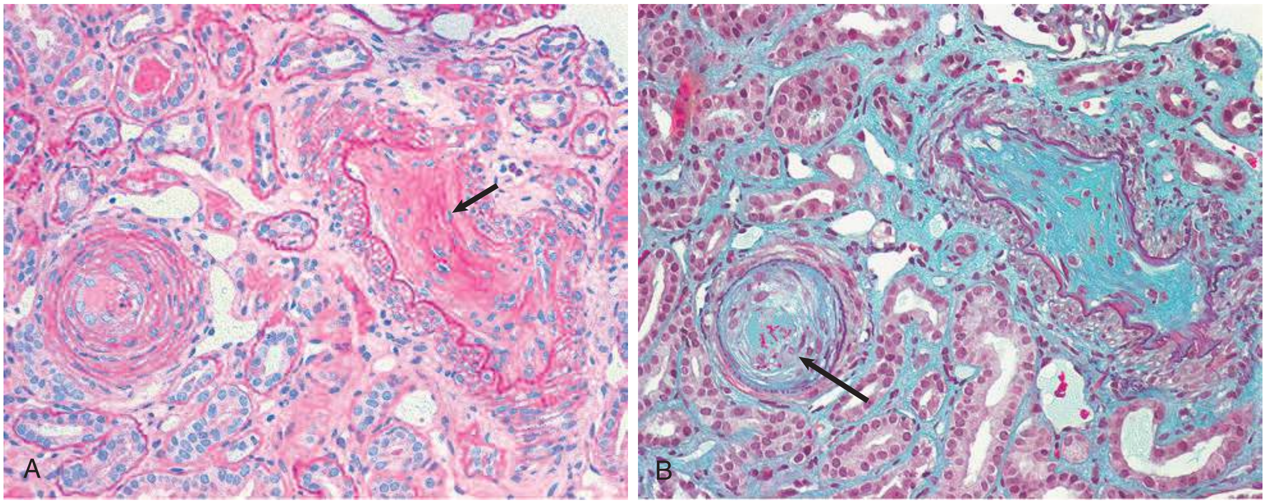

Fig. 28.2 **Scleroderma.** (A) Two interlobular arteries, one transversely and one tangentially cut, show a pronounced subendothelial thickening with weakly periodic acid–Schiff–positive mucinous material and myofibroblasts *(arrow).* (B) Fragmented erythrocytes (schistocytes) can be seen in the Goldner elastica stain in *red (arrow).* The process is limited to the intima because the lamina elastica interna is preserved. Surrounding tubules are collapsed and have atrophic epithelia secondary to postarteriolar ischemia. (Courtesy H. J. Groene, Heidelberg, Germany.)

of renal function.[14] Captopril is the preferred agent for treatment, largely because it is the agent with widest experience in this condition.[14] Delayed recovery of renal function is common in patients requiring dialysis support. ACE inhibitor treatment should continue during dialysis therapy. Transplantation may be a reasonable treatment option, but disease in other visceral organs may limit life expectancy. Various biologic agents, including TGF-α inhibitors, anti-CD20 (rituximab), interleukin 6 (IL6) monoclonal antibodies, eculizumab, and tyrosine kinase inhibitors are undergoing evaluation as therapies for scleroderma or SRC.[15,16]

Relapsing Polychondritis

Polychondritis is a chronic relapsing disorder characterized by destructive inflammation of cartilage (ear, nose, trachea, costal cartilage). It may be associated with crescentic GN, MesPGN, or MN.[17] Cartilage lesions may lead to deformities (saddle nose, floppy ears, tracheal collapse or stenosis), and the renal disease may be severe and progressive. Aggressive management of progressive disease with corticosteroids and cytotoxic agents (e.g., cyclophosphamide) is indicated to control both the systemic and renal manifestations. TNF-α antagonists are useful therapeutic agents in relapsing polychondritis. Tocilizumab or abatacept also can be used as third-line agents.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

The antiphospholipid antibody syndrome (aPLA syndrome) is a prothrombotic disorder characterized by venous and arterial thrombosis and by the presence of circulating autoantibodies to phospholipid-protein complexes, including those of the coagulation cascade.[18,19] The syndrome was first recognized by Hughes in 1983,[18] and has protean manifestations ranging from migraine headaches to multiple thrombosis and multiorgan failure (catastrophic aPLA syndrome; CAPS).[18,19] Thrombotic episodes occur at a frequency of about 7.5 per 100 patient years for 5 years after the first thrombotic event and often can be the presenting feature.[20] Neurologic symptoms and signs are common, including transient cerebral ischemic attacks (TIAs), strokes, migraine headaches, seizures, myelitis, and balance and sensory disturbances (often resembling multiple sclerosis).[18,19] Cardiovascular problems, such as pulmonary hypertension, premature atheromatous disease, renal artery stenosis, and myocardial infarction, are common.[18,19] Livedo reticularis is an important diagnostic clue (Fig. 28.3). Adrenal infarction or hepatic venous thrombosis may lead to acute adrenal insufficiency or Budd-Chiari syndrome, respectively. Visual loss, visual field defects, anosmia, aseptic bone necrosis, fracture, spinal claudication, and autonomic dystrophy are other, less well-described complications. Pulmonary hemorrhage or fibrosing alveolitis can be a presenting feature.[21] Repeated pregnancy loss is common.

The kidneys are frequently involved with a form of thrombotic microangiopathy (TMA; see also Chapter 29).[22,23] CAPS is a rare but often fatal form of the aPLA syndrome frequently associated with SLE or infections. It involves many organ systems, including the brain, kidneys, heart, and lungs.[24]

The aPLA syndrome may occur without known systemic disease or may accompany SLE (see also Chapter 26). The presence of aPLA syndrome in SLE confers a much worse prognosis and greater risk for neuropsychiatric and cardiovascular complications. The aPLA syndrome (primary or SLE related) always should be suspected whenever a history of migraine headache, TIA or stroke, multiple pregnancy loss, or arterial or venous thrombosis is identified or a family history of autoimmune disease is elicited. The criteria for the definite diagnosis of aPLA syndrome include the presence of at least both one clinical criterion plus one laboratory criterion[25]: *Clinical*—(1) thrombosis (arterial or venous) or (2) spontaneous abortions or stillbirths. *Laboratory* (two or more occasions at least 6 to 12 weeks apart)[25]—(1) Lupus anticoagulant, (2) anticardiolipin antibody, or (3) anti–β_2 glycoprotein I antibody. The pathogenic antibodies in aPLA syndrome appear to be primarily directed to the domain I of β_2-glycoprotein I.[26] Antibodies to prothrombin, thrombin, or phosphotidylserine may be predictive of severe thrombophilia and/or pregnancy loss.

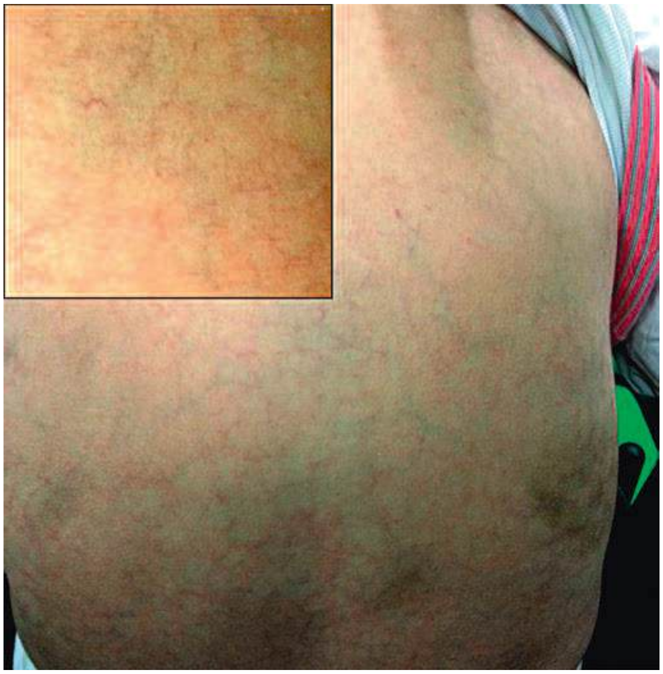

Fig. 28.3 **Livedo reticularis in patient with antiphospholipid antibody syndrome.** Note reticulated skin changes (*insert,* higher magnification) on the patient's back, in addition to some hematomas related to her warfarin therapy. (Courtesy J. Floege, Aachen, Germany.)

The pathogenesis of aPLA is probably multifactorial.[27] The thrombotic state seems to involve generation of reactive oxygen species leading to alterations in β_2-glycoprotein I function, impaired function of endothelial nitric oxide synthase, activation of prothrombotic receptors by autoantibodies, increased expression/activation of tissue factor, increased modified forms of prothrombotic factor XI, disruption of annexin A5 shield, and antibody-mediated activation of C3 and/or C5.[27] There is a prominent involvement of the mammalian target of rapamycin complex (mTORC) in aPLA syndrome.[28] Transplanted patients with aPLA syndrome who receive the mTORC inhibitor sirolimus for prevention of allograft rejection have a lower risk for recurrence of vascular lesions. However, mTORC inhibition in primary or secondary aPLA syndrome has not yet been tested in randomized trials.

Laboratory testing usually reveals an autoantibody to phospholipids (anticardiolipin, anti–β_2-glycoprotein 1, or prothrombin), but "antibody-negative" aPLA syndrome has been described.[24,26] False-positive test results for syphilis and a lupus anticoagulant are common. A prolonged prothrombin or partial thromboplastin time that does not correct when plasma is diluted 1 : 1 with normal plasma is found in such circumstances. Antiphospholipid antibodies may cross-react with platelet factor 4–heparin complex and thus may be associated with a false positive for antibody in heparin-induced thrombocytopenia. Mild thrombocytopenia is common (platelet counts about 100,000/mm^3, but usually not less than 80,000/mm^3). Thrombocytopenia may be an in vitro phenomenon related to the effect of the aPLA antibody on platelet membrane biology. Lymphocytopenia is common in patients with SLE and aPLA syndrome.

A mild hemolytic anemia (Coombs negative or positive) may coexist, giving rise to confusion with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and Evans syndrome. A frank microangiopathic hemolytic anemia is relatively uncommon. Patients with aPLA syndrome and reduced ADAMTS13 activity may be at higher risk for thrombotic events.[29] Anti-C1q autoantibodies are found frequently in primary aPLA syndrome and might contribute to abnormal complement activation, particularly in severe refractory cases.

In primary aPLA syndrome, overt renal manifestations are generally mild and are frequently absent. Nephrotic syndrome is relatively rare. In aPLA syndrome associated with SLE, the renal manifestations are determined largely by the severity of the underlying glomerular lesions, but the coexistence of aPLA syndrome contributes to a worse prognosis and extrarenal manifestations (neurologic, cardiovascular, osseous, ophthalmologic, pulmonary, hepatic, visceral, and obstetric) (see also Chapter 26). A strong association of aPLA with alveolar hemorrhage exists in SLE.[21]

The therapy for primary aPLA syndrome and that accompanying SLE is controversial.[30] Immunosuppressive agents, such as steroids or cytotoxic agents, even when they are used to control SLE, have yielded disappointing results. Symptomatic patients are best treated with anticoagulation. Aspirin (or clopidogrel) can be used routinely in mild cases. Combinations of aspirin and low-dose warfarin might be effective, but the risk for bleeding is increased. Vitamin K antagonism is the mainstay of treatment in severe cases, with the international normalized ratio (INR) adjusted to a level depending on symptoms; INR between 2.0 and 3.5 may be required. Low-molecular-weight heparin (subcutaneous or intravenous) is the treatment of choice for pregnancy complicated by aPLA syndrome and is also useful in alleviating migraine headache. Aspirin therapy in pregnancy with an aPLA-like syndrome does not appear to be effective. Long-term use of hydroxychloroquine can be beneficial in patients with primary aPLA syndrome without evidence of SLE.[31] Direct-acting oral anticoagulants (e.g., rivaroxaban, apixaban, dabigatran) may be equivalent or superior to warfarin, but it is premature to make any recommendations.[32]

Sirolimus, an inhibitor of mTORC, has been suggested for treatment of aPLA syndrome,[27] but mTORC inhibitors also can increase the risk for thrombosis in susceptible individuals. High-dose intravenous IgG (IVIG) can have dramatic beneficial effects, especially in acutely evolving disease associated with SLE. Combinations of plasma exchange and intravenous immunoglobulin seem to be beneficial in high-risk pregnancy with aPLA syndrome,[33] and plasma exchange alone can be helpful in CAPS.[34]

The benefits of immunomodulating agents such as rituximab have not been adequately evaluated in aPLA syndrome, but preliminary reports are encouraging when used alone or with plasma exchange. In severe, life-threatening disease, combinations of rituximab and plasma exchange should be seriously considered. Intensive plasma exchange (plus immunosuppression) has been used in other circumstances, such as in aPLA syndrome associated with SLE, with variable degrees of success. Monoclonal antibodies to C5 (eculizumab) or to CD20 (rituximab) also have been used to treat CAPS with some success.[35,36]

Novel therapeutic approaches to the aPLA syndrome, such as coenzyme Q10, statins, *N*-acetylcysteine, phosphodiesterase inhibitors, and factor XI inhibitors have not yet been thoroughly tested for safety and efficacy.

OTHER UNCOMMON GLOMERULAR DISORDERS

Lipoprotein Glomerulopathy

Lipoprotein glomerulopathy is apparently caused by an abnormality in lipoprotein metabolism.[37,38] It is characterized by extensive deposits of apolipoproteins A, B, and E in the glomeruli (mostly apo E), leading to greatly expanded capillaries filled with a pale-staining, PAS-negative, mesh-like substance having the appearance of lipid thrombi (Fig. 28.4), also described as "foam cells." These cells also may be seen in crystal-storing histiocytosis, macrophage activation syndrome, TMA, and lecithin–cholesterol acyltransferase deficiency (see later discussion).[39] IF stains for APO E are strongly positive, but immunoglobulins and complement are absent.[37,38] Clinically, there may be heavy proteinuria with nephrotic syndrome. Apo B and E levels are increased in plasma in association with a type III hyperlipoproteinemia. Apo E usually shows a heterozygous E2/E3 or E2/E4 phenotype, but homozygosity for Apo E2 or E3 also has been observed. Homozygous Apo E2 is also seen in familial type III hyperlipoproteinemia. Decreased low-density lipoprotein (LDL) receptor binding and increased heparin affinity may explain some of the pathogenetic processes in lipoprotein glomerulopathy. The disease may be associated with psoriasis and hypertensive emergencies (formerly called malignant hypertension) accompanied by TMA. Otherwise, there are no distinctive clinical features. Familial cases have strongly suggested a hereditary abnormality. The characteristics of Chinese patients with familial lipoprotein glomerulopathy secondary to the *APOE* Kyoto mutation have been described. Lipoprotein glomerulopathy may recur in the renal transplant.

Treatment with bezafibrate or fenofibrate may be effective and is the initial treatment of choice.[40] About three quarters of patients with

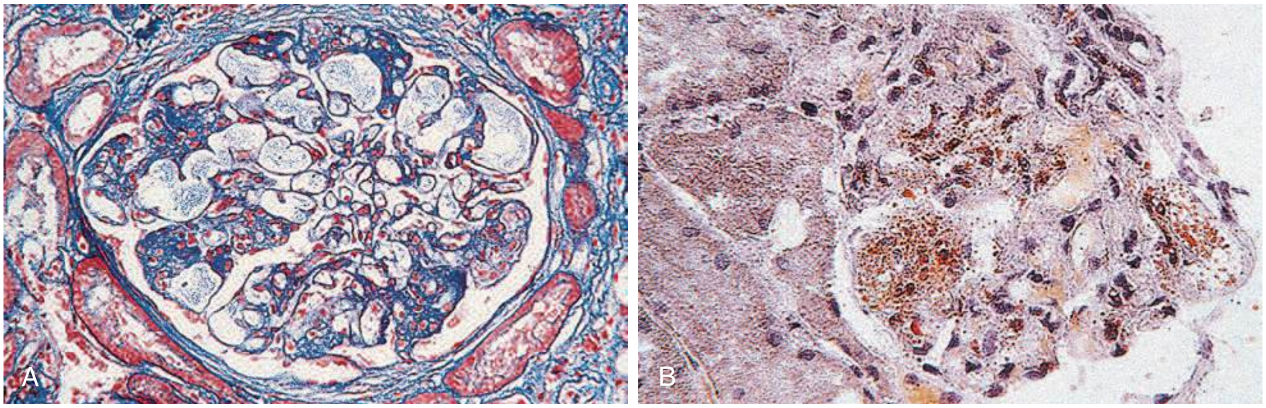

Fig. 28.4 **Lipoprotein glomerulopathy.** (A) Dilated capillary lumina containing a pale, trichrome-stained, mesh-like or granular substance. (×260.) (B) The granules stain positively with oil red O and antilipoprotein E antisera. (×260.) (Modified from Churg J, Berstein J, Glassock R. *Renal Disease: Classification and Atlas of Glomerular Disease.* New York: Igaku-Shoin; 1995.)

nephrotic syndrome treated with fibrates will achieve a complete or partial remission. Treatment with heparin-induced extracorporeal lipoprotein precipitation–apheresis systems (HELP-apheresis) also can achieve a complete remission in some patients.[41]

Lecithin–Cholesterol Acyltransferase Deficiency

Lecithin–cholesterol acyltransferase (LCAT) deficiency is an autosomal recessive disorder associated with a very low high-density lipoprotein (HDL) cholesterol but a remarkably variable and often low frequency of cardiovascular disease in carriers[42,43] (see also Chapter 19). The clinical characteristics include corneal opacities (misty deposits, also known as "fish eye"), splenomegaly, normocytic normochromic anemia (with target cells), low HDL and α-lipoprotein levels, and elevated LDL levels. Fish eye disease also can exist without anemia, splenomegaly, or renal disease. It is likely that the accumulation in plasma of a cholesterol-rich multilamellar particle called lipoprotein-X is pathogenic in the kidneys.[44]

Proteinuria, including nephrotic syndrome, as well as hypertension and progressive renal failure, are the main renal manifestations. On light microscopy, the glomeruli have foam cells, intimal hyperplasia, and thickening of the GBM with effacement of the foot processes (Fig. 28.5). Progressive renal failure is the rule; however, it has an often slow and insidious onset and is usually first detected in the fourth decade of life. Treatment is generally ineffective, but theoretically, an inhibitor of hepatic acyl coenzyme A–cholesterol acyltransferase activity might be of benefit. The disease can recur in the renal allograft and sequential kidney-liver transplantation might be curative.[45]

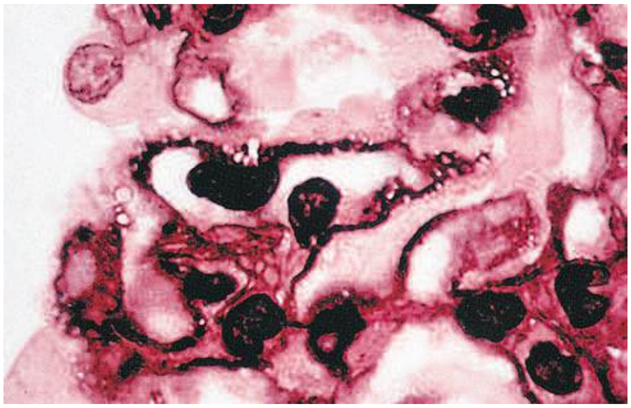

Fig. 28.5 Lecithin–cholesterol acyltransferase deficiency. Note the irregular, thickened glomerular capillary walls containing clear vacuoles, which are characteristic of the LCAT lesion. (Periodic acid–Schiff reaction, ×1000.) (Modified from Churg J, Berstein J, Glassock R. *Renal Disease: Classification and Atlas of Glomerular Disease.* New York: Igaku-Shoin; 1995.)

Collagen III Glomerulopathy

Collagen III glomerulopathy, also known as collagenofibrotic glomerulopathy, is an autosomal recessive systemic disorder with prominent renal manifestations that may be a *forme fruste* of nail-patella syndrome (see Chapter 46) because the glomerular abnormalities are similar.[46] Nevertheless, patients with collagen III glomerulopathy lack the typical skeletal abnormalities observed in the nail-patella syndrome. Mutations of the *LMX1B* gene are believed to be causative.[47] Clinically, patients present with proteinuria and slowly progressive renal failure. Patients may be of any age, and males predominate. Marked elevation of serum hyaluronan concentration might be a diagnostic biomarker.

On light microscopy the glomeruli are enlarged, with a marked expansion of the mesangial matrix by material weakly positive for PAS reaction (Fig. 28.6). Immunohistology is usually negative, but rarely will show "full-house" immunoglobulin and complement deposition. Antisera to collagen type III strongly react with the glomerular deposits. EM shows bundles of spirally arranged and frayed fibrillar deposits (Congo red negative) with periodicity characteristic of collagen. Similar deposits may be found in the spleen, liver, myocardium, and thyroid in fatal cases. No treatment is known to be effective, and there are no data yet on recurrent disease after renal transplantation.

Fibronectin Glomerulopathy

Fibronectin glomerulopathy is a rare, autosomal dominant, nonamyloid, fibrillary glomerular disease with onset usually in early adolescence with proteinuria, microhematuria, hypertension, distal (type 4), renal tubular acidosis, and slowly progressive renal failure.[48] The gene *(FN1)* responsible for the disorder maps to chromosome 2q32.[49] Most patients reach ESRD between the second and sixth decades of life. The renal pathology usually reveals enlarged, hyperlobular, and normocellular glomeruli with a homogeneous or fibrillary material (on PAS staining) in the mesangium and subendothelial area. EM shows randomly oriented fibrils (12 to 16 nm wide and 120 to 170 nm long). IF is negative for antibody and complement components but will stain brightly with use of an antifibronectin antibody. The pathogenesis of the disease is unknown. Mice knocked out for uteroglobin develop a similar lesion,

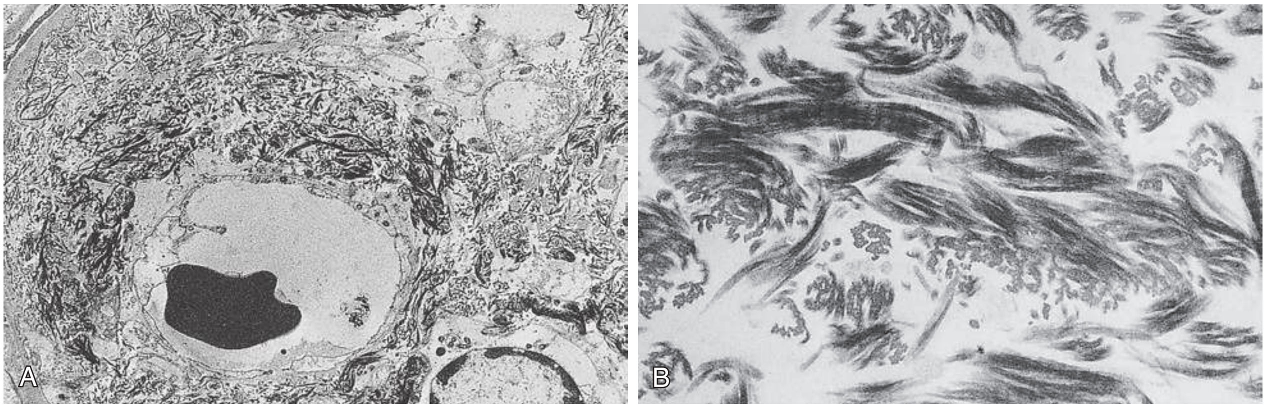

Fig. 28.6 Electron microscopy of collagen III (collagenofibrotic) glomerulopathy. (A) Fine fibrils occur in the mesangial and subendothelial areas. (×3000.) (B) These fibrils are randomly oriented with typical periodicity and average 30 nm in diameter. The fibrils are strongly positive for periodic acid–Schiff reaction with anti–collagen type III antibodies. (×15,000.) (Modified from Churg J, Berstein J, Glassock R. *Renal Disease: Classification and Atlas of Glomerular Disease.* New York: Igaku-Shoin; 1995.)

but studies in humans have not documented any linkage to genes for uteroglobin or fibronectin. The differential diagnosis includes other disorders associated with fibril deposition (see Chapter 27). There is no known effective treatment of fibronectin glomerulopathy. The disease can recur in renal allografts.

Nephropathic Cystinosis

Late-onset adult cystinosis, a variant of typical pediatric cystinosis with mutations in the cystinosin gene *(CTNS)*, results in a milder phenotype.[50] Cystinosin deficiency results in podocyte damage and proteinuria.[51] Patients with cystinosis also may present with glomerular disease during the teenage years. Nephrotic syndrome may occur. The glomerular lesions resemble FSGS except that cystine crystals are found in glomerular and tubular epithelial cells. Patients with cystinosis tend to have blond hair, photophobia, hypothyroidism, corneal deposits, rickets, and Fanconi syndrome with tubular proteinuria, or nephrogenic diabetes insipidus (see also Chapter 48). The treatment of choice is long-term cysteamine administration.[52]

Miscellaneous Storage Diseases Rarely Associated With Glomerular Lesions

Diseases associated with storage of abdominal lipids or carbohydrates in tissue may rarely provoke glomerular lesions, usually in infants and children. These include Hurler syndrome (type I mucopolysaccharidoses), von Gierke disease (glycogen storage disease), Gaucher disease, Refsum disease, nephrosialidosis, and I cell disease (mucolipidosis type II). Juvenile malabsorption of vitamin B_{12} with megaloblastic anemia (Imerslund syndrome; cubulin deficiency) can be associated with prolonged glomerular proteinuria (albuminuria), but progressive renal disease does not develop. Asphyxiating thoracic dystrophy (Jeune syndrome) is associated with glomerular, tubular, and interstitial abnormalities. Hereditary osteolysis causing arthralgias and deformities of wrists and ankles can be accompanied by chronic GN. The nail-patella syndrome and Fabry disease are discussed in Chapter 46.

Idiopathic (Nondiabetic) Nodular Glomerulosclerosis

An intercapillary nodular expansion of the mesangium encroaching on the glomerular capillary lumina, that is, the Kimmelstiel-Wilson lesion, is most commonly associated with diabetes mellitus and proliferative diabetic retinopathy (see Chapter 30). A small group of patients has been described in whom a similar lesion is seen in the absence of any overt features of diabetes mellitus or disordered glucose metabolism or other known causes of a similar lesion, such as κ light-chain deposition disease (see Chapter 27), chronic TMA, monoclonal immunoglobulin deposition disease (MIDD), fibrillary GN, and fibronectin glomerulopathy. Thus idiopathic nodular glomerulosclerosis is a diagnosis of exclusion.

The first examples of this new disorder were recognized in 1989.[53] Although some of these patients may have had intermittent manifestation of diabetes or only mild abnormalities of glucose homeostasis, such as an abnormal glucose tolerance test result, most have not had features diagnostic of diabetes. Recent marked weight loss with remission of glycemic abnormalities can mask the prior presence of type 2 diabetes and give rise to diagnostic confusion.

The clinical features are nonspecific and nondiagnostic. Patients with idiopathic nodular glomerulosclerosis are usually older (average age ~70 years) and female. Nephrotic syndrome is a common presentation. A heavy smoking history, obesity, and long-standing hypertension are frequent, but the pathogenic role of these abnormalities is uncertain.[54] It is possible that the long-term consequences of cigarette smoking and intermittent TMA are pathogenetically important.[54]

The pathology includes typical nodular glomerulosclerosis with thickening of the GBM and varying degrees of arteriolo-nephrosclerosis and hyalinosis identical to the diabetes-associated Kimmelstiel-Wilson lesions. No electron-dense or organized deposits are seen on EM. The GBM and tubular basement membrane may stain with IgG and albumin on IF. Neovascularization can be seen within the nodules. Some cases may resemble the lesions of chronic TMA.

The prognosis is poor and relates to the persistence of nephrotic-range proteinuria. Most patients with idiopathic nodular glomerulosclerosis will progress to ESRD, sometimes quite rapidly. The 50% renal survival in those who continue to smoke heavily is about 1 year after diagnosis. There is no known effective therapy other than angiotensin inhibition to reduce the proteinuria and smoking cessation where relevant.

Macrophage Activation Syndrome

The macrophage activation syndrome (MAS; also known as the hematophagocytic syndrome [HPS] or hematophagocytic lymphohistiocytosis [HLH]) is an uncommon disorder characterized by massive infiltration of the bone marrow by activated macrophages often accompanied by pancytopenia, fever, rash, coagulopathy, liver function abnormalities, adenopathy, hepatosplenomegaly, erythrophagocytosis, and TMA.[55] Primary MAS is seen in children with inherited dysfunction of the immune response, particularly natural killer (NK) cells. Secondary MAS in adults can be triggered by infections (particularly viral infections), autoimmune disease (SLE and Still disease) and neoplasia. Excessive production of cytokines (TNF-α and IL-1, -4, -6, -8, -10), extreme hyperferritinemia, marked hyper-triglyceridemia, and hypo-fibrinogenemia are common findings that often lead to the correct diagnosis. The erythrocyte sedimentation rate may be low.

Renal manifestations include AKI and nephrotic syndrome. Post-transplant MAS also can occur. When nephrotic syndrome or TMA is evident the underlying lesion is often collapsing FSGS.[56]

Treatment is difficult, and the mortality rate of MAS is high. Treatment consists of removal of the triggering agent (if possible). High-dose steroids, calcineurin inhibiting agents, IVIG, anti–TNF-α agents, anti–IL-1 receptor, and anti–IL-6 monoclonal antibodies, rituximab, and plasma exchange have been used with varying degrees of success.[57]

DRESS Syndrome

DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) is an uncommon manifestation of severe drug hypersensitivity characterized by extensive mucocutaneous rashes, fever, lymphadenopathy, hepatitis, eosinophilia, and atypical lymphocytosis with multisystem organ injury.[58] Reactions to aromatic anticonvulsants, such as phenytoin and carbamazepine, are a common cause. AKI and proteinuria due to glomerular damage can be seen. Untreated, the DRESS syndrome can be fatal. For severe cases, parenteral and oral steroids are indicated.[59]

Kimura Disease

Kimura disease (or angiolymphoid hyperplasia with eosinophilia [ALHE]) is a rare disorder characterized by nonmalignant masses in the head and neck, lymphadenopathy, marked eosinophilia, elevation of serum IgE, and immune thrombocytopenia, mostly in subjects of Asian ancestry.[60] Renal involvement with nephrotic syndrome due to MN, FSGS (tip lesion variant), or MesPGN is common. Steroid therapy is successful in most cases.

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SELF-ASSESSMENT QUESTIONS

1. A 42-year-old man is discovered to have proteinuria, impaired renal function (serum creatinine 2.3 mg/dl), and normocytic normochromic anemia (hemoglobin [Hb] 8.2 g/dl). The physical examination shows hypertension (150/98 mm Hg), mild obesity (body mass index 31 kg/m^2), bilateral corneal opacities, and 1+ edema. The albumin is 3.2 g/dl, total cholesterol is 120 mg/dl, low-density lipoprotein cholesterol is 80 mg/dl, high-density lipoprotein cholesterol is 15 mg/dl, and triglycerides is 200 mg/dl. Serum C3 is normal. A fasting blood sugar is 120 mg/dl. Urinary total protein excretion is 4.6 g/day. Which of the following is the *most* likely diagnosis?
   A. Alport syndrome
   B. Adult-onset cystinosis
   C. Lecithin–cholesterol acyltransferase deficiency
   D. C3 glomerulopathy
   E. Obesity-related glomerulopathy
2. Which of the following can be an effective for treatment of lipoprotein glomerulopathy?
   A. Cyclosporine
   B. Bezafibrate
   C. Atorvastatin
   D. Corticosteroids
   E. Plasma infusions
3. A 65-year-old woman is found to have nephrotic syndrome, and renal biopsy shows membranous nephropathy. Serum C3 is normal, and antinuclear antibody (ANA) is 1:80. Anti-dsDNA is negative. Immunofluorescence staining of the biopsy reveals extensive deposits of immunoglobin G4 (IgG4) and weak deposits of IgG1 and IgG3. Serologic studies for hepatitis B are negative. Which of the following is the *most* likely diagnosis?
   A. Membranous lupus nephritis
   B. Membranous nephropathy secondary to cancer
   C. Idiopathic (primary) membranous nephropathy
   D. Membranous nephropathy secondary to hepatitis C infection
4. A 46-year-old woman complains of frequent "migraine" headaches. She is found to be anemic (Hb 9.8 g/dl), and serum creatinine is elevated to 1.6 mg/dl. Her blood pressure is 156/94 mm Hg. Urinalysis reveals 2+ protein and a trace of blood. The serum C3 and C4 are normal, and ANA is negative. She takes an NSAID for headache. She has had three miscarriages and is presently amenorrheic. Her physical examination is otherwise unremarkable. There are no localizing neurologic findings. Which of the following tests would be *most* appropriate as a next step in the diagnostic evaluation of this patient?
   A. Anti-dsDNA autoantibody
   B. Magnetic resonance imaging of the brain
   C. Serum iron and iron-binding capacity
   D. Antiphospholipid antibody test
   E. Serum protein electrophoresis

29

Thrombotic Microangiopathies, Including Hemolytic Uremic Syndrome

Marina Noris, Piero L. Ruggenenti, Giuseppe Remuzzi

DEFINITIONS

Thrombotic microangiopathy (TMA) is a lesion of arteriolar and capillary vessel wall thickening with intraluminal platelet thrombosis and a partial or complete obstruction of the vessel lumina. Laboratory features of thrombocytopenia and microangiopathic hemolytic anemia are almost invariably present. Depending on whether renal or brain lesions prevail, two pathologically indistinguishable but somehow clinically different entities have been described: hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Because HUS can involve extrarenal manifestations and TTP may be associated with severe renal disease, the two can be difficult to distinguish on clinical grounds.[1] In comparison to HUS, TTP is associated with more severe thrombocytopenia and less severe acute kidney injury (AKI),[2] but changes in platelet count and kidney function largely overlap in HUS and TTP and there are no cut-off values that discriminate the two syndromes. However, newly identified pathophysiologic mechanisms have allowed for the differentiation of the two syndromes on a pathogenetic basis and have paved the way to specific diagnosis and treatment (Table 29.1 and Fig. 29.1).

The term HUS was introduced in 1955 by Gasser and coworkers in their description of an acute fatal syndrome in children characterized by hemolytic anemia, thrombocytopenia, and severe AKI. HUS occurs most frequently in children under the age of 5 years (incidence 5 to 6 per 100,000 children per year compared with an overall incidence of 0.5 to 1 per 100,000 per year). Over 90% of cases are associated with infection by Shiga-like toxin (Stx) producing *Escherichia coli* (STEC). STEC-HUS occurs primarily in children, except in epidemics, when it may occur in patients with a wider range of ages. For example, from May 2011 until July 2011, several European Countries, particularly Northern Germany, experienced one of the largest STEC-HUS outbreaks ever reported with 3816 patients suffering from *E. coli* O104:H4 infection, with 845 cases. Almost 90% of affected patients were adults and, compared with previous STEC epidemics, there was a higher prevalence of affected women.[3] *Streptococcus pneumoniae* causes a distinctive form of HUS accounting for 40% of childhood cases not associated with Stx-producing bacteria.[4] Approximately 10% of HUS cases are classified as atypical, caused neither by Stx-producing bacteria (STEC or *Shigella dysenteriae*) nor by *Streptococcus*.[5] Atypical HUS is less common than STEC-HUS, with an annual incidence of 0.5 to 2 per million per year. It can occur at any age and is a very severe disease. Before the introduction of complement inhibition therapy, 50% of patients with atypical HUS progressed to end-stage renal disease (ESRD) and 25% died in the acute phase.[4,5] Neurologic symptoms and fever can occur in 30% of patients. Pulmonary, cardiac, and gastrointestinal (GI) manifestations also can occur.

TTP was first described in 1925 by Moschcowitz in a 16-year-old female patient with fever, hemolytic anemia, bleeding, AKI, neurologic involvement, and a fulminant clinical course. Pathologic changes were characterized by widespread hyaline thrombosis of small vessels. TTP is a rare disease, with an incidence of approximately 2 to 4 cases per 1 million per year. TTP can affect any age group and classically presents with the pentad of thrombocytopenia, microangiopathic hemolytic anemia, fever, and neurologic and renal dysfunction. Neurologic symptoms are seen in over 90% of patients. Central nervous system (CNS) involvement mainly represents thrombo-occlusive disease of the gray matter, and clinical features include headache, cranial nerve palsies, confusion, stupor, and coma. Up to half of patients who present with neurologic involvement may be left with sequelae. Chronic kidney disease (CKD) may occur. One group has reported 25% of patients with creatinine clearance less than 40 ml/min on long-term follow-up. Cardiac involvement may be common in TTP.[6]

LABORATORY SIGNS

Laboratory features of thrombocytopenia and microangiopathic hemolytic anemia are almost invariably present in patients with TMA lesions.[5] Thrombocytopenia is due to platelet consumption by platelet-rich thrombi in the microcirculation of several organs. Thrombocytopenia may be severe, but is usually less so in patients with predominant renal involvement.[2,7] Giant platelets in the peripheral smear, reduced platelet survival time, or both are consistent with peripheral consumption. In children with STEC-HUS, the duration of thrombocytopenia is variable and does not correlate with the course of renal disease. Microangiopathic hemolysis is likely caused by the passage of blood through the damaged capillaries and arterioles occluded by thrombi, but other explanations also have been suggested.[8] Hemoglobin levels are low (<10 g/dl in >90% of patients). Reticulocyte counts are uniformly elevated. The peripheral smear reveals increased schistocyte numbers, with polychromasia and often nucleated red blood cells (RBCs). Detection of fragmented erythrocytes is crucial to confirm the microangiopathic nature of the hemolytic anemia—provided that valvular heart disease and other anatomic artery abnormalities that may cause erythrocyte fragmentation are excluded. Other indicators of intravascular hemolysis include elevated lactate dehydrogenase (LDH), increased indirect bilirubin, and low haptoglobin level.[5] The Coombs test is negative. Serum C3 levels may be low during the acute phase of the disease in STEC-HUS and atypical HUS, but also in TTP. Moderate leukocytosis may accompany

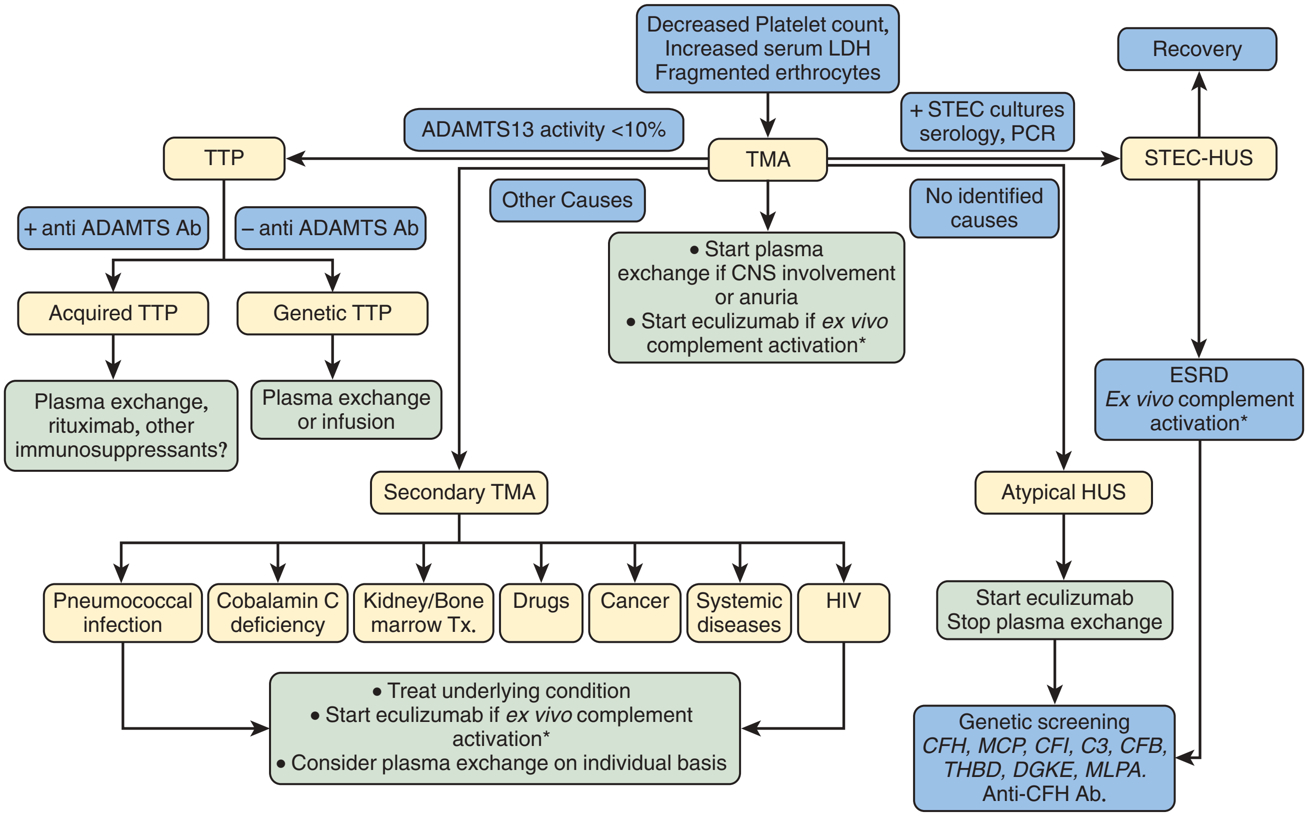

Decreased Platelet count,
Increased serum LDH
Fragmented erthrocytes
Recovery
ADAMTS13 activity <10%
+ STEC cultures serology, PCR
TTP
TMA
STEC-HUS
Other Causes
No identified causes
+ anti ADAMTS Ab
– anti ADAMTS Ab
• Start plasma exchange if CNS involvement or anuria
• Start eculizumab if *ex vivo* complement activation*
Acquired TTP
Genetic TTP
ESRD
Ex vivo complement activation*
Plasma exchange, rituximab, other immunosuppressants?
Plasma exchange or infusion
Secondary TMA
Atypical HUS
Pneumococcal infection
Cobalamin C deficiency
Kidney/Bone marrow Tx.
Drugs
Cancer
Systemic diseases
HIV
Start eculizumab
Stop plasma exchange
• Treat underlying condition
• Start eculizumab if *ex vivo* complement activation*
• Consider plasma exchange on individual basis
Genetic screening
CFH, MCP, CFI, C3, CFB, THBD, DGKE, MLPA.
Anti-CFH Ab.

Fig. 29.1 Investigation, diagnosis, and management of thrombotic microangiopathies. *Ab,* Antibody; *CNS,* central nervous system; *HIV,* human immunodeficiency virus; *LDH,* lactate dehydrogenase; *STEC-HUS,* Shiga toxin–producing *Escherichia coli*–associated hemolytic uremic syndrome; *TMA,* thrombotic microangiopathy; *TPP,* thrombotic thrombocytopenic purpura; *Tx,* transplantation. *The authors recommend empirical treatment with ecluzimab in particular if there is evidence for in vivo complement activation (and ideally ex vivo complement activation if such diagnostic testing is available). This latter testing involves evaluating for serum induced complement deposition on cultured endothelial cells and is done only in a few specialized centers.[29]

the hemolytic anemia. Bone marrow biopsy usually shows erythroid hyperplasia and an increased number of megakaryocytes. Prothrombin time, partial thromboplastin time, fibrinogen level, and coagulation factors are normal, thus differentiating TMA from disseminated intravascular coagulation. Mild fibrinolysis with minimal elevation in fibrin degradation products, however, may be observed. Evidence of renal involvement is present in all patients with HUS (by definition) and in about 25% of patients with TTP.[1,9,10] STEC-HUS in 90% of cases is preceded by diarrhea, often bloody.

PATHOLOGY

The histologic lesions of TMA consist of widening of the subendothelial space and microvascular thrombosis. Electron microscopy best identifies the characteristic lesions of swelling and detachment of the endothelial cells from the basement membrane and the accumulation of fluffy material in the subendothelium, intraluminal platelet thrombi, and partial or complete obstruction of vessel lumina (Figs. 29.2 and 29.3).[11] These lesions are similar to those seen in other renal diseases such as scleroderma, malignant nephrosclerosis, chronic transplant rejection, and calcineurin inhibitor nephrotoxicity. In HUS, microthrombi are present primarily in the kidneys, whereas in TTP they mainly involve the brain. In children, particularly in those younger than 2 years of age, and in those with STEC-HUS, the glomerular injury predominates (Fig. 29.4).[11]

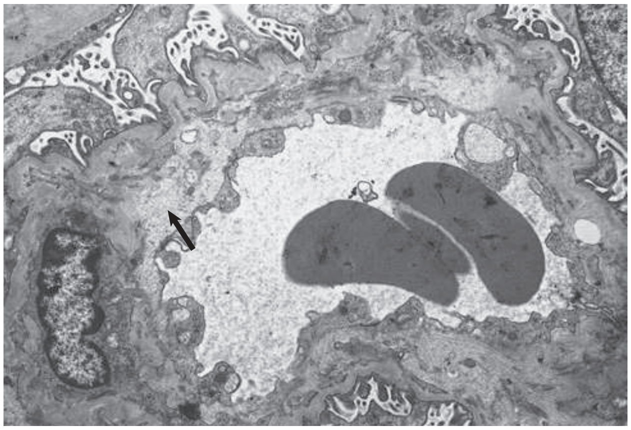


Fig. 29.2 Electron micrograph of a glomerular capillary in hemolytic-uremic syndrome. The endothelium is detached from the glomerular basement membrane (GBM); the subendothelial space is widened and occupied by electron-lucent fluffy material and cell debris *(arrow).* Beneath the endothelium is a thin layer of newly formed GBM.

TABLE 29.1 Classification of Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura According to Underlying Etiology

Clinical Presentation	Etiology
Hemolytic Uremic Syndrome	
Stx associated	Infections by Shiga toxin-producing bacteria
Neuraminidase associated	Infections by *Streptococcus pneumoniae*
Atypical	
Familial	*Mutations: CFH,* 40%-45%; *CFI,* 5%-10%; *C3,* 8%-10%; *MCP,* 7%-15%; *THBD,* 9%; *CFB,* 1%-2% *CFH/CFHR* hybrid genes: 5%; *DGKE:* 10% of patients under 1 yr of age
Sporadic	
Idiopathic	*Mutations: CFH,* 15%-20%; *CFI,* 3%-6%; *C3,* 4%-6%; *MCP,* 6%-10%; *THBD,* 2%; *CFB,* <1%; *CFH/CFHR* hybrid genes: 3%. *Anti-CFH antibodies:* 6%-10%
Pregnancy associated	*Mutations: CFH,* 40%-50%; *CFI,* 10-20%; *MCP,* 10%; *C3,* 14%
HELLP syndrome	*Mutations: CFH,* 10%; *CFI,* 20%; *MCP,* 10%
Transplantation (*de novo* aHUS)	*Mutations: CFH,* 15%; *CFI,* 16%
Thrombotic Thrombocytopenic Purpura	
Congenital	Homozygous or compound heterozygous mutations in *ADAMTS13* gene
Acquired	Anti-ADAMTS13 autoantibodies
Other TMAs	
Cobalamin C deficiency	Mutations in *MMACHC*
Drug induced	Ticlopidine and clopidogrel: Anti-ADAMTS13 antibodies. Other drugs: Unknown
BM/HSC transplantation	Unknown, rarely low ADAMTS13 levels
Malignancies	Unknown, rarely low ADAMTS13 levels
HIV	HIV virus, rarely low ADAMTS13 levels
SLE, APS, and other systemic diseases	Depends on the specific underlying diseases

aHUS, Atypical hemolytic uremic syndrome; *APS,* antiphospholipid syndrome; *HELLP,* hemolytic anemia, elevated liver enzymes; and low platelet count; *HIV,* human immunodeficiency virus; *BM/HSC,* bone marrow/hematopoietic stem cell; *SLE,* systemic lupus erythematosus.

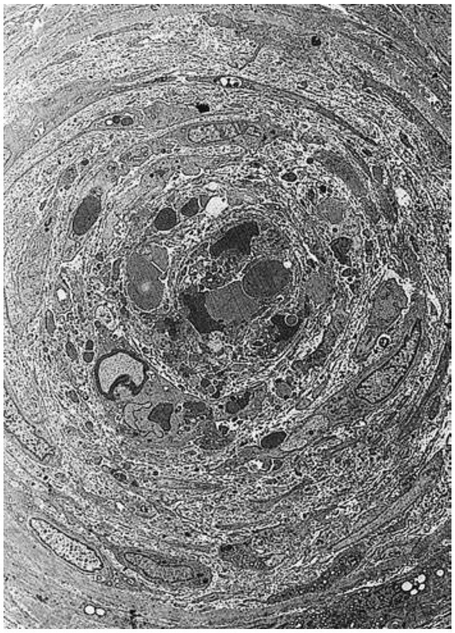


Fig. 29.3 Electron micrograph of a renal arteriole in hemolytic uremic syndrome. The vascular lumen is completely occluded by thrombi. There is marked intimal edema with consequent separation of myointimal cells.

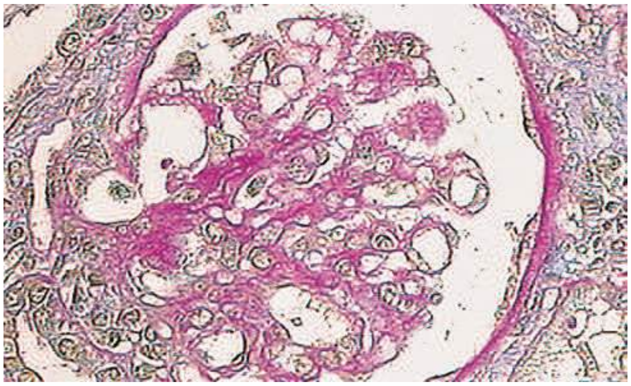


Fig. 29.4 Glomerulus from a patient with STEC-associated hemolytic uremic syndrome. A marked thickening of the glomerular capillary wall occurs with many double contours.

Thrombi and leukocyte infiltration are common in the early phases and usually resolve after 2 to 3 weeks. Patchy cortical necrosis may be present in severe cases; crescent formation is uncommon. In idiopathic and familial forms and in adults, the injury mostly involves arteries and arterioles, with thrombosis and intimal thickening (see Figs. 29.3 and 29.5), secondary glomerular ischemia, and retraction of the glomerular tuft (Fig. 29.6). Focal segmental glomerulosclerosis may be a long-term sequela of acute HUS and is usually seen in children with long-lasting hypertension and progressive loss of renal function.

The typical pathologic changes of TTP are the thrombi that occlude capillaries and arterioles in many organs and tissues. These thrombi consist of fibrin and platelets, and their distribution is widespread. They are most commonly detected in kidneys, pancreas, heart, adrenals, and brain. Compared with HUS, pathologic changes of TTP are more extensively distributed, probably reflecting the more systemic nature of the disease.

MECHANISMS, CLINICAL FEATURES, AND MANAGEMENT OF SPECIFIC FORMS OF THROMBOTIC MICROANGIOPATHY

Shiga Toxin–Producing *Escherichia coli*–Associated Hemolytic Uremic Syndrome

Mechanisms

Shiga toxin–producing *E. coli*–associated hemolytic uremic syndrome (STEC-HUS) may follow GI infections by certain strains of *E. coli* or *S. dysenteriae* that produce powerful exotoxins (Shiga toxins or Stxs)[12] (see Fig. 29.1 and Table 29.1). Most patients present with bloody diarrhea that may still be present or resolved at the time of presentation of HUS. Multiple strains of *E. coli* (mostly serotype 0157:H7, but also about 200 other serotypes, with the predominance of serogroups 026,

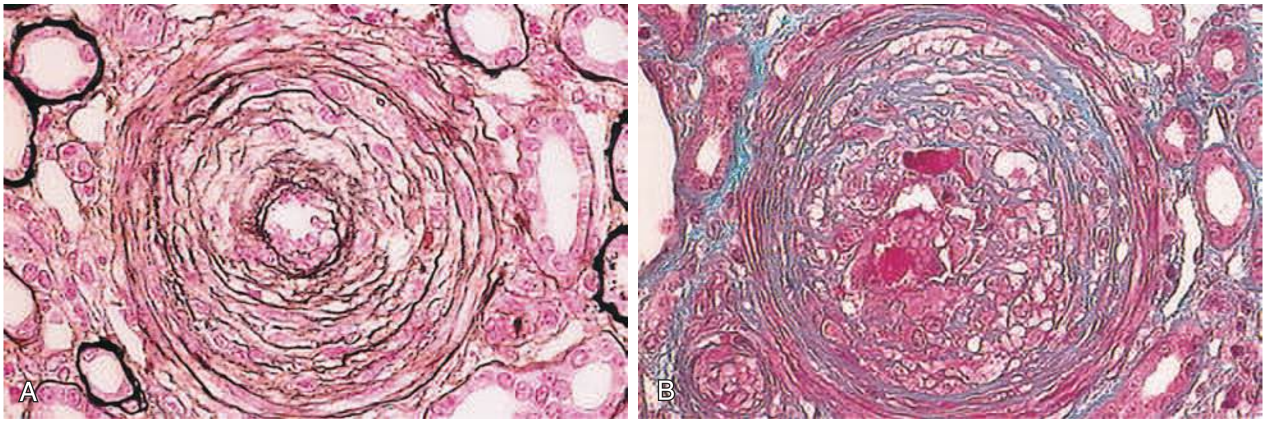


Fig. 29.5 **Interlobular artery in a case of hemolytic-uremic syndrome with severe vascular involvement.** (A) The vascular lumen is almost completely occluded. Changes include myointimal proliferation and reduplication of the lamina elastica. (B) Thrombotic material and erythrocytes can be seen in the lumen and within the vascular wall.

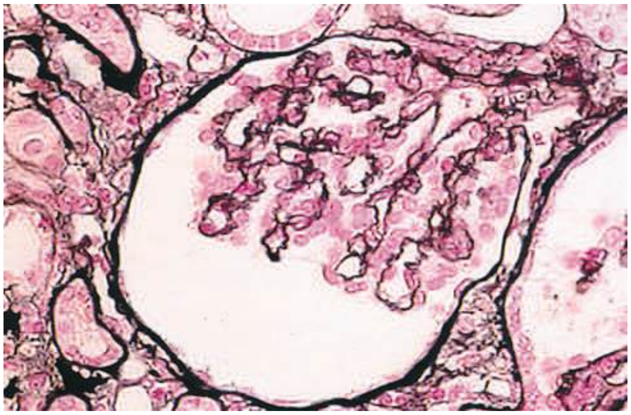


Fig. 29.6 **Glomerulus from a patient with atypical hemolytic uremic syndrome with predominant vascular involvement.** Severe ischemic changes have occurred. Note the shrinkage of the glomerular tuft and marked thickening and wrinkling of the capillary wall.

0103, 0117, 091, 0145, 0128, 0111, and 0146) isolated from human cases with diarrhea were found to produce Stxs (STEC). The natural reservoir of STEC is the GI tract of ruminants (mainly cattle). Most STEC-infected cattle remain free of disease because they lack vascular Stx receptors. Undercooked ground beef, meat patties, raw vegetables, fruit, milk, and recreational or drinking water contaminated by ruminants' excreta, have been implicated in the transmission of STEC.

E. coli 0157:H7 and other STECs have been responsible for multiple outbreaks throughout the world, becoming a public health problem in both developed and developing countries.[12] The very large HUS outbreak in Germany in 2011 was caused by ingestion of sprouts contaminated by an unusual STEC strain, O104:H4.[3] The chain of transmission appeared to have started in Egypt with fecal contamination of fenugreek seeds. It has been suggested that the higher prevalence of women in this outbreak reflects a gender-specific dietary preference.[3] Because no O104:H4 strains were detected in cattle feces collected in the outbreak area, infected ruminants are unlikely the cause of the O104:H4 STEC outbreak.

After food or water is ingested, the toxin is released into the gut and may cause watery or, most often, bloody diarrhea because of a direct effect on the intestinal mucosa. STEC closely adheres to the GI mucosa, causing destruction of brush border villi. Stxs are transported to the intracellular space of GI cells via transcellular pathways and are then translocated into the circulation. Free Stxs have not been detected in the sera of HUS patients, but Stx binds to neutrophils that serve as Stx carriers from the intestine to the kidney and other target organs. It has been proposed that other human blood cells (erythrocytes, platelets, and monocytes) also bind Stx, but the data are controversial.[13]

In the kidney, Stxs bind mainly to specific Gb3 receptors on glomerular endothelial cells but also to podocytes, mesangial cells, and proximal tubules. After binding to cell receptors, the toxin is internalized and inhibits protein synthesis. Treatment of endothelial cells with sublethal doses of Stx, exerting minimal influence on protein synthesis, increased mRNA and protein expression of chemokines and cell adhesion molecules. By altering endothelial cell adhesion properties and metabolism, Stxs favor leukocyte-dependent inflammation and induce loss of thromboresistance in endothelial cells, leading to microvascular thrombosis.

Evidence is also emerging that complement activation at the renal endothelial level may contribute to microangiopathic lesions in STEC-HUS. Low serum levels of C3 were reported in children with STEC-HUS since the 1980s. High serum levels of complement activation products Bb and C5b-9 were measured in children with STEC-HUS, indicating complement activation via the alternative pathway. Stxs might directly contribute to complement activation, as documented by C3 deposition on endothelial cell lines exposed to Stx and then perfused with human serum.[14] Stx-induced complement depostion was associated with loss of endothelial thromboresistance. In a murine model of HUS induced by Stx/lipopolysaccharide (LPS), factor B–deficient mice that cannot activate the alternative pathway of complement, exhibited less thrombocytopenia and were protected against glomerular abnormalities and renal function impairment.[14]

In vitro, tubular epithelial and mesangial cells are as susceptible to the cytotoxic effects of Stxs as endothelial cells. The tubular damage caused by Stx can lead to a reduction in the renal water handling capacity. Stxs inhibit water absorption across human renal tubular epithelial cell monolayers, which may contribute to the early events underlying renal dysfunction in STEC-HUS.

Diagnosis

Diagnosis depends on the detection of *E. coli* O157:H7 and other STECs and their products in stool cultures (see Fig. 29.1). When infection with STEC is suspected, physicians should ensure that stool specimens are collected promptly and specifically cultured for STEC.[12] Unlike most other *E. coli,* serotype O157:H7 does not ferment sorbitol rapidly and thus forms colorless colonies on sorbitol containing MacConkey agar (SMAC). The use of SMAC provides a simple, inexpensive, and generally reliable method of screening stools for *E. coli* O157. The polymerase chain reaction is increasingly being used to detect Stx-encoding genes using DNA directly isolated from stool specimens, providing same-day results.[13] Convalescent-phase serum samples can be assayed for antibodies to O157 or other specific strain-derived LPS; however, the results may be biased by false-positive results due to antibodies preformed during antecedent STEC exposure.[12]

Clinical Course

After exposure to STEC, 38% to 61% of individuals develop hemorrhagic colitis and 3% to 9% (in sporadic infections) to 20% (in epidemic forms) progress to overt HUS (Fig. 29.7).[12,13]

STEC-induced hemorrhagic colitis not complicated by HUS is self-limiting and is not associated with an increased long-term risk for renal dysfunction. STEC-HUS is characterized by prodromal diarrhea followed by AKI. The average interval between *E. coli* exposure and illness is 3 days. Illness typically begins with abdominal cramps and nonbloody diarrhea; diarrhea may become hemorrhagic in 70% of cases usually within 1 or 2 days.[12] Vomiting occurs in 30% to 60% of cases and fever in 30%. Leukocyte count is usually elevated. HUS is usually diagnosed 6 to 10 days after the onset of diarrhea. Seventy-percent of patients who develop HUS require RBC transfusions, 40% to 50% need dialysis for an average duration of 10 days, and the remainder has milder renal involvement without the need for dialysis.[12,15] About 25% of patients with STEC-HUS have neurologic involvement, including lethargy, apnea, cortical blindness, hemiparesis, stroke, seizures, and coma. Rare complications include pancreatitis, diabetes mellitus, myocardial ischemia, and pleural and pericardial effusions. Still, 1% to 2% of patients die during the acute phase.

More than 90% of childhood cases of STEC-HUS fully recover from the acute disease. However a meta-analysis of 49 published studies (3476 patients, including children and adults) describing the long-term prognosis of patients who survived an episode of STEC-HUS, reported death or permanent ESRD in 12% and GFR below 80 ml/min/1.73 m^2 in 25%.[15]

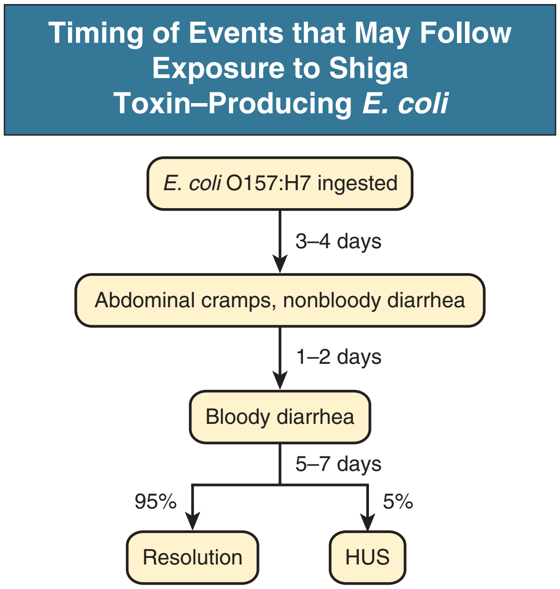

Timing of Events that May Follow Exposure to Shiga Toxin–Producing *E. coli*
E. coli O157:H7 ingested
3–4 days
Abdominal cramps, nonbloody diarrhea
1–2 days
Bloody diarrhea
5–7 days
95%
5%
Resolution
HUS

Fig. 29.7 Timing of events that may follow exposure to Shiga-toxin producing *E. coli*. *HUS,* Hemolytic uremic syndrome.

Disease presentation and outcome were particularly severe during the STEC O104:H4 German outbreak, in which 53 of the 855 HUS cases died.[3] Compared with previous STEC epidemics there was a higher incidence of dialysis-dependent AKI (20% vs. 6%) and death (6% vs. 1%).[3] Nearly half of the patients presented with neurologic symptoms and 20% suffered seizures. The severe clinical phenotype was explained by the lack of previous immunity to this novel STEC strain and its exceptional virulence.[3] *E. coli* O104:H4 not only produces the same Stx as STEC enterohemorrhagic strains but also has 93% of the genomic sequence of enteroaggregative *E. coli* strains, defined by their "stacked-brick" pattern of adhesion to host cells, which form fimbriae that facilitate adhesion to the intestinal wall. The evolution of *E. coli* O104:H4 is likely the result of the acquisition by an enteroaggregative strain of *E. coli* of a Stx-encoding phage from an enterohemorrhagic strain of *STEC*. The combination of these two virulence factors would lead to increased gut colonization and thus the release of increased quantities of toxin into the circulation. Whereas enterohemorrhagic *E. coli* are found in the GI tract of ruminants, enteroaggregative *E. coli* appear to have their reservoir in humans. This might explain why the *E. coli* O104:H4 strain has acquired new resistances to antibiotics most commonly used in human disease.

Therapy

Typical pediatric STEC-HUS treatment relies on supportive management of anemia, renal failure, hypertension, and electrolyte and water imbalance (see Fig. 29.1). Intravenous isotonic volume expansion as soon as an *E. coli* O157:H7 infection is suspected, even before culture results are available, may limit the severity of AKI and the need for renal replacement therapy.[16] Up to 80% of patients receive packed RBCs for symptomatic anemia. Heparin and antithrombotic agents may increase the risk for bleeding and should be avoided. Patients with severe STEC-HUS require careful monitoring, including urine output, weight, volume status, cardiovascular/respiratory function, and early signs of CNS or other organ involvement. Bowel rest is important for the enterohemorrhagic colitis associated with STEC-HUS. Antimotility agents should be avoided because they may prolong the persistence of *E. coli* in the intestinal lumen and therefore increase patient exposure to its toxin.

The use of antibiotics should be restricted to the very few patients presenting with bacteremia because, at least in children with gastroenteritis, they may increase the risk for HUS 17-fold.[17] A possible explanation is that antibiotic-induced injury to the bacterial membrane might favor the acute release of large amounts of preformed toxin. Alternatively, antibiotic therapy might give *E. coli* O157:H7 a selective advantage if these organisms are not as readily eliminated from the bowel as the normal intestinal flora. Moreover, several antimicrobial drugs, particularly the quinolones, trimethoprim, and furazolidone, are potent inducers of the expression of the Stx gene. Azithromycin may be an interesting exception because its use appeared to have some benefit on the duration of bacterial shedding in adult patients from the German O104:H4 epidemic.[18] In contrast to STEC-HUS, hemorrhagic colitis and HUS caused by *S. dysenteriae* should be treated with antibiotics because treatment shortens the duration of diarrhea, decreases the incidence of complications, and reduces the risk for transmission by shortening the duration of bacterial shedding.

Careful blood pressure control and renin-angiotensin system blockade may be beneficial in the long term for patients who develop CKD after an episode of STEC-HUS.[4]

Among newer treatments for Stx-HUS, new Stx-neutralizing monoclonal antibodies are under preclinical development. Other potential therapeutics under development are designed to limit Stx receptor expression or to prevent toxin binding, trafficking, or activity within the cells.[19]

TABLE 29.2 **Specific Therapies Used in Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura, Dosing, and Efficacy**

Therapy	Dosing	Efficacy
Immunosuppressives		
Prednisone	200 mg tapered to 60 mg/day then 5 mg reduction per wk	Probably effective in addition to plasma exchange in patients with TTP and anti-ADAMST13 autoantibodies or in aHUS with anti–factor H autoantibodies and in forms associated with autoimmune diseases. Lack of evidence from controlled trials in immune-mediated HUS or TTP.
Prednisolone	200 mg, tapered to 60 mg/day, then 5 mg reduction per wk	
Immunoglobulins	400 mg/kg/day	
CD20 cell depleting (Rituximab)	375 mg/m^2/wk up to CD20 depletion	Effective in treatment or prevention of TTP associated with immune-mediated ADAMTS 13 deficiency resistant to, or relapsing after, immunosuppressive therapy.
Fresh frozen plasma		
Exchange	1-2 plasma volumes/day	First-line therapy for aHUS and TTP.
Infusion	20-30 ml/kg followed by 10-20 ml/kg/day	Unproven efficacy in childhood STEC-HUS.
Cryosupernatant	See plasma infusion/exchanges.	To be considered if plasma exchange not available.
Solvent-detergent treated plasma	See plasma infusion/exchanges.	To replace whole plasma in case of plasma resistance or sensitization. To limit the risk for infections.
Liver-kidney transplant	Perioperative plasma infusion/exchange and eculizumab	To prevent CFH-associated HUS recurrence post-transplant. About 20% mortality risk.
Complement inhibition (Eculizumab)	900 mg wkly for the first 4 wk 1200 mg every 14 days up to 6 mo	Reported efficacy in aHUS

aHUS, Atypical hemolytic uremic syndrome; *CFH*, complement factor H; *STEC-HUS*, Shiga toxin–producing *Escherichia coli*–associated hemolytic uremic syndrome; *TTP*, thrombotic thrombocytopenic purpura.

The efficacy of specific treatments in adult patients is difficult to evaluate because most information is derived from uncontrolled series that may include atypical HUS cases. No prospective, randomized trials demonstrate whether plasma infusion or exchange are superior to supportive treatment alone (Table 29.2). However, comparative analyses of two large series of patients treated[20] or not treated[21] with plasma suggest that plasma therapy may dramatically decrease overall mortality of STEC 0157:H7–associated HUS. Plasma exchange should therefore be considered in adult patients with severe AKI and CNS involvement.

Kidney transplantation is safe for children who progress to ESRD. Recurrence rates range from 0% to 10%, and graft survival at 10 years is even better than in children with other causes of ESRD.

Evidence that uncontrolled complement activation may contribute to microangiopathic lesions of STEC-HUS[14] led to complement inhibitor therapy with the anti-C5 monoclonal antibody eculizumab in three children with severe STEC-HUS who fully recovered.[22] Eculizumab therapy in the STEC O104:H4 outbreak in Germany led to no significant difference in outcome between patients who received eculizumab together with plasma exchange and those who received plasma exchange alone.[23] However, these data were retrospectively collected. Moreover, patients given eculizumab were also the most severely ill. Whether eculizumab is a useful adjunct to treating the most severe forms of STEC-HUS needs to be clarified by randomized controlled trials.

Hemolytic Uremia Syndrome Associated With *Streptococcus pneumoniae*

Mechanisms

This is a rare (see Fig. 29.1 and Table 29.1) but potentially fatal disease that may complicate pneumonia or, less frequently, meningitis caused by *S. pneumoniae*.[24] Neuraminidase produced by *S. pneumoniae* cleaves N-acetylneuraminic acid from the glycoproteins on the cell membrane of erythrocytes, platelets, and glomerular cells; this exposes the normally hidden Thomsen-Friedenreich antigen (T antigen), which can then react with anti-T IgM antibodies naturally present in human serum. This reaction occurs more frequently in infants and children and causes polyagglutination of RBCs in vitro, so the Coombs test is positive, unlike in other forms of HUS. T-antigen exposure on RBCs is detected using the lectin *Hypogaea*. The finding of severe consumption of complement components in serum during the acute phase and the identification of complement-related gene mutations in a few patients suggests a role for complement dysregulation in this form of HUS.[25]

Clinical Course and Therapy

Patients, usually younger than 2 years, present with a severe illness, including respiratory distress, neurologic involvement, and coma. The acute mortality rate is about 25%. The outcome depends strongly on the effectiveness of antibiotic therapy. In theory, plasma infusion or exchange is contraindicated because adult plasma contains antibodies against the T antigen that may accelerate polyagglutination and hemolysis. Thus patients should be treated with only antibiotics and washed RBCs. In some cases, however, plasma therapy, occasionally in combination with steroids, has been associated with recovery.

Atypical Hemolytic Uremic Syndrome

Atypical HUS (aHUS) has several mechanisms, mainly associated with genetically determined complement dysregulation (see Fig. 29.1 and Table 29.1).[5,26] aHUS is usually sporadic, and fewer than 20% of cases are familial. Although some are in siblings, suggesting autosomal recessive transmission, others occur across two or three generations, indicating an autosomal dominant mode. Incomplete penetrance of the disease in mutation carriers is a common feature that confounds the interpretation of inheritance. Indeed, many sporadic cases of aHUS inherited the genetic defect from an unaffected parent.[27]

Various precipitants of aHUS have been described in complement gene mutation carriers, including nonenteric bacterial and viral infections,[5] immunotherapeutic agents (e.g., cyclosporine, tacrolimus), malignant hypertension, transplantation, and pregnancy.[5] De novo post-transplant HUS has been reported in patients receiving renal transplants or other organs, due to calcineurin inhibitors or humoral rejection. It occurs in 5% to 10% of renal transplant patients who receive cyclosporine and in approximately 1% of those given tacrolimus. In 20% of female patients, aHUS manifests during pregnancy; the disease tends to occur at term or postpartum, within 3 months of delivery in most cases.[4] Pregnancy-associated increased concentrations of procoagulant factor, decreased fibrinolytic activity, and reduced expression of endothelial thrombomodulin may be predisposing factors. A severe form of pregnancy-associated TMA is the HELLP syndrome, in which microangiopathic hemolysis and liver injury accompany hypertension and renal dysfunction. About 50% of atypical HUS cases show no clear trigger (see Table 29.1).

Mechanisms

aHUS is linked to genetically determined dysregulation of the alternative pathway of complement (see Fig. 29.1 and Table 29.1).[5,26] Reduced serum levels of C3 with normal C4 in aHUS patients were reported in about 50% of patients with aHUS.[28] Low C3 reflects complement activation, as documented by high levels of activated products and C3 deposits in glomeruli and other kidney vessels. The complement system is part of innate immunity and consists of several plasma- and membrane-bound proteins protecting against invading organisms. Three activation pathways (Fig. 29.8)—classic, lectin, and alternative pathways—produce protease complexes, termed C3 and C5 convertases, that cleave C3 and C5, respectively, eventually leading to the membrane attack complex (MAC or C5b-9) that causes cell lysis. The alternative pathway (Fig. 29.9) is initiated spontaneously in plasma by C3 hydrolysis responsible for deposition of a low amount of C3b onto all plasma-exposed surfaces. On bacterial surfaces, C3b leads to phagocytosis by neutrophils and macrophages. Without regulation, a small initiating stimulus is quickly amplified to a self-harming response until complement components are depleted. On host cells, such a dangerous cascade is controlled by membrane-anchored and fluid-phase regulators (see Fig. 29.9). They both favor the cleavage of C3b to inactive iC3b by the plasma serine protease factor I (CFI, cofactor activity) and dissociate the C3 and C5 convertases (decay acceleration activity). Foreign targets and injured cells that either lack membrane-bound regulators or cannot bind soluble regulators are attacked by complement.

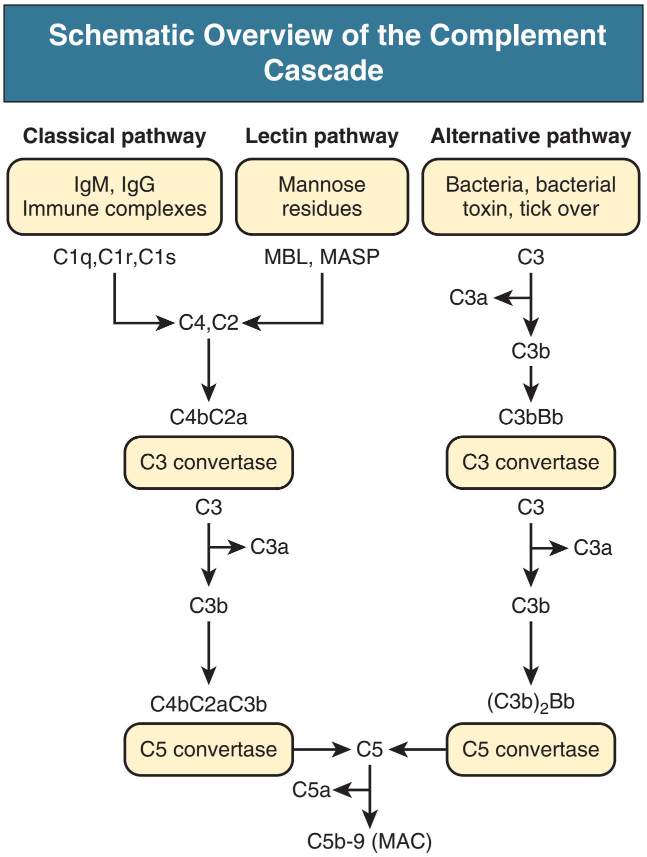


Fig. 29.8 Schematic overview of the complement cascade illustrating the three activation pathways (classical, lectin and alternative) and the membrane attack complex. *MBL,* membrane binding lectin; *MASP,* mannose-associated serine protease; *MAC,* membrane attack complex.

The C3 convertases of the classic/lectin pathways are formed by C2 and C4 fragments, whereas the alternative pathway convertase requires cleavage of C3 only (see Fig. 29.9). Thus low serum C3 levels in aHUS with normal C4 indicated selective alternative pathway activation.[28]

Several genetic abnormalities in members of the alternative pathway of complement have been described in aHUS, which account for about 60% of cases (see Table 29.1). Functional studies revealed that aHUS-associated mutations mainly result in complement activation that is restricted on the cell surface—which explains the normal circulating complement profile in about half of patients—and proceeds until the formation of C5b-9.[29]

Complement factor H. Complement factor H (CFH) regulates the alternative pathway both in the fluid phase and on the cell surface by acting as a cofactor for CFI and enhancing dissociation of C3 convertase (see Fig. 29.9). Over 120 *CFH* mutations (http://www.FH-HUS.org) have been identified in aHUS patients (mutation frequency about 30%).[30] These mutations most commonly are associated with normal CFH levels, but instead result in a protein that is unable to bind to and regulate complement on endothelial cells and platelets.[31] A high degree of sequence identity between *CFH* and the genes *CFHR1-5* for five factor H–related proteins (CFHR) located in tandem to *CFH* may predispose to gene conversions and genomic rearrangements.[32] Hybrid *CFH/CFHR1* and *CFH/CFHR3* genes, coding abnormal FH proteins in which the carboxy-terminal domains that mediate complement regulation on cell surface are substituted for those of FHR1 or by the entire FHR3 have been reported in 3% to 5% of patients with aHUS. The resulting gene products are hybrid FH molecules with decreased complement regulatory activity on endothelial surfaces.[32] Additional forms of *CFH/CFHRs* hybrid genes have been recently described.[33]

Anti-CFH inhibitory antibodies have been reported in 5% to 10% of aHUS patients and around 25% to 50% of pediatric cases.[34] Analogous to *CFH* genetic defects, these autoantibodies predominantly target the C-terminal end, thereby impairing complement regulation on host cell surfaces. The development of CFH autoantibodies in aHUS has a genetic predisposition, being strongly associated with the homozygous deletion of the *CFHR1* and *CFHR3* genes.[34]

Membrane cofactor protein. MCP is a transmembrane complement regulator widely expressed on all cells apart from erythrocytes. MCP serves as a cofactor for CFI to cleave C3b and C4b (see Fig. 29.9). *MCP* mutations account for 8% to 10% aHUS cases.[30] Most are heterozygous (http://www.FH-HUS.org). The majority cluster in critical extracellular modules for regulation. Expression on blood leukocytes was reduced for about 75% of mutants. Others have low C3b-binding capability and decreased cofactor activity.[30]

Complement factor I. CFI is a plasma serine protease that regulates the three complement pathways by cleaving C3b and C4b in the presence of cofactor proteins (see Figs. 29.8 and 29.9). *CFI* mutations affect 4% to 8% of patients.[30,35] All mutations are heterozygous, 80% cluster in the serine-protease domain. Approximately 50% of mutants are not

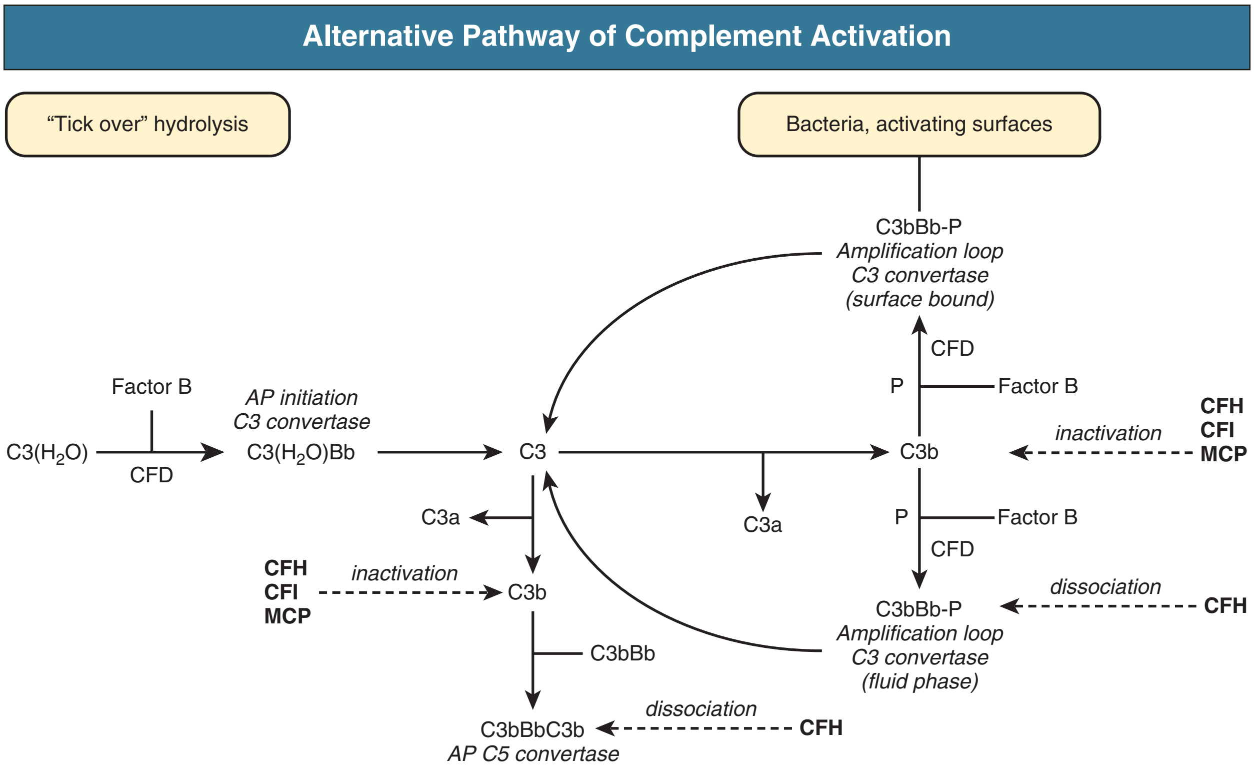


Fig. 29.9 Alternative pathway of complement activation. The alternative pathway *(AP)* is continuously activated in plasma by low-grade hydrolysis of C3. The latter binds factor B, to form a C3(H$_2$O)B complex. Factor D *(CFD)* cleaves factor B to form the AP initiation C3 convertase that cleaves C3 to C3b. The activation is then amplified by the covalent binding of a small amount of C3b to hydroxyl groups on cell-surface carbohydrates and proteins of target cells such as bacterial cells. This C3b binds factor B, to form the amplification loop C3 convertase C3bBb. C3 convertase enzymes cleave many molecules of C3, resulting in a positive feedback amplification loop. C3b also binds to the C3 convertase forming the C5 convertase enzyme C3b$_2$Bb. The AP is highly regulated as to prevent nonspecific damage to host cells and limit the deposition of complement to the surface of pathogens. This fine regulation occurs through a number of membrane-anchored and fluid phase regulators. *CFH,* Complement factor H (acts as cofactor for factor I for C3b cleavage and favors the decay of the C3 convertase of the AP); *CFI,* complement factor I (degrades C3b and C4b); *CR1,* complement receptor 1 (has decay accelerating activity as well as cofactor activity for factor I–mediated cleavage of C3b and C4b); *DAF,* decay accelerating factor (destabilizes the C3 and C5 convertases of the classic and alternative pathways); *MCP,* membrane cofactor protein (binds C3b and C4b and has cofactor activity for both the classic and alternative pathways).

secreted; however, some mutants are secreted but have impaired proteolytic activity.[30,35]

Complement factor B and C3. Gain-of-function mutations can affect genes encoding the alternative pathway C3 convertase components, CFB and C3.[36,37] *CFB* mutations are rare (1% to 2%).[37] CFB mutants have excess C3b affinity and form a hyperactive C3 convertase resistant to dissociation.[37] About 4% to 8% of aHUS patients have heterozygous mutations in *C3,* usually with low C3 levels.[36] Most mutations reduce C3b binding to complement regulators, severely impairing its inactivation and result in increased C3 deposition on endothelial cells.[36]

Thrombomodulin. Heterozygous mutations in the gene *THBD* encoding thrombomodulin, an endothelial surface anticoagulant protein that also modulates complement on cell surfaces, have been found in 3% to 4% of patients with aHUS.[38] Cells expressing *THBD* variants inactivate C3b less efficiently.[38]

Determinants of disease penetrance. Two other factors are thought to determine the development of aHUS. First, in most patients there is a trigger, most frequently infection and pregnancy.[39] Second, a further genetic variant (modifier) can increase the risk for developing the disease. This can be an additional mutation in one of the aforementioned genes; it is now recognized that approximately 10% of aHUS patients will have mutations in more than one gene.[40] Common genetic risk variants (single-nucleotide polymorphisms [SNPs] and haplotype blocks) in *CFH, MCP,* and *CFHR1* have been shown to act as susceptibility factors for the development of aHUS.[40]

***Diacylglycerol kinase* ε.** Homozygous or compound heterozygous mutations in *DGKE,* encoding the intracellular protein diacylglycerol kinase ε, have been recently associated with infantile recessive aHUS.[41] Mutation carriers presented with aHUS before 1 year of age (see Table 29.1), with hypertension, hematuria, and severe proteinuria, often in nephrotic range. *DGKE* is expressed in endothelium, platelets, and podocytes, is involved in terminating diacylglycerol signaling, and is not directly linked to complement. *DGKE* silencing in endothelial cells induced a proinflammatory and prothrombotic phenotype.

Diagnosis of Atypical Hemolytic Uremia Syndrome and Testing for Genetic Mutations

Differential diagnosis of aHUS requires exclusion of infections by STEC or neuroaminidase-producing *S. pneumoniae* of ADAMTS13 deficiency or autoantibodies against ADAMTS13 and systemic associated diseases

TABLE 29.3 Outcome of Atypical Hemolytic Uremic Syndrome According to the Associated Genetic Abnormality

Affected Gene	Affected Protein and Main Effect	Frequency in aHUS (%)	Rate of Remission With Plasma Exchange* (%)	5- to 10-Year Rate of Death or ESRD† (%)	Recurrence Rate After Kidney Transplant† (%)
CFH	Factor H (no binding to endothelium)	30	60 (dose and timing dependent)	70-80	60-70
CFHR1/3	Factor HR1, R3 (anti–factor H antibodies)	5-10	70-80 (combined with immunosuppression)	30-40	30
MCP	Membrane cofactor protein (no surface expression)	10-15	No indication to plasma exchange	<20	15-20
CFI	Factor I (low levels/low cofactor act)	4-10	30-40	60-70	70-80
CFB	Factor B (C3 convertase stabilization)	1-2	30	70	One case reported
C3	Complement C3 (resistance to C3b inactivation)	8-10	40-50	60	40-50
THBD	Thrombomodulin (reduced C3b inactivation)	4-5	60	60	One case reported

*Complete remission or hematologic remission with renal sequelae.

†The data are related to the period before the introduction of anticomplement therapy.

(see Fig. 29.1).[26] Full analysis of disease-associated genes and testing for anti-CFH antibodies is recommended for patients who progress to ESRD and are candidates for kidney transplantation. Reference laboratories in several countries are equipped for genetic and antibody testing. Although new sequencing techniques have reduced cost and time, a complete evaluation still requires several days. Treatment of acute episodes (plasma therapy or eculizumab when available, see later discussion) should be started very rapidly after clinical diagnosis, without waiting for results of genetic and anti-CFH antibody tests.

Clinical Course

Sixty percent of patients, irrespective of mutation type, are affected during childhood,[30] and almost all patients with anti-CFH antibodies developed the disease before 16 years of age.[42] Acute episodes manifest with severe hemolytic anemia, thrombocytopenia, and AKI. Extrarenal involvement (CNS or multivisceral) occurs in 20% of cases.[5,30,39] Short- and long-term outcomes vary according to the underlying complement abnormality (Table 29.3). Until a few years ago, 50% to 70% of patients with *CFH, CF, C3, CFB, or THBD* mutations and 40% of children with anti-CFH autoantibodies lost renal function, died during the presenting episode, or developed ESRD after relapses (see Table 29.3).[5,30] Chronic complement dysregulation may lead to atheroma-like lesions with cardiovascular complications and excess mortality. In *MCP*-mutation carriers, recurrences were frequent but long-term outcome was good and 80% of patients remained dialysis-free.[5,30] However, rare patients with *MCP* mutations had severe disease, immediate ESRD, intractable hypertension, and coma, possibly because of concurrent genetic abnormalities.[40]

Therapy

Fresh frozen plasma. Plasma therapy (plasma exchange, 1 to 2 plasma volumes/day; plasma infusion, 20 to 30 ml/kg/day) has been the gold standard of aHUS therapy since the 1980s and was essentially the only therapy available until 2011 (see Table 29.2). Consensus-based guidelines recommended that plasma therapy should be started within 24 hours of diagnosis and then continued until remission or a declaration of nonresponse.[5] Because CFH is a plasma protein, plasma infusion or exchange provides normal CFH to patients carrying *CFH* mutations.[30,39] Long-term treatment, however, may fail as a result of development of plasma resistance.[43] Heterozygous *CFH* mutation carriers usually have normal levels of CFH, half of which is dysfunctional. The beneficial effect of plasma is strongly dependent on the amount, frequency, and modality of administration, with plasma exchange being superior to plasma infusion by removal of mutant CFH that could antagonize the normal protein. Plasma exchange in association with immunosuppressive therapy (induction with corticosteroids and cyclophosphamide, and maintenance with azathioprine or mycophenolate mofetil), is recommended in patients with anti-CFH antibodies, to remove the inhibitory antibodies[26,34] and allowed long-term dialysis-free survival in 60% to 70% of patients.[34] Data on the effect of rituximab, an anti-CD20 antibody, in such circumstances are scanty and inconsistent: of five patients treated with rituximab alone or with plasma exchange, only two showed disappearance of anti-CFH antibodies.[34]

Patients with *CFI* mutations showed a partial response to plasma (see Table 29.3).[5,30,39] Thirty to forty percent of patients with *CFB* mutations and 50% of those with *C3* mutations responded to plasma infusion or exchange.[5,36,37] Possibly these patients need frequent large-volume plasma exchange to clear the hyper-functional mutant *CFB* and *C3*.[5] Because MCP is a cell-associated protein, effects of plasma are unlikely in patients with *MCP* mutations. Indeed 80% of patients with an *MCP* mutation underwent spontaneous remission independently of plasma treatment (see Table 29.3).[5,30,39]

Kidney transplantation The outcome of kidney transplantation in aHUS was poor because of the high frequency of disease recurrence. Disease recurred in 60% to 80% of transplanted patients with mutations in complement circulating proteins (CFH, CFI, CFB, and C3) and graft failure occurred in 80% to 90%[36,37,44] (see Table 29.3). The risk for post-transplant aHUS recurrence in patients with anti-CFH autoantibodies is not well known because available information is limited to 27 renal transplants in 21 patients.[34] Recurrence of HUS was documented in eight (30%) cases. A reduction in autoantibody levels with plasma exchange, steroids, and/or rituximab, enabled successful renal transplantation in few patients.[34]

The lowest incidence of recurrence was observed in patients with *MCP* and *DGKE* mutations.[41,44] *MCP* and *DGKE* are highly expressed in the kidney, and a graft that brings normal proteins corrects the defect. However, about 20% of patients with *MCP* mutations also carry a mutation in another complement gene. Such patients have a worse graft outcome with higher incidence of recurrences than patients with an isolated *MCP* mutation.[40]

Testing affected patients for mutations on all disease-associated genes should allow patients and clinicians to make informed decisions regarding listing for transplantation based on risk for recurrence.

Most studies have shown that plasma exchange therapy fails to prevent graft loss in patients with recurrent post-transplant HUS.[44] A preemptive plasma infusion or exchange strategy has been successful in preventing recurrent aHUS in renal transplant recipients, although aHUS recurred in some when plasma therapy was tapered.[45]

Living-related kidney donation is contraindicated given the high risk for recurrence, and it even may be risky to donors because uninephrectomy may precipitate aHUS if they are complement gene mutation carriers.

Complement inhibitors. The humanized anti-C5 monoclonal antibody eculizumab was approved in 2011 in the United States and Europe for the treatment of aHUS and has profoundly changed aHUS management. The efficacy and safety of eculizumab in inducing remission of acute episodes of aHUS and maintaining long-term remission, both in native kidneys and in the kidney grafts, was documented in two prospective clinical trials of primarily adult patients with plasma-dependent or plasma-resistant aHUS[46] and in a pediatric trial in 22 children, of whom 12 had no prior plasma treatment.[47] Eculizumab is now widely used as a first-line therapy for aHUS, provided that other causes of TMA are excluded (see Fig. 29.1).[26] The main concern with eculizumab is increased susceptibility to infection with encapsulated organisms, particularly *Neisseria* infections. For this reason, patients must receive meningococcal vaccination. Patients should receive vaccination against meningococcus, including type B; however, vaccination should not delay the start of eculizumab. Antibiotic prophylaxis is mandated during the first 2 weeks and is recommended for the overall treatment duration because not all serotypes are covered by vaccination.[26]

It is not clear how long eculizumab therapy should be extended, a relevant issue because of the very high cost of the drug. In addition, the risk for sensitization associated with chronic eculizumab exposure or with its deposition in tissue, and the recent report of hepatoxicity in pediatric patients,[48] suggest that careful tapering to withdrawal whenever possible, should be attempted, under tight control of disease and complement activity.[29]

Conceivably, chronic lifetime treatment with eculizumab at doses able to persistently block the complement cascade might be indicated to prevent disease recurrence in some cases. A retrospective study of aHUS patients who discontinued eculizumab in the French Registry showed no relapse in patients without identified complement gene mutations, whereas disease relapses occurred in 72% of patients with *CFH* mutations and 50% of those with *MCP* mutations.[49] However, whether and to what extent this applies to all patients with aHUS and complement abnormalities is unknown, and controlled clinical studies are required. Different clinical courses before eculizumab therapy, and different residual complement activity while on eculizumab therapy, should be taken into consideration when strategies of chronic eculizumab therapy or discontinuation are planned.

Liver-kidney transplant. In patients with *CFH* mutations combined liver-kidney transplant have been done with the rationale of correcting the genetic complement defect, thus preventing disease recurrence in the transplanted kidney (see Table 29.2). Liver transplantation, in contrast to eculizumab therapy, cures aHUS definitively without the need of specific therapies other than standard immunosuppression to prevent graft rejection. The short-term mortality risk associated with acute complement activation in the liver graft observed in initial attempts has been substantially reduced with prophylactic plasma exchange and perioperative eculizumab. Over 80% of patients with aHUS who received liver transplants to date with the previously described preparative regimen have had excellent long-term outcomes.[50,51] However, the risks for kidney and liver transplantation have limited the widespread dissemination of this option and a careful assessment of benefits in candidate patients is required.

Thrombotic Microangiopathy Associated With Cobalamin C Deficiency

A renal TMA can manifest in methylmalonic aciduria and homocystinuria caused by recessive mutations in the *MMACHC* gene, which result in deficiency of cobalamin C type (cblC), the most common genetic functional variant of cobalamin (vitamin B_{12}) (see Fig. 29.1 and Table 29.1). It is a rare condition, and only 36 cases of TMA associated with cblC defect have been reported. Pulmonary hypertension may accompany the disease. Diagnosis is facilitated by finding elevated plasma homocysteine and methylmalonic aciduria. TMA usually presents in early infancy, although adult onset has also been reported. Mortality is high if untreated, but metabolic therapy with hydroxycobalamin is very effective.

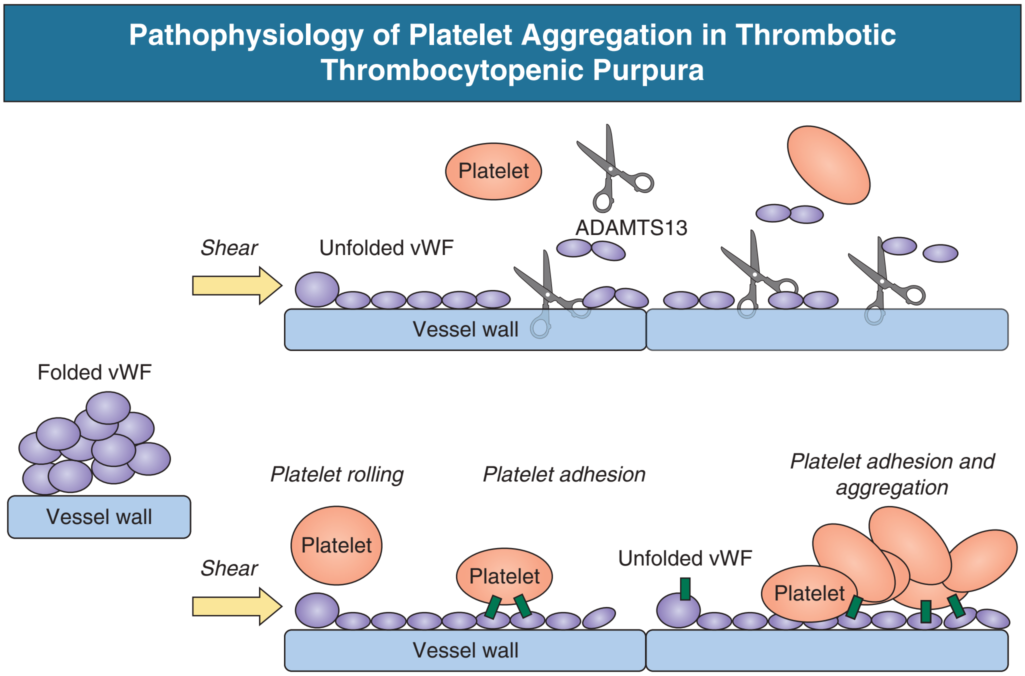
Thrombotic Thrombocytopenic Purpura

In the microvasculature of patients with TTP, systemic platelet thrombi develop, mainly formed by platelets and von Willebrand factor (VWF). VWF plays a major role in primary hemostasis, forming platelet plugs at sites of vascular injury under high shear stress. VWF is synthesized in vascular endothelial cells and megakaryocytes as a high-molecular-weight polymer[52] and stored in the Weibel-Palade bodies. On stimulation, VWF is secreted by endothelial cells as ultra-large (UL) multimers that form string-like structures attached to the endothelial cells, possibly through interaction with P-selectin. Under fluid shear stress, the UL-VWF strings are cleaved to generate the range of VWF multimer sizes that normally circulate in the blood.[53] The proteolytic cleavage of VWF multimers appears to be critical to prevent thrombosis in the microvasculature.

ADAMTS13 is the protease responsible for cleaving VWF, creating 140- and 176-kDa fragments (Fig. 29.10). It derives primarily from the stellate cells of the liver. ADAMTS13 is also expressed, albeit at lower levels, in other types of cells such as renal podocytes and tubular cells, vascular endothelial cells, and platelets. The plasma concentration of ADAMTS13 is approximately 1 μg/ml (5 nmol/l). The elimination half-life of ADAMTS13 is 1 to 2 days in the circulation.

Mechanisms

ADAMTS13 is severely deficient in patients with primary TTP leading to accumulation of UL-VWF multimers that are highly reactive with platelets.[54,55] Exposure of UL-VWF multimers and platelets to shear stress leads to platelet aggregation. The levels of shear stress necessary for inducing platelet aggregation is in the range found in normal arteriolar and capillary circulation. Therefore VWF and platelets have a propensity to form aggregates in normal arterioles and capillaries that need to be constantly regulated. By cleaving UL-VWF multimers before they are activated by shear stress to cause platelet aggregation, ADAMTS13 prevents spontaneous microvascular thrombosis in the normal circulation (see Fig. 29.10). The platelet aggregation observed in patients with TTP and ADAMTS13 deficiency is thus a direct consequence of the accumulation of UL-VWF multimers. Consequently, microvascular thrombi occur in almost all organ vessels,



Pathophysiology of Platelet Aggregation in Thrombotic Thrombocytopenic Purpura

Fig. 29.10 The pathophysiology of platelet aggregation in thrombotic thrombocytopenic purpura. Von Willebrand factor *(VWF)* is synthesized and stored as ultra-large (UL) multimers in endothelial cells and megakaryocytes. On stimulation, UL-VWF multimers are secreted by endothelial cells into the circulation in a folded structure. On exposure to enhanced shear stress, UL multimers form string-like structures that adhere to endothelial cells. Normally, UL-VWF strings are cleaved by ADAMTS13 to generate VWF multimers from 500 kDa to 20 million Da and prevent thrombosis in the microvasculature *(upper panel)*. When the ADAMTS13 proteolytic activity is defective because of the inhibitory effect of anti-ADAMTS13 autoantibodies or congenital defective synthesis of the protease, UL-VWF multimers accumulate and interact with activated platelets to facilitate platelet adhesion and aggregation, with thrombi formation and occlusion of the vascular lumen *(lower panel)*.

resulting in diffuse organ ischemia and thrombocytopenia secondary to platelet consumption.

Two mechanisms for deficiency of the ADAMTS13 activity have been identified, an acquired deficiency secondary to the formation of anti-ADAMTS13 autoantibodies (acquired TTP) and a genetic deficiency resulting from homozygous or compound heterozygous mutations in *ADAMTS13* (genetic TTP) (see Fig. 29.1).

TTP associated with Anti-ADAMTS13 antibodies. This form accounts for the majority of acute primary cases (60% to 90%) and is characterized by severe functional deficiency of ADAMTS13 because of transient, specific autoantibodies that tend to disappear during remission (see Fig. 29.1 and Table 29.1).[55] Patients with TTP secondary to hematopoietic stem cell transplantation, malignancies, or HIV infection rarely have severe ADAMTS13 deficiency and inhibitory IgG antibodies.[56] Severe ADAMTS13 deficiency and ADAMTS13 inhibitory antibodies were detected in 80% to 90% of patients with ticlopidine-associated TTP and in a few patients with clopidogrel-induced TTP (see Table 29.1). The deficiency resolved after the drugs were discontinued. ADAMTS13 inhibitors have not been described in other drug-associated TTP. TTP diagnosed during pregnancy comprises approximately 7% of all TTP cases. Most of these cases have acquired ADAMTS13 deficiency, but pregnancy also has been reported as a triggering event in patients with genetic ADAMTS13 deficiency (see later discussion).

The pathogenicity of TTP-associated anti-ADAMTS13 autoantibodies is supported by the observation that they usually disappear from the circulation when remission is achieved by effective treatment and that this occurs in parallel with the normalization of ADAMTS13 activity.

TTP associated with genetic deficiency of ADAMTS13. This rare inherited form of TTP is associated with homozygous or compound heterozygous mutation in the *ADAMTS13* gene and accounts for about 5% of all of cases of TTP (see Table 29.1). The disease is inherited as a recessive trait in patients with and without a family history of TTP[57]; more than 120 *ADAMTS13* mutations have been identified.[58] Studies on secretion and activity of the mutated forms of *ADAMTS13* showed that most of these mutations led to impaired secretion of the protease from the cells, and when the mutated protein is secreted the proteolytic activity is greatly reduced.

Most patients are carriers of compound heterozygous mutations; only 20% of mutations have been observed in homozygous form.

Clinical Course

Compared with patients with less severe ADAMTS13 deficiency, severely deficient patients experience a higher proportion of therapy-induced remissions (82% to 88% vs. 20% to 75%) and lower mortality (8% to 18% vs. 18% to 80%).[56] The high mortality risk in non–severely deficient patients may be due to the higher proportion of secondary causes and death from underlying diseases, such as patients with hematologic malignancies.

Among patients who have a severe ADAMTS13 deficiency, patients with inhibitory antibodies experience a more severe manifestation of the disease, take a substantially longer time to achieve clinical remission and require a higher plasma volume than patients with genetic ADAMTS13 deficiency. In patients with inhibitory antibodies, a risk as high as 50% to develop relapses has been reported and undetectable ADAMTS13 activity and persistence of anti-ADAMTS13 inhibitors during remission predict recurrences.

TTP has been reported in 1 in every 1600 to 5000 patients treated with ticlopidine, and 11 cases have been reported during treatment with clopidogrel. The overall survival rate is 67% and is improved by early treatment withdrawal and plasma therapy.

Approximately 60% of patients with genetic deficiency of ADAMTS13 experience their first acute episode of disease in the neonatal period or during infancy, but a second group (10% to 20%) manifests the disease after the third decade of life. TTP recurrences occur in 80% of patients,[58] but their frequency varies widely. Whereas some patients with genetic ADAMTS13 deficiency depend on frequent chronic plasma infusions to prevent recurrences, other patients remain free of disease for long periods after plasma discontinuation. The type and location of *ADAMTS13* mutations may influence the age of onset of TTP and the penetrance of the disease in mutation carriers. Mutations resulting in very low residual ADAMTS13 activity (<1%) were associated with childhood onset, relapsing disease, and renal impairment.[10]

Environmental factors may contribute to induce full-blown manifestation of the disease. According to this "two hit model," deficiency of ADAMTS13 predisposes to microvascular thrombosis and TMA supervenes after a triggering event that activates microvascular endothelial cells and causes the secretion of UL-VWF multimers. Potential triggers of these phenomena are infections and pregnancy.

Therapy

Plasma is the cornerstone of therapy in an acute episode because it replaces defective protease activity. Plasma exchange, as compared with infusion, may offer the additional advantage of rapidly removing anti-ADAMTS13 antibodies, if present (see Table 29.2).[6]

Because of the potential for sudden clinical deterioration, treatment should be initiated as soon as possible after diagnosis. Treatment consists of a daily 1 to 2 plasma volume exchange until clinical symptoms have resolved and the platelet count is stably normal (≥150,000/µl). Fresh-frozen plasma and cryosupernatant plasma are considered equivalent because of comparable levels of ADAMTS13.

Corticosteroids (see Table 29.2) given in combination with plasma therapy may be beneficial in autoimmune forms of TTP by inhibiting the synthesis of anti-ADAMTS13 autoantibodies; plasma exchange will have only a temporary effect on the autoimmune basis of the disease, but additional immunosuppressive treatment may cause a more durable response. A recent randomized clinical trial found that caplacizumab, an anti-VWF humanized single-variable-domain immunoglobulin (nanobody), combined with plasma exchange was associated with a shorter time to normalization of the platelet count than was plasma exchange plus placebo in patients with acquired TTP.[59]

Prospective studies have successfully and safely used rituximab (see Table 29.2) in patients who failed to respond to standard daily plasma exchange and methylprednisolone and in patients with relapsed acute TTP who previously had antibodies to ADAMTS13. Treatment was associated with clinical remission, disappearance of anti-ADAMTS13 antibodies, and increase of ADAMTS13 activity to levels greater than 10%.[60] However, time to remission has been variable, from 1 to 4 weeks after the first dose. The duration of remission has ranged between 9 months and 4 years, with relapses reported in approximately 10%. Rituximab also has been used electively to prevent relapses in patients with autoantibodies and recurrent disease.[61] Longitudinal evaluation of ADAMTS13 activity and autoantibody levels may help monitor patient response to treatment. Re-treatment with rituximab should be considered when ADAMTS13 activity decreases and inhibitors reappear into the circulation, to prevent a relapse. The proteasome inhibitor bortezomib induces and maintains remission in patients with relapsed or refractory acquired TTP, but prospective trials are needed to determine the treatment schedule and the efficacy.[62]

In genetic forms of TTP, ADAMTS13 is constitutively lacking and can be replaced by plasma therapy. During acute episodes, patients often require plasma exchange to restore a stable clinical and laboratory state. Providing sufficient ADAMTS13 to achieve 5% normal enzymatic activity may be sufficient to degrade large VWF multimers—which may induce remission of the microangiopathic process—and this effect is sustained over time. Infused ADAMTS13 has a plasma half-life of 2 to 3 days in vivo, and although plasma levels fall below 5% within 3 to 7 days after plasma administration, the effect of plasma on platelet count and clinical parameters may last up to 3 weeks, suggesting that ADAMTS13 remains available, for example, on platelets and endothelial cells. Patients with genetic ADAMTS13 deficiency tend to relapse. Patients with frequent relapses, a severe clinical course with neurologic sequelae, renal insufficiency, and siblings who have died of TTP, should be put on regular prophylactic plasma infusions every 2 to 3 weeks, a regimen that has been shown to be effective in preventing episodes of acute TTP and maintaining the patients in good health for years.

Other Forms of Thrombotic Microangiopathies Associated With Systemic Diseases or Drugs

Antiphospholipid Syndrome, Scleroderma, and Hypertensive Emergencies

Plasma therapy always should be attempted in TMA that is associated with systemic diseases even though its efficacy is poorly defined (see Fig. 29.1 and Table 29.1). In antiphospholipid syndrome (see Chapter 28), oral anticoagulation remains the only treatment of proven efficacy to prevent and treat microvascular and macrovascular thrombosis, even if concomitant thrombocytopenia may increase the risk for bleeding. Preliminary reports suggest that rituximab may be efficacious, but further controlled studies are needed.[63]

Blood pressure control is fundamental in TMA associated with scleroderma crisis and hypertensive emergencies.

Human Immunodeficiency Virus

HUS and TTP are both possible complications of acquired immunodeficiency syndrome (AIDS) that may account for as many as 30% of hospitalized TMA patients where AIDS is epidemic (see Fig. 29.1 and Table 29.1). Plasma therapy is the only feasible approach in these forms, although the prognosis is poor.

Malignancy

Spontaneous TMA complicates almost 6% of cases of metastatic gastric carcinoma, which in turn accounts for about 50% of all malignant disease–associated TMA (see Fig. 29.1 and Table 29.1). The prognosis is extremely poor. Therapy is minimally effective.

Thrombotic Microangiopathy After Bone Marrow Transplantation

TMA complicates 10% to 40% of allogeneic bone marrow and hematopoietic stem cell transplants and is associated with high mortality[64] (see Fig. 29.1 and Table 29.1). The disease is multifactorial, with risk factors including immunosuppressive drugs, graft-versus-host disease, chemotherapy, radiation, and infections. Treatment remains controversial. Some evidence suggests that complement is activated and favorable outcomes with eculizumab have been described in a few cases, but prospective trials are needed to establish a consensus.

Drugs

TMA, more commonly resembling HUS, is described in 2% to 10% of cancer patients treated with mitomycin C[65] (see Fig. 29.1 and Table 29.1). Patients who develop mitomycin C–associated TMA are usually in remission from their malignancy. The fatality rate is about 70%;

patients surviving the acute phase often remain on chronic dialysis or die later of recurrence of the tumor or metastases. The possibility of preventing the disease by giving corticosteroids during mitomycin treatment has been suggested and needs to be confirmed. Plasma exchange is usually attempted, but its effectiveness is unproven. Quinine is one of the most common drugs associated with TMA.[65] It is generally used to treat muscle cramps but is also contained in beverages and nutrition health products (e.g., tonic water, herbal preparations). Quinine-dependent platelet, erythrocyte, granulocyte, lymphocyte, and endothelial antibodies may contribute to the pathogenesis. Severe renal impairment is frequent, and hemodialysis is required in most cases. High rates of death and CKD have been reported. Quinine cessation and plasma therapy should be initiated rapidly. TMA associated with interferon-α is characterized by predominant renal impairment. Recovery of the disease is common in cases of early discontinuation of the drug and prompt supportive therapy. However, kidney prognosis is usually poor, with ESRD reported in about 42% of cases.

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SELF-ASSESSMENT QUESTIONS

1. Which are the common clinical features characterizing patients with thrombotic microangiopathies?
   A. Thrombocytopenia, nonimmune hemolytic anemia, with or without neurologic and/or renal dysfunction
   B. Diarrhea and renal dysfunction
   C. Anemia, antiplatelet antibodies, and purpura
   D. Disseminated intravascular coagulation
2. Which is the *most* common form of thrombotic microangiopathy?
   A. Atypical hemolytic uremic syndrome
   B. Shiga toxin *E. coli*–associated hemolytic uremic syndrome
   C. Thrombotic thrombocytopenic purpura
   D. Antiphospholipid syndrome
3. Which is the *most* common genetic abnormality associated with atypical hemolytic uremic syndrome (aHUS)?
   A. *C3* mutations
   B. *ADAMT13* mutations
   C. *CFH* mutations
   D. *CFTR* mutations
4. Which of the following is *not* indicated for treatment of aHUS?
   A. Conservative therapy
   B. Eculizumab
   C. Plasma exchange
   D. Antibiotics
5. For which of the following is there an indication for rituximab?
   A. Thrombotic thrombocytopenic purpura (TTP) with congenital ADAMTS13 deficiency
   B. Shiga-toxin producing *Escherichia coli*–associated HUS
   C. TTP with anti-ADAMTS13 antibodies
   D. aHUS-associated with *MCP* mutations

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Pathogenesis, Clinical Manifestations, and Natural History of Diabetic Kidney Disease

Sydney Tang, Kumar Sharma

DEFINITIONS

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) in the developed world. It can develop in the course of both type 1 and type 2 diabetes and as a consequence of other forms of diabetes mellitus (DM). *Type 1 diabetes* is an autoimmune disease characterized by antibody-mediated and cell-mediated destruction of pancreatic islets. Type 1 diabetes may occur at any age but usually presents before the age of 30 years. *Type 2 diabetes* is characterized by a combination of insulin resistance and insulin deficiency. The *metabolic syndrome* (insulin resistance, visceral obesity, hypertension, hyperuricemia, and dyslipidemia) is often followed by type 2 diabetes. For a long period, insulin resistance is compensated by increased insulin secretion, but a gradual decline in pancreatic β-cell function finally culminates in hyperglycemia, and patients with type 2 diabetes may require treatment with insulin. Type 2 diabetes was typically a disease of elderly adults, but recently it is increasingly seen in younger adults, adolescents, and even children. Other types of DM include maturity-onset diabetes of the young, gestational diabetes, and diabetes secondary to various metabolic disorders or the result of corticosteroid or other immunomodulatory treatments.

PATHOGENESIS OF DIABETIC KIDNEY DISEASE

Genetic and Environmental Factors

The risk for development of DKD is equal in type 1 and type 2 diabetes, and only 30% to 40% of patients with type 1 or type 2 diabetes will ultimately develop nephropathy. The prevalence of nephropathy in diabetic patients varies among different racial and ethnic groups such that it is relatively increased in African Americans, Native Americans, Mexican Americans, Polynesians, Australian aborigines, and urbanized South Asian immigrants in the United Kingdom compared with Whites. Although barriers to care seem likely to account for some of these interpopulation differences, polygenetic factors likely also contribute.

Familial clustering of DKD has been reported in type 1 and type 2 diabetes and in White and non-White populations. In a person with type 1 diabetes who has a first-degree relative with diabetes and nephropathy, the risk for development of DKD is 83%. The frequency is only 17% if there is a first-degree relative with diabetes but without nephropathy.[1] In type 2 diabetes, familial clustering has been well documented in Pima Indians.[2] A familial determinant is also suggested by higher albumin excretion rates in offspring of patients with type 2 diabetes with nephropathy. The risk is particularly high in the offspring if the mother had been hyperglycemic during pregnancy, perhaps because this causes reduced formation of nephrons (“nephron underdosing”) in the offspring.[3,4] Low birth weight and nephron underdosing are also associated with hypertension, metabolic syndrome, and perhaps DKD, although for DKD the data are somewhat controversial. Nephron underdosing[5] is believed to lead to compensatory glomerular hypertrophy and increased single-nephron glomerular filtration rate (GFR), thus aggravating glomerular injury in diabetes.

The risk for DKD does not show simple mendelian inheritance, and multiple genes are presumably involved. In patients with type 1 diabetes the estimate of heritability for nephropathy was 35%; however, replication studies did not identify any single genetic variances reaching whole genome levels of significance.[6] Nevertheless, single nucleotide polymorphisms in the engulfment and cell motility 1 *(ELMO1)* gene have been associated with risk for DKD in several ethnic groups with type 2 diabetes.[7-9] Gene polymorphisms also may contribute to familial clustering. A study suggested a predisposition to DKD caused by a polymorphism in the carnosinase gene, causing accumulation of carnosine with antioxidant properties.[10] A detrimental effect of the double-deletion polymorphism of the angiotensin-converting enzyme (ACE) genotype on disease progression[11] has not been uniformly confirmed.[12,13]

Environmental factors, especially diet, may be involved in the pathogenesis of diabetes and DKD. One of the strongest risk factors is the intake of soft drinks containing added sugars such as sucrose or high-fructose corn syrup. Fructose increases uric acid levels, a potent predictor for the development of type 2 diabetes as well as DKD, probably via uric acid inducing oxidative stress and endothelial dysfunction. Low birth weight may increase the risk for hypertension and diabetes later in life because it results in an elevation of uric acid that persists from birth throughout childhood. Smoking is a strong environmental risk factor for progression of DKD and may be related to hypoxia in the kidney. Recent studies also demonstrate important roles for sleep apnea, overall caloric intake, and the degree of exercise, although quantitative relationships have not been established.

Hemodynamic Changes

Hyperfiltration is common in early diabetes but can be corrected with good glycemic control. Increased GFR involves glucose-dependent effects causing afferent arteriolar dilation, mediated by a range of vasoactive mediators, including insulin-like growth factor 1 (IGF-1), transforming

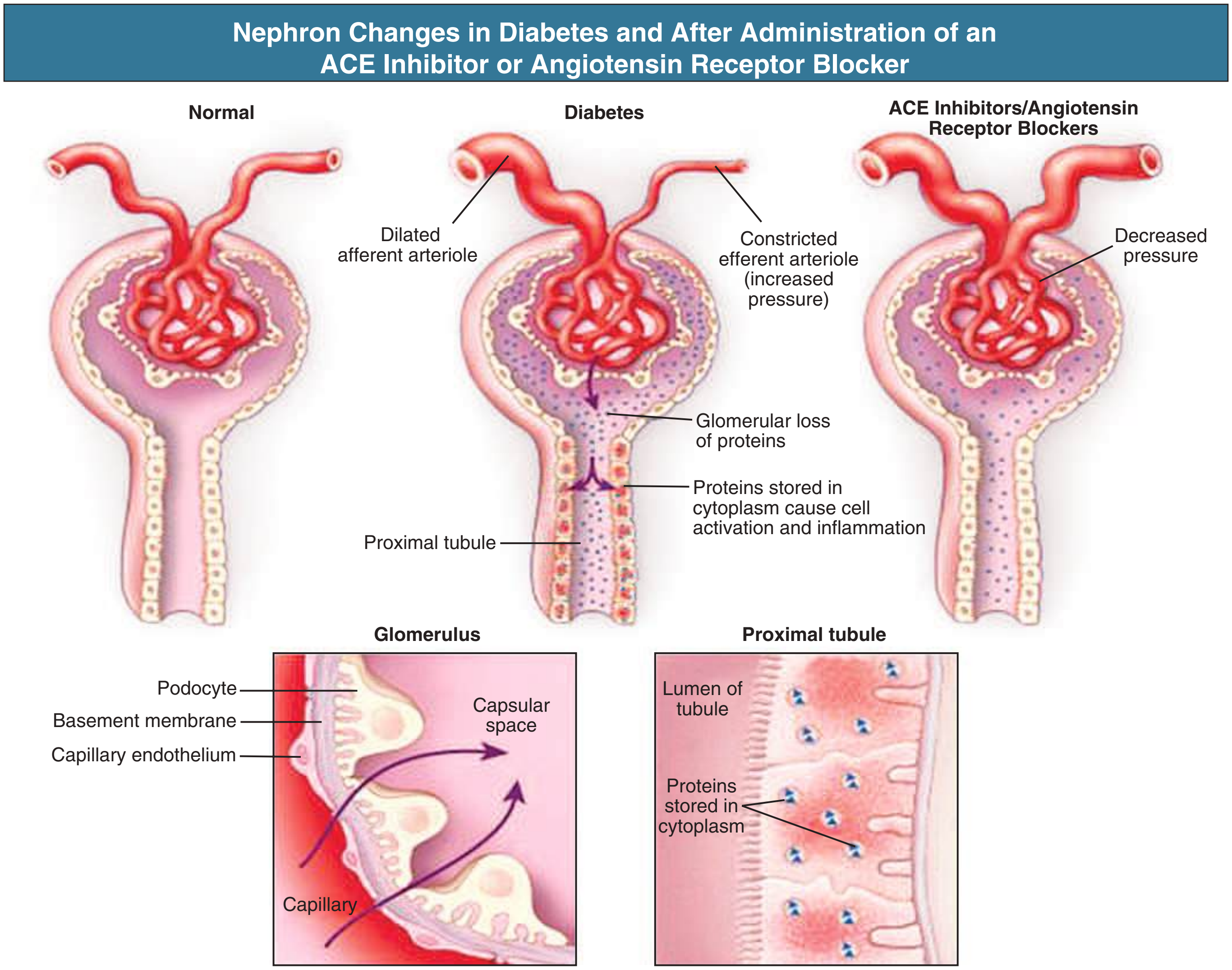
Nephron Changes in Diabetes and After Administration of an ACE Inhibitor or Angiotensin Receptor Blocker
Normal
Diabetes
ACE Inhibitors/Angiotensin Receptor Blockers
Dilated afferent arteriole
Constricted efferent arteriole (increased pressure)
Decreased pressure
Glomerular loss of proteins
Proteins stored in cytoplasm cause cell activation and inflammation
Proximal tubule
Glomerulus
Proximal tubule
Podocyte
Basement membrane
Capillary endothelium
Capsular space
Capillary
Lumen of tubule
Proteins stored in cytoplasm

Fig. 30.1 **Schematic comparison of normal nephron, nephron in diabetic kidney disease (DKD), and nephron in DKD after angiotensin-converting enzyme *(ACE)* inhibitor/angiotensin receptor blocker (ARB) administration.** Note afferent vasodilation and efferent angiotensin II (Ang II)–mediated vasoconstriction in DKD causing glomerular hypertension, which is relieved by an ACE inhibitor and ARB therapy. Note also protein leakage into the filtrate and tubular loading, with endocytosed protein causing an inflammatory reaction that promotes interstitial fibrosis. This is reversed by ACE inhibitor/ARB treatment.

growth factor-β (TGF-β1), vascular endothelial growth factor (VEGF), nitric oxide (NO), prostaglandins, and glucagon (Fig. 30.1). Over time, development of vascular disease of the afferent arteriole may result in permanent alterations in renal autoregulation that favor glomerular hypertension. Renal injury in DKD is caused not only by hemodynamic disturbances (e.g., hyperfiltration, hyperperfusion) but also by disturbed glucose homeostasis, and the two pathways interact. For example, shear stress increases glucose transport into mesangial cells by upregulation of specific glucose transporters. Furthermore, shear stress and mechanical strain resulting from altered glomerular hemodynamics trigger autocrine and paracrine release of cytokines and growth factors in the glomerulus.

DKD is also associated with tubular abnormalities; hyperfiltration increases the colloid osmotic pressure in postglomerular capillaries, facilitating reabsorption of sodium in the proximal tubule. Angiotensin II (Ang II) also appears to have a role, causing hypertrophic proximal tubular growth and increased sodium reabsorption.[14] Specific inhibition of the sodium-glucose cotransporter 2 (SGLT2) in proximal tubular cells is associated with reduced progression of diabetic kidney disease, emphasizing the role of tubuloglomerular feedback and glomerular hyperfiltration in DKD (see Chapter 31).[15]

Renal Hypertrophy and Mesangial Matrix Expansion

Renal growth occurs early after the onset of diabetes. Glomerular enlargement is associated with increased numbers of mesangial cells, mesangial cell hypertrophy, and increase of capillary loops, thus enhancing the filtration surface area. Renal tubular hypertrophy is primarily the result both tubular epithelial cell proliferation and hypertrophy.

Experimentally, avoidance of hyperglycemia prevents renal hypertrophy. Hyperglycemia causes hypertrophy by stimulating growth factors in the kidney, including IGF-1, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), VEGF, TGF-β, and Ang II. Hyperglycemia also induces the expression of thrombospondin, a potent activator of latent TGF-β. Experimentally, neutralizing antibodies to TGF-β attenuated diabetes-related renal hypertrophy and extracellular matrix (ECM) accumulation and preserved renal function. However, a recent study in diabetic patients did not show beneficial effects on serum creatinine or proteinuria.[16] Similarly, inhibition of VEGF prevented glomerular hypertrophy in models of DKD and reduced albuminuria.[17] Urine EGF levels are linked to progression of chronic kidney disease (CKD) of multiple etiologies, including diabetic kidney disease,[18] and such prognostic and efficacy biomarkers may guide future interventional studies.

The pathological hallmarks of DN are mesangial expansion, nodular diabetic glomerulosclerosis (the acellular Kimmelstiel-Wilson lesion), and diffuse glomerulosclerosis. Mesangiolysis likely plays a key role in cell loss and nodule formation. Increasing evidence suggests that local NO deficiency contributes to these histologic lesions, in particular nodule formation. Indeed, endothelial cell nitric oxide synthase (NOS)-deficient mice made diabetic represent one of the most promising models for DN.

Inflammation and Diabetic Kidney Disease

Inflammatory processes and immune cells are involved in the development and progression of DKD.[17] Glomerular and interstitial infiltration by monocytes/macrophages and activated T lymphocytes, as well as heightened Nlrp-3 inflammasome activation, are observed both in human and experimental DKD.[19] Chemokines and their receptors, in particular monocyte chemotactic protein-1 (MCP-1/CCL2), RANTES/CCL5, IL-6, and TNF receptors, as well as adhesion molecules (e.g., ICAM-1), seem to contribute to this (Fig. 30.2).[17,20] Interestingly, soluble

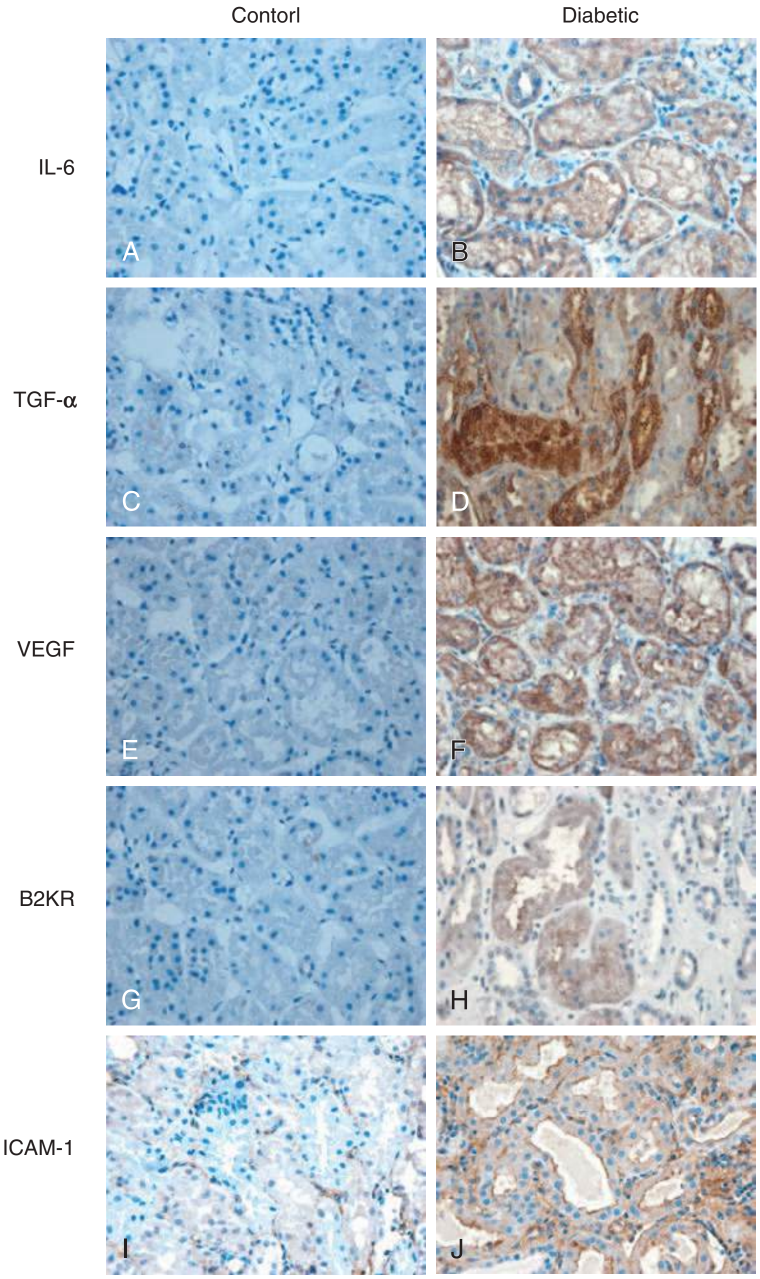

Fig. 30.2 Overexpression of inflammatory chemokines, adhesion molecules, and growth factors in the renal tubules of human diabetic kidney disease (DKD). (Left panels) DKD biopsies. (Right panels) Normal, nondiabetic kidney biopsies. *B2KR*, Bradykinin receptor 2; *ICAM*, intercellular adhesion molecule; *IL-6*, interleukin-6; *TGF*, transforming growth factor; *VEGF*, vascular endothelial growth factor. (Counterstained with hematoxylin-eosin stain; magnification, ×100. (From reference 20.)

TNF receptors appear to be a robust biomarker for progressive kidney disease in both type 1 and type 2 diabetes. Bardoxolone methyl, as an inducer of the KEAP1-Nrf2 pathway, exhibits antiinflammatory effects, but in a phase III clinical trial caused significantly more adverse effects and increased mortality (see Chapter 31). Another trial using the oral CCR2 inhibitor CCX140-B for 52 weeks yielded more promising results in reducing residual albuminuria in subjects with type 2 diabetes.[21]

Mechanisms Underlying Proteinuria

Widening of the glomerular basement membrane (GBM) is associated with accumulation of type IV collagen and net reduction in negatively charged heparin sulfate proteoglycan (see "Renal Pathology"). The expression of one permeability-controlling protein, nephrin, is abnormally low in DN.[17] The transcription of nephrin is suppressed by Ang II and restored by inhibitors of the renin-angiotensin system (RAS). In addition, in DN, apoptosis of podocytes is triggered by various factors, including Ang II and TGF-β, and adhesion of podocytes to the GBM is reduced by advanced glycation end-products (AGEs)-induced suppression of neuropilin-1. Podocyte loss also follows hyperglycemia-induced ROS generation, causing podocyte apoptosis or detachment. Migration of podocytes is also attenuated by the reduction of neuropilin-1, thereby preventing surviving podocytes from covering denuded areas of GBM, which promotes development of focal segmental glomerulosclerosis (FSGS).

Crosstalk between glomerular endothelial cells and podocytes involves activated protein C (APC). APC formation is regulated by endothelial thrombomodulin and is reduced in diabetic mice.[22] In DN, thrombomodulin-dependent APC formation inhibits podocyte apoptosis (Fig. 30.3).[23] In cultured podocytes, adipocyte-specific hormone adiponectin administration prevented high glucose–induced podocyte dysfunction. Endothelial cell dysfunction associated with altered fenestrations and glycocalyx may contribute to enhanced permeability. Adiponectin levels are low in patients with the metabolic syndrome or type 2 diabetes, which may contribute to development of albuminuria; however, once diabetes is established, elevated adiponectin levels correlate with faster progression of disease. In advanced stages of DN, albuminuria evolves into nonselective proteinuria with high-molecular-weight serum proteins escaping across the GBM with disrupted texture, gaps, and holes.

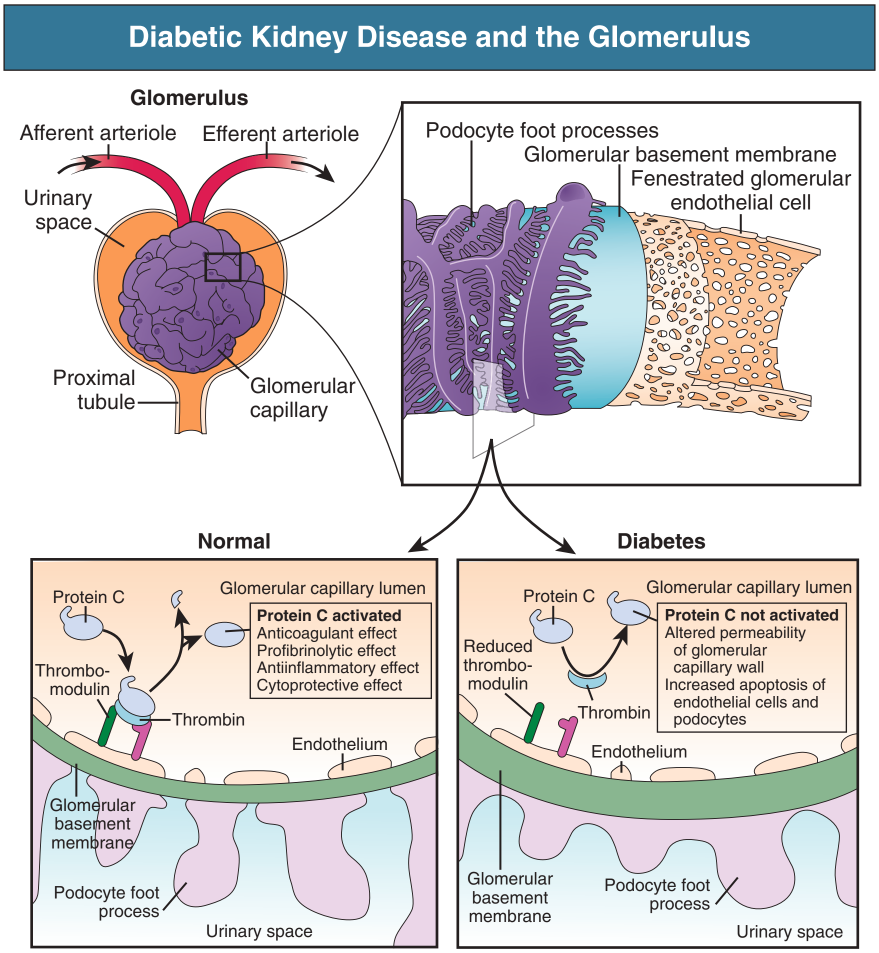
Diabetic Kidney Disease and the Glomerulus
Glomerulus
Afferent arteriole
Efferent arteriole
Urinary space
Proximal tubule
Glomerular capillary
Podocyte foot processes
Glomerular basement membrane
Fenestrated glomerular endothelial cell
Normal
Diabetes
Protein C
Glomerular capillary lumen
Protein C activated
Anticoagulant effect
Profibrinolytic effect
Antiinflammatory effect
Cytoprotective effect
Thrombomodulin
Thrombin
Endothelium
Glomerular basement membrane
Podocyte foot process
Urinary space
Protein C
Glomerular capillary lumen
Protein C not activated
Altered permeability of glomerular capillary wall
Increased apoptosis of endothelial cells and podocytes
Reduced thrombomodulin
Thrombin
Endothelium
Glomerular basement membrane
Podocyte foot process
Urinary space

Fig. 30.3 Crosstalk between endothelial cells and podocytes involving protein C. Under physiologic conditions, protein C is activated by the binding of thrombin to its receptor, thrombomodulin, on glomerular endothelial cells. The formed complex catalyzes the conversion of protein C to its catalytically activated form, which has potent anticoagulant, profibrinolytic, antiinflammatory, and cytoprotective effects. In diabetic nephropathy, the production of activated protein C (APC) in the glomerulus is reduced because of suppression of thrombomodulin expression. Decreased functional activity of APC affects the permeability of the glomerular capillary wall and enhances apoptosis of glomerular endothelial cells and podocytes. (From reference 23.)

Tubular Changes

Although glomerulosclerosis is a cardinal feature of DKD, tubulointerstitial injury ultimately determines the rate of attrition of renal function. In vitro studies have demonstrated the pathogenic role of various diabetic substrates in promoting tubule hypertrophy, stimulating ECM production and inducing a proinflammatory and profibrotic phenotype in proximal tubular epithelial cells (PTECs), including high glucose, accumulation of glycated proteins, AGEs and their carbonyl intermediates, elevated intrarenal Ang II, oxidative stress, and hypertension-induced mechanical stress.[24] Another mechanism by which glucose may promote diabetic tubulopathy is by conversion through the polyol pathway to fructose, where it is degraded by local fructokinase to induce oxidative stress and local inflammation.

Glomerular cells, tubular epithelial cells, macrophages/lymphocytes, and fibroblasts/myofibroblasts all contribute to matrix accumulation along the glomerular and tubular basement membranes and within the interstitial space. In particular, matrix-producing myofibroblasts promote progression of fibrosis in DKD by facilitating deposition of interstitial ECM (Fig. 30.4).

Clinical studies showed that even mild anemia (hemoglobin level <12.5 g/dl for men, 11.5 g/dl for women) increases the risk for progression of DKD. Anemia presumably causes renal hypoxia. Moreover, hypoxia is exacerbated by the progressive hyalinosis of the afferent and efferent arterioles and loss of peritubular capillaries. In experimental chronic renal injury, hypoxia is an important factor aggravating interstitial fibrosis, partly by the induction of TGF-β and VEGF. The transition of tubular epithelial cells into fibroblasts is stimulated by cellular hypoxia.[26] The induction of growth factors and cytokines is mediated by hypoxia-inducible factor-1 (HIF-1), which can be amplified by Ang II. Whether early treatment of anemia with erythropoietin or HIF1 stabilizers delays DKD progression remains unproven.

Hyperglycemia and Diabetic Kidney Disease

Role of Glucose Control

Evidence of the role of tight glycemic control in retarding the development of DKD includes the following:

- In the Diabetes Control and Complications Trial (DCCT), there was a remarkable reduction in progression from normoalbuminuria to microalbuminuria and other microvascular complications, specifically retinopathy, in patients with type 1 diabetes with tight glycemic control.[27]
- Euglycemia that followed isolated pancreatic transplantation was associated with regression of diabetic glomerulosclerosis after 10 years.[28]
- In the United Kingdom Prospective Diabetes Study (UKPDS), reducing the hemoglobin A_{1c} (HbA_{1c}) level by approximately 0.9% in patients with type 2 diabetes reduced the risk for microvascular complications, including nephropathy.[29]
- In the ADVANCE study, intensive glucose control with a target HbA_{1c} level of 6.5% was associated with a long-term reduction in ESRD, without evidence of any increased risk for cardiovascular events or death.[30]
- In the EMPA-REG study, type 2 diabetics treated with empagliflozin with lower glycated hemoglobin levels had significant reduction in cardiovascular and renal events, though the protective effects of the SGLT2 inhibitor is likely beyond simply glycemic control.[15]

A unifying theory was that hyperglycemia leads to diabetic complications through an accumulation of mitochondrial superoxide production and oxidative sequelae.[31] However, in vivo studies do not show an increase in mitochondrial superoxide[32]; indeed there appears to be a consistent reduction in mitochondrial electron transport chain activity with diabetes. There is also a reduction of mitochondrial biogenesis in animal models as well as in patient biopsy samples. Stimulation of

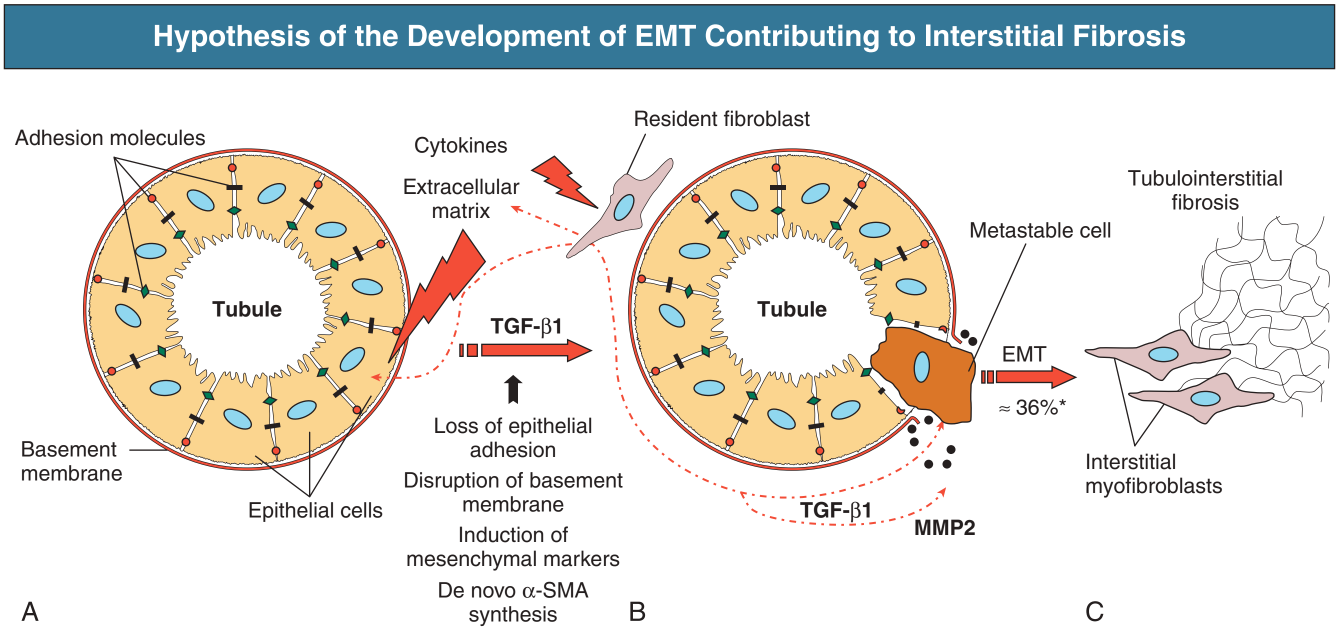
Hypothesis of the Development of EMT Contributing to Interstitial Fibrosis
Adhesion molecules
Tubule
Basement membrane
Epithelial cells
A
Cytokines
Extracellular matrix
Resident fibroblast
TGF-β1
Loss of epithelial adhesion
Disruption of basement membrane
Induction of mesenchymal markers
De novo α-SMA synthesis
Tubule
Metastable cell
TGF-β1
MMP2
B
EMT
≈ 36%*
Tubulointerstitial fibrosis
Interstitial myofibroblasts
C

Fig. 30.4 **Hypothesis of the development of epithelial-mesenchymal transition *(EMT)* contributing to interstitial fibrosis.** Initiated by external stimuli (e.g., cytokines), tubular cells lose their cell-cell contacts (e.g., E-cadherin) (A) and start to express mesenchymal markers (e.g., α-SMA, vimentin) (B). After disruption of tubular basement membrane (by MMP2) metastable cells disengage themselves from cell connective and transdifferentiate to interstitial myofibroblasts that synthesize extracellular matrix and contribute to fibrosis (C). *MMP,* Matrix metalloproteinase; *SMA,* smooth muscle actin; *TGF,* transforming growth factor. *Up to 36% of all interstitial myofibroblasts in diabetic kidney disease are thought to derive from EMT. (Modified from reference 25.)

oxidative phosphorylation and mitochondrial biogenesis is associated with reduced inflammation and fibrosis in experimental models of diabetic kidney disease.

Protein kinase C pathway. Many of the adverse effects of hyperglycemia have been attributed to activation of protein kinase C (PKC), a family of serine-threonine kinases that regulate diverse vascular functions. The activity of PKC-β, especially the membrane-bound form, is increased in the retina, aorta, heart, and glomeruli of diabetic animals. In short- and long-term studies of diabetic rats, an orally effective PKC-β inhibitor reduced albuminuria and renal TGF-β overexpression, as well as ECM accumulation. PKC-α may represent an additional therapeutic target because albuminuria was virtually absent in diabetic PKC-α knockout mice.

Advanced glycation end products pathway. Chronic hyperglycemia can lead to nonenzymatic glycation of amino acids and proteins (Maillard or Browning reaction)[33] (Fig. 30.5). Over time, these products undergo rearrangement, including cross-linking, to become irreversible AGEs. Both circulating and tissue proteins, as well as lipids and nucleic acids, may thus be glycated. Although primarily observed in diabetes, AGEs also accumulate in aging and in renal failure.[33]

The concentration of AGEs is increased in the serum, glomeruli, and tubules of DN patients. AGEs bind to macrophages, mesangial cells, and tubular cells and mediate cellular actions, including expression of adhesion molecules, cell hypertrophy, ECM synthesis, epithelial-mesenchymal transition (EMT), and inhibition of NOS. AGEs injected in vivo induce albuminuria and glomerulosclerosis.[33] AGEs have profound effects on podocytes, including induction of hypertrophy, followed by apoptosis and suppression of nephrin synthesis. Among several binding sites, the most important is RAGE (receptor for AGE), which is present in tubular cells and podocytes. Ang II stimulates upregulation of RAGE on podocytes.[34] This effect is mediated by angiotensin-2 (AT$_2$) receptors not blocked by sartanes.[34] One of the actions of RAGE is activation of nuclear factor-κB (NF-κB). sRAGE, the soluble extracellular domain of RAGE, acts as a decoy receptor and experimentally ameliorates the renal lesions in diabetes.[33]

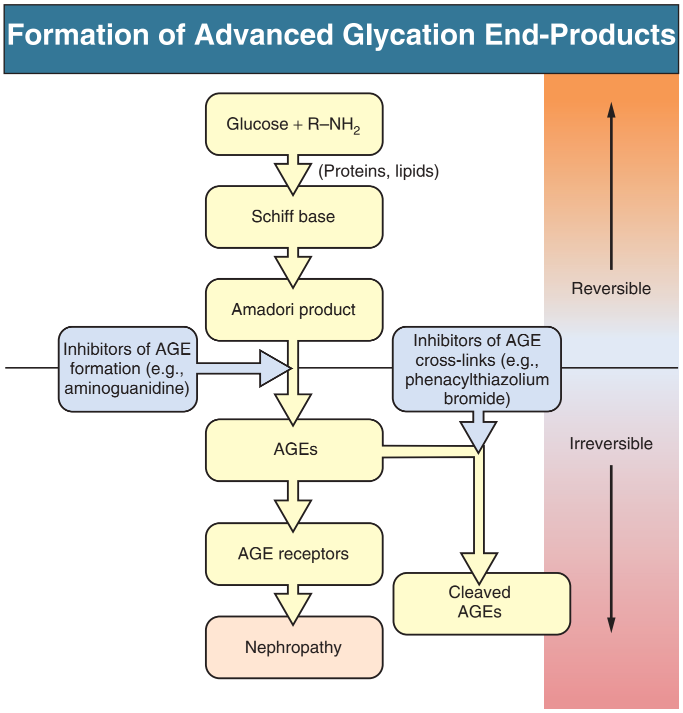
Formation of Advanced Glycation End-Products
Glucose + R–NH$_2$
(Proteins, lipids)
Schiff base
Amadori product
Inhibitors of AGE formation (e.g., aminoguanidine)
Inhibitors of AGE cross-links (e.g., phenacylthiazolium bromide)
AGEs
AGE receptors
Nephropathy
Cleaved AGEs
Reversible
Irreversible

Fig. 30.5 Mechanism of formation of advanced glycation end-products *(AGEs)*.

Administration of aminoguanidine, an inhibitor of AGE formation, to diabetic animals reduces AGE deposition, mesangial matrix expansion, and albuminuria, but has inconsistent effects on GBM thickening. The clinical experience with aminoguanidine has been disappointing and riddled with side effects. Newer, more specific and potent agents include phenacylthiazolium bromide, which cleaves covalent AGE-derived protein cross-links, but so far there has not been any report of its utility in experimental DKD.

Polyol pathway. The polyol pathway involves the conversion of glucose to sorbitol and eventually fructose. The role of polyols in diabetic complications has been assessed with aldose reductase inhibitors such as sorbinil, tolrestat, and ponalrestat, which have shown promise in preventing diabetic cataracts. Aldose reductase inhibitors also blunt hyperfiltration in DKD and have a mild effect on reducing albuminuria. Overall, however, the experience with aldose reductase inhibitors in DKD has been disappointing and associated with hypersensitivity reactions and liver function abnormalities. More recent experimental studies have focused on blocking fructokinase, which is in the distal polyol pathway, with more promising results. Other studies with regulation of myoinositol in the proximal tubule of the kidney reproduced many of the features of tubulointerstitial disease and may be an important target for future intervention.

Hexosamine pathway. Although most of the intracellular glucose is metabolized by the glycolytic pathway, some fructose-6-phosphate is diverted into the hexosamine pathway, increasing the concentrations of *N*-acetylglucosamine. This glucosamine modifies certain transcription factors, such as Sp1 activity, by post-translational *O*-linked β-*N*-acetyl glucosaminylation (O-GlcNAc). In turn, Sp1 then leads to enhanced transcription of key mediators, such as TGF-β1 and plasminogen activator inhibitor 1. Glucosamine-mediated modification of the enzyme Akt/PKB reduces expression of endothelial NOS and promotes apoptosis of cells. The role of O-GlcNAc modification has been linked to diabetic cardiac effects, although interventions have not yet been assessed in clinical trials.

Adenosine monophosphate kinase. Recent studies suggest an alternative pathway that may contribute to DKD. The energy-sensing enzyme 5′-adenosine monophosphate kinase (AMPK) pathway may contribute to DKD. Inhibition of 5′-AMP-activated protein kinase in caloric-excess states has been linked to inflammation (NF-κB, nicotinamide adenine dinucleotide phosphate [NADPH] oxidase, MCP-1 stimulation), vascular dysfunction (eNOS inhibition), stimulation of hypertrophy (mammalian target of rapamycin complex [activation]), and profibrotic pathways (TGF-β signaling).[35-37] Stimulation of AMPK is beneficial in both type 1 and type 2 models of diabetic kidney disease. Fatty acid oxidation stimulated by the LKB1-AMPK-PGC1a pathway is also beneficial for both diabetic and nondiabetic kidney disease. Future studies with specific AMPK activators are eagerly awaited.

Kallikrein-kinin pathway. The effects of the plasma and tissue serine protease enzyme kallikrein are primarily through bradykinin (BK). In vitro, high glucose stimulates expression of renal tubular kallikrein (KLK1), and BK promotes proinflammatory and profibrotic responses in PTECs.[20,24] Blocking the BK$_2$ receptor in *db/db* mice reduced serum creatinine and albuminuria. Recombinant KLK1 stimulated the production of inflammatory cytokines in PTECs.[38] Pancreatic kallikrein administered systemically could ameliorate renal injury in both STZ-induced and *db/db* mice.[39] Nonetheless, the human tissue kallikrein-binding protein, kallistatin, has been shown to ameliorate tubulointerstitial injury and renal fibrosis in *db/db* mice via multiple mechanisms, including suppression of oxidative stress, TGF-β and NF-κB signaling and hemodynamic effects.[40] The discrepancy may be due to different experimental models.

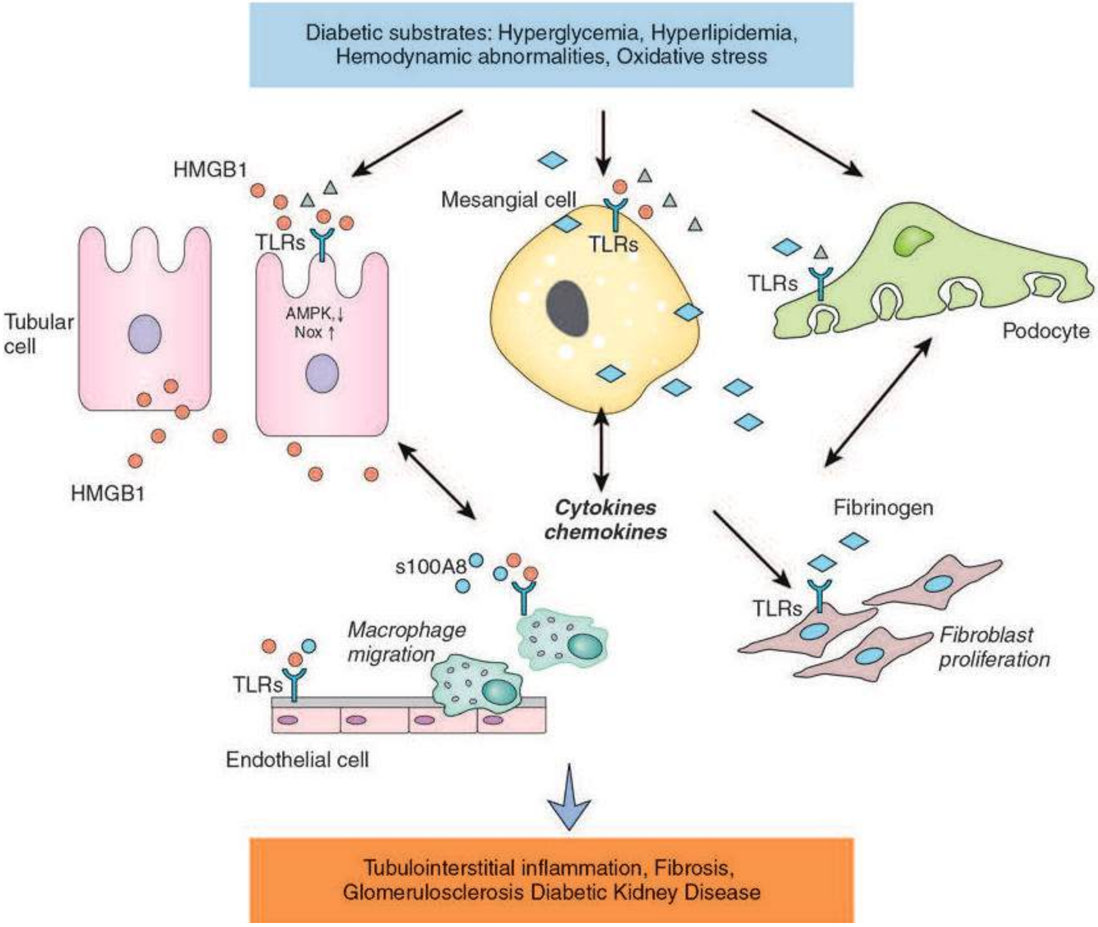
Diabetic substrates: Hyperglycemia, Hyperlipidemia, Hemodynamic abnormalities, Oxidative stress
HMGB1
TLRs
Tubular cell
AMPK ↓
Nox ↑
HMGB1
Mesangial cell
TLRs
TLRs
Podocyte
Cytokines chemokines
Fibrinogen
s100A8
TLRs
Fibroblast proliferation
Macrophage migration
TLRs
Endothelial cell
Tubulointerstitial inflammation, Fibrosis, Glomerulosclerosis Diabetic Kidney Disease

Fig. 30.6 Role of Toll-like receptors (TLRs) in diabetic kidney disease. TLRs in resident renal cells could recognize and respond to the metabolic stress of diabetes or endogenous ligands activated during the diabetic state, inducing downstream signaling events to propagate the synthesis proinflammatory cytokines and chemokines, which act as effectors to further facilitate macrophage recruitment and fibroblast proliferation, leading to a self-perpetuating cycle of renal inflammation and subsequent tubulointerstitial fibrosis and glomerulosclerosis. *HMGB1,* High-mobility group box-1 protein; *S100A8,* S100 calcium binding protein A8. (Modified from reference 42.)

Activation of innate immunity. Diabetes can be considered a metabolic danger signal that is effected via Toll-like receptors (TLRs), a conserved family of pattern recognition receptors that play a fundamental role in innate immunity. In particular, TLR-4 is overexpressed in the renal tubules of human diabetic nephropathy (DN) biopsies.[41,42] In vitro, silencing TLR-4 ameliorated high glucose–induced tubular cell inflammation. In experimental DKD, either systemic deletion or the application of a TLR-4 antagonist conferred renoprotection.[42] In addition, TLRs are also expressed in other resident renal cell types such as podocytes and mesangial cells, as well as infiltrating macrophages, that could act in concert to bring about an inflammatory phenotype observed in diabetic kidney disease (Fig. 30.6).

A key component of innate immunity includes the NADPH oxidase pathway, expressed primarily in the lysosomes of phagocytic cells, but also in the kidney. Enhanced Nox4 in podocytes may contribute to glomerular disease involving a pathway linking Nox to the citric acid cycle.[43]

Renin-Angiotensin-Aldosterone System and Diabetic Kidney Disease

Experimental and clinical studies in type 1 and type 2 diabetes suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) retard progression of DKD (see Chapter 31). Although plasma renin activity is low in DKD, it is inappropriate in relation to increased extracellular volume and exchangeable sodium, suggesting activation of the RAS.[44] In experimental diabetes, sites of local RAS activation have been identified in glomeruli, renal vessels, and tubular cells.[44] High glucose concentration and AGEs stimulate angiotensinogen and renin expression in various renal cells, mainly through reactive oxygen species.[44] Proteinuria further activates the local RAS of tubular cells. Adipocytes are another source of Ang II in obese patients.

In patients with DKD, prorenin levels are elevated, possibly reflecting increased synthesis. Specific prorenin and renin receptors have been demonstrated in the kidney; ligand binding causes nonenzymatic activation of prorenin to yield renin activity and locally produced Ang II.[45] Moreover, prorenin and renin can directly bind to specific receptors on mesangial and tubular cells and induce proinflammatory and profibrogenic cytokines. Interestingly, 1,25-dihydroxyvitamin D_3 (calcitriol) suppresses the RAS. Thus, in diabetic patients with advancing CKD, decreasing calcitriol production further activates the RAS.

Ang II has many nonhemodynamic effects and mediates cell proliferation, hypertrophy, ECM expansion, and cytokine (TGF-β, VEGF) synthesis.[44] Therefore ACE inhibitors and ARBs presumably act by hemodynamic as well as nonhemodynamic actions.

Aldosterone accelerates progression in renal damage models independently of Ang II. In DKD, aldosterone escape has been linked to progression of proteinuria (see Chapter 31). Aldosterone synthesis is stimulated in DKD, and this steroid hormone stimulates the synthesis of other proinflammatory and profibrogenic cytokines (MCP-1, TGF-β).[46]

Other vasoactive agents may be involved in the pathogenesis of DKD, including alterations in systemic or intrarenal production of endothelin, NO, the kallikrein-kinin system, and natriuretic peptides. A randomized controlled clinical trial examining the efficacy of a selective endothelin-A receptor antagonist, the Study Of Diabetic Nephropathy with Atrasentan (SONAR) is currently under way.

Uric Acid and Fructose

As discussed earlier, an elevated uric acid level can predict the development of DKD as well as diabetic CKD, and pilot studies have reported an early benefit of allopurinol therapy on diabetic albuminuria.[47]

Uric acid is generated during the metabolism of fructose, when it appears to induce oxidative stress in mitochondria. In addition to dietary fructose from added sugars, there is increasing evidence that in diabetes, fructose is generated in the kidney, where it is metabolized to generate uric acid and oxidative stress that may mediate renal injury. Thus both dietary fructose and endogenous production of fructose may be involved in the development of diabetes and its complications.[48]

A phase III study (Preventing Early Renal Function Loss [PERL]) is ongoing to determine the role of allopurinol on uric acid levels and progression of DKD in patients with type 1 diabetes.

EPIDEMIOLOGY

In most Western countries, DKD has become the leading cause of ESRD. According to the U.S. Renal Data System (www.USRDS.org), in 2016, DKD was the most frequent primary diagnosis, with over 150 cases per 1 million population per year. In China, a large-scale hospital-based survey found that DKD exceeded glomerulonephritis (GN) as the most prevalent cause of ESRD since 2011.[49] The proportion of diabetics among patients with ESRD varies considerably among countries, but in many developed countries the figure currently stands between 40% and 60%. Classic features of DKD were observed in about 60% of diabetic patients (i.e., normal kidney size despite ESRD; proteinuria >1 g/2 h with or without retinopathy); 13% had an atypical presentation with ischemic nephropathy, and in 27% a known primary renal disease coexisted with diabetes. An important mode of presentation has become irreversible acute kidney injury (AKI), for example, after administration of nonsteroidal antiinflammatory drugs (NSAIDs), cardiac events, and septicemia. Many patients also lose the clinical manifestations of overt diabetes (e.g., hyperglycemia) because of CKD-associated weight loss, impaired renal gluconeogenesis, or increased insulin half-life in CKD.

Currently, with better treatment of hypertension and coronary heart disease, an increasing proportion of patients with type 2 diabetes survive to develop DKD and ESRD. The proportion of patients with type 1 and type 2 diabetes who develop proteinuria and elevated serum creatinine concentration is related to the duration of diabetes. Diabetes caused an estimated 4 million deaths worldwide in 2017, of which half occurred in patients below the age of 60 and more than half were caused by increased risks for cardiovascular and other diseases. There is a more rapid increase in the prevalence of type 2 diabetes in the developing world compared with the developed world. Indeed, 4 out of 5 people with diabetes live in low- and middle-income countries, and it has been projected that these countries will experience the greatest surge in diabetes over the next two decades (Fig. 30.7).[50] For example, the prevalence of diabetes is predicted to increase by 110% in Africa, 70% in Southeast

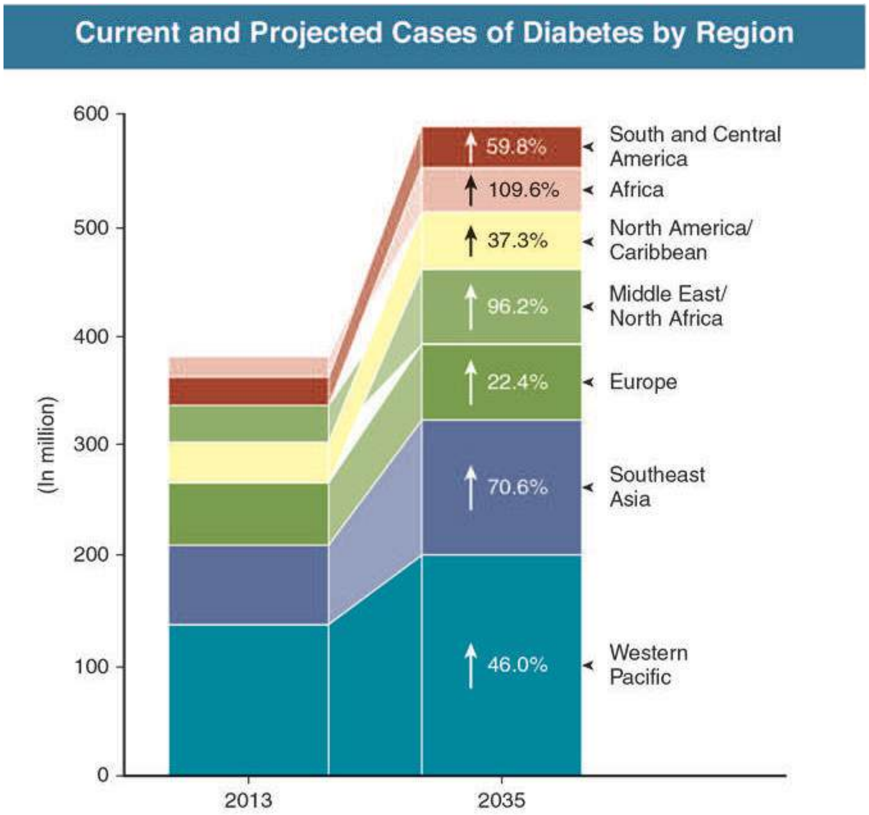

Fig. 30.7 **Predicted increase in diabetes prevalence by geographical region over the next two decades.** The rate of increase is greatest in the developing world. (Modified from reference 50.)

Asia, and 60% in South and Central America by 2035, versus 37% in North America and 22% in Europe. In Asia, high mortality from diabetes is most prominent in patients aged 50 to 60 years, which translates to a reduction in life expectancy of more than a decade. Up to 60% of Asian diabetic patients have elevated albuminuria, compared with 30% to 40% reported in Western diabetic populations in cross-sectional surveys.[51] Also, the incidence of diabetes-associated ESRD varies in Western countries, with very high numbers of patients in the United States. The reasons are complex and include genetic variability,[52] differences in lifestyle, and different national health care systems, with variable access to screening programs and early management for diabetes.[53]

CLINICAL MANIFESTATIONS AND NATURAL HISTORY

DKD is part of a generalized microvascular syndrome that is accompanied by macrovascular disease.

Obesity, Metabolic Syndrome, and Renal Disease

The metabolic syndrome—defined as having at least three of the five parameters of increased waist circumference, elevated triglycerides, decreased high-density lipoprotein, elevated blood pressure (BP), and elevated fasting blood glucose concentration—is increasingly being recognized not only as a major contributor to cardiovascular diseases but also as a negative influence on renal function[54,55] Obesity is often defined as body mass index greater than 30, although different values define obesity in other countries (e.g., India, Japan). Obese individuals have large kidneys and glomerulomegaly, with increased renal blood flow, increased filtration fraction, and glomerular hyperfiltration.[56] Obese patients have moderate increased albuminuria even in the absence of hypertension. The resemblance of obesity-related kidney disease to the early features of diabetic kidney disease is striking. In addition, sleep apnea, which is common in obese individuals, leading to hypoxic episodes, may contribute to kidney impairment. Visceral adipocytes are a potent source of deleterious factors[57] and could have an impact on renal function (Ang II, leptin, TNF-α). By contrast, the secretion and plasma concentration of adiponectin, an adipokine with cardiovascular protective, antidiabetic, and antiinflammatory properties, are markedly decreased in obesity and its related pathologies (see "Mechanisms Underlying Proteinuria"). Thus renal changes may occur years before the manifestation of type 2 diabetes during obesity and the development of the metabolic syndrome.

Evolution of Diabetic Kidney Disease

One of the earliest changes of renal function in in patients with type 1 as well as many with type 2 diabetes is an increase in GFR, or hyperfiltration, which is accompanied by an increase in renal size. The next observable change is the development of microalbuminuria (30 to 300 mg albumin/24 h; now often termed *moderately increased albuminuria*), which later progresses to macroalbuminuria (>300 mg albumin/24 h; now often termed *severely increased albuminuria*). Diabetic patients with persistent microalbuminuria are at greatly increased risk for development of overt DKD, which is heralded by the development of proteinuria (albuminuria >300 mg/24 h/day), on average 15 years after disease onset, with progressive increase in proteinuria and BP and development of progressive CKD. Williams[59] proposed a scheme of the natural history and pathophysiology of nephropathy typically observed in type 2 diabetes over a period of 20 years (Fig. 30.8).

Mogensen[58] proposed a scheme of the different stages of DKD that is largely valid in type 1 diabetes but less reliable in type 2 diabetes. In the latter, CKD may occur in the absence of albuminuria, possibly as a result of macrovascular disease. Of note, with improved management of glycemic control and BP control there is a growing population of patients with type 1 diabetes with normoalbuminuria that have progressive DKD.[59] In this cohort, progressive renal decline, not albuminuria, is the predominant clinical feature. The putative mechanisms that initiate and sustain progressive renal decline in type 1 diabetes are not well known. Whether the initial lesion of progressive renal decline is in the glomerulus, tubule, interstitium, or vasculature remains to be elucidated via clinical and epidemiologic studies, because a pure animal model of progressive renal decline with normoalbuminuria is lacking.

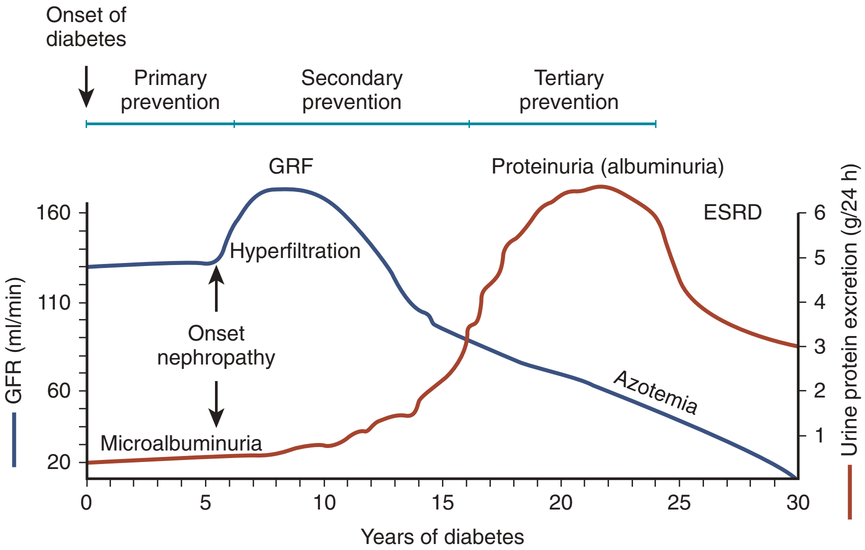

Fig. 30.8 **Natural history of diabetic nephropathy (DN).** Changes in glomerular filtration and proteinuria over time from the onset of diabetes. Proteinuria reduction is shown as a tertiary prevention. *ESRD,* end-stage renal disease; *GFR,* glomerular filtration rate. (From reference 59.)

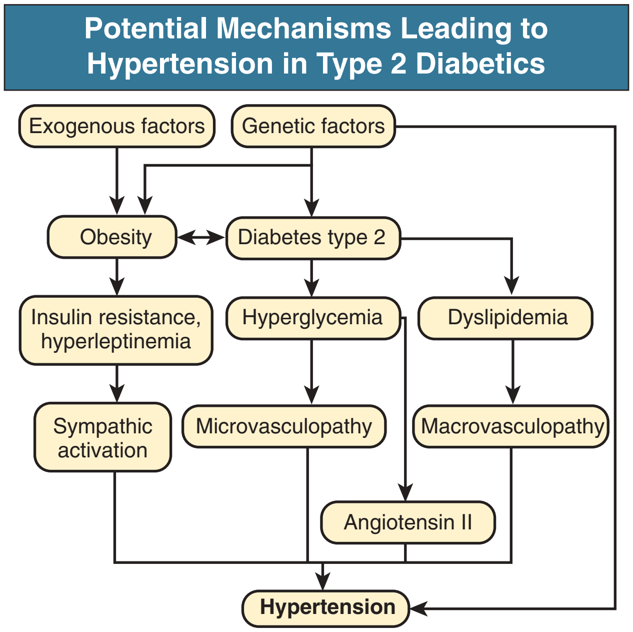

Fig. 30.9 **Overview of potential mechanisms leading to hypertension in patients with type 2 diabetes.** Genetic susceptibility factors for primary hypertension and diabetes may be clustered so that an individual patient may have a higher incidence of both diseases. Obesity and the metabolic syndrome lead to insulin resistance and hyperleptinemia associated with sympathetic nerve activation. Hyperglycemia directly activates the renin-angiotensin system and, in addition, through renal microvasculopathy stimulates development of hypertension. Dyslipidemia leads through macrovasculopathic alteration to stiffness of vessels and hypertension.

Hypertension and Diabetic Kidney Disease

If hypertension develops in a patient with type 1 diabetes, it is almost always caused by renal parenchymal disease. At present, however, patients with type 1 diabetes survive longer, and a minority of elderly patients with type 1 develop primary hypertension with no evidence of nephropathy. In patients with type 2 diabetes, hypertension often precedes the onset of diabetes by many years as a feature of metabolic syndrome. At diagnosis of type 2 diabetes, an abnormal BP and an abnormal circadian BP profile are found in 80% of patients. Prediabetic hypertension increases the risk for onset and progression of DKD. If patients with type 2 diabetes ultimately develop nephropathy, the prevalence of hypertension further increases, with greater BP elevation, but the relationship between hypertension and nephropathy is generally much less than in type 1 diabetes. The pathogenesis of hypertension in type 2 diabetes is complex and involves RAS activation, direct sympathetic nerve activation, and macrovascular changes.[60] Furthermore, there is evidence that genetic factors defining primary hypertension as well as diabetes are clustered (Fig. 30.9).

In DKD, it has been well documented that the nocturnal BP decrease is frequently attenuated, or nondipping, which even precedes the onset of microalbuminuria.[60] Furthermore, the BP response to exercise tends to be exaggerated, even when the BP is normal under basal conditions. Stiffening of the aorta increases the peak systolic pressure and decreases the diastolic pressure, resulting in increased BP amplitude, which explains why isolated systolic hypertension is so common in patients with type 2 diabetes.[61] Low diastolic pressure increases the risk for coronary events because coronary perfusion occurs during diastole only.[62] Ambulatory pulse pressure and impaired nocturnal BP decline are independent predictors of nephropathy progression in patients with type 2 diabetes (Fig. 30.10). The increased prevalence of sleep apnea in DKD also contributes to hypertension.[63]

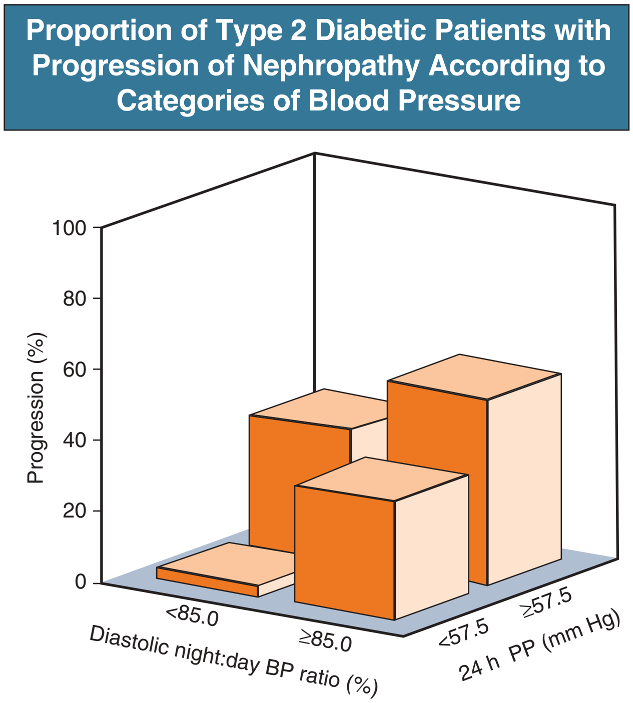

Fig. 30.10 **Proportion of patients with type 2 diabetes with progression of nephropathy according to categories of blood pressure *(BP).*** Progression risk according to categories of night to day diastolic BP (median value <85% or ≥85%) and 24-hour ambulatory pulse pressure *(PP)* (median value <57.5% or ≥57.5%). (From reference 64.)

Associated Extrarenal Microvascular and Macrovascular Complications

Diabetic retinopathy is present in virtually all patients with type 1 diabetes and albuminuria from DN. In contrast, only 50% to 60% of proteinuric patients with type 2 diabetes have retinopathy.[66,67] Consequently, the absence of retinopathy does not exclude the diagnosis of DN in patients with type 2 diabetes.[67] In patients with DN, retinopathy tends to progress more rapidly so that yearly or half-yearly ophthalmologic examination is indicated.

Many patients with DN also have polyneuropathy. Sensory polyneuropathy is an important aspect of the diabetic foot. There is a strong inverse correlation between the incidence of diabetic foot and renal function. Motor and sensory neuropathy may cause areflexia, wasting, and sensory disturbances such as paresthesia, anesthesia, and impaired perception of vibration and pain, but the most vexing clinical problems are the results of autonomic polyneuropathy. Because cardiac innervation is defective, pain and angina are frequently absent when the patient has coronary heart disease and myocardial infarction. Further consequences of autonomic polyneuropathy are gastroparesis and diarrhea or constipation (see Chapter 86). These problems are caused by impaired intestinal innervation, often complicated by intestinal bacterial overgrowth because of stasis. Also, urogenital abnormalities are common, including erectile impotence and detrusor paresis with delayed and incomplete emptying of the bladder.

The major macrovascular complications associated with DKD are stroke, coronary heart disease, and peripheral vascular disease.[64,65] These complications occur up to five times more frequently in diabetic patients with than without DKD.

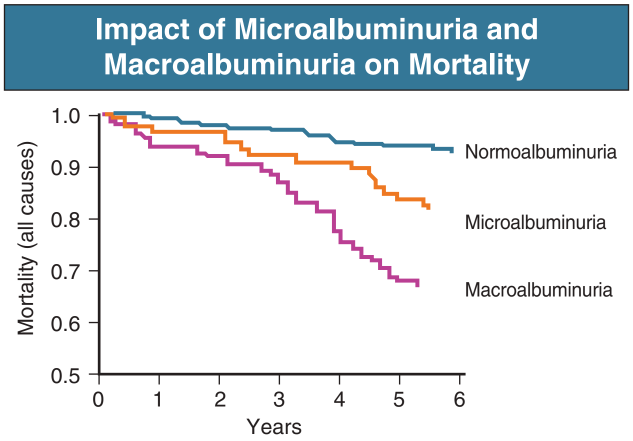

Fig. 30.11 Impact of microalbuminuria and macroalbuminuria on mortality. The impact of microalbuminuria and macroalbuminuria on mortality was evaluated prospectively in 328 White patients with non–insulin-dependent diabetes mellitus observed for 5 years. Microalbuminuria and macroalbuminuria led to a significant increase in total mortality compared with that in patients who remained normoalbuminuric. (From reference 68.)

Survival in Patients With Diabetic Kidney Disease

The presence of DKD greatly increases mortality in patients with both type 1 and type 2 diabetes. Compared with the background population, mortality in patients with type 1 diabetes and no proteinuria is elevated only 2-fold to 3-fold; in contrast, it is increased 20-fold to 200-fold in patients with proteinuria.[68,69]

The major increase in risk starts when abnormal levels of albuminuria have developed (Fig. 30.11). An increased risk is found even in the upper normal range of albuminuria (Fig. 30.12). Urinary albumin excretion is a good predictor of cardiovascular events the first 5 years after measurement, but repeating the measurement several years later also detects progression, which is associated with increased cardiovascular risk.[69] The presence of albuminuria likely reflects generalized endothelial cell dysfunction, thus increasing the risk for atherosclerosis.[69] Albuminuria is also associated with many cardiovascular risk factors, such as elevated BP, dyslipoproteinemia, increased platelet aggregation, and increased C-reactive protein concentration. An added risk factor is presumably the association with autonomic polyneuropathy, which is a predictor of death from myocardial infarction or arrhythmia. A recent observation has been the predictive value of soluble TNFR1 or TNFR2 for progressive diabetic kidney disease in the type 1 and type 2 population.[70]

RENAL PATHOLOGY

After the onset of diabetes, kidney weight increases by an average of 15%. Renal size remains increased until overt nephropathy is established. Most patients with type 1 diabetes have a sustained increase in glomerular volume and glomerular capillary luminal volume. These changes are accompanied by hypertrophy of the interstitium.[71]

In patients with diabetes of more than 10 years duration, regardless of whether nephropathy is present, GBM thickening up to three times the normal range of 270 to 359 nm is an almost universal feature (Fig. 30.13). In advancing DKD, there is a consistent correlation between GBM thickness and fractional mesangial volumes with the urinary albumin excretion rate.

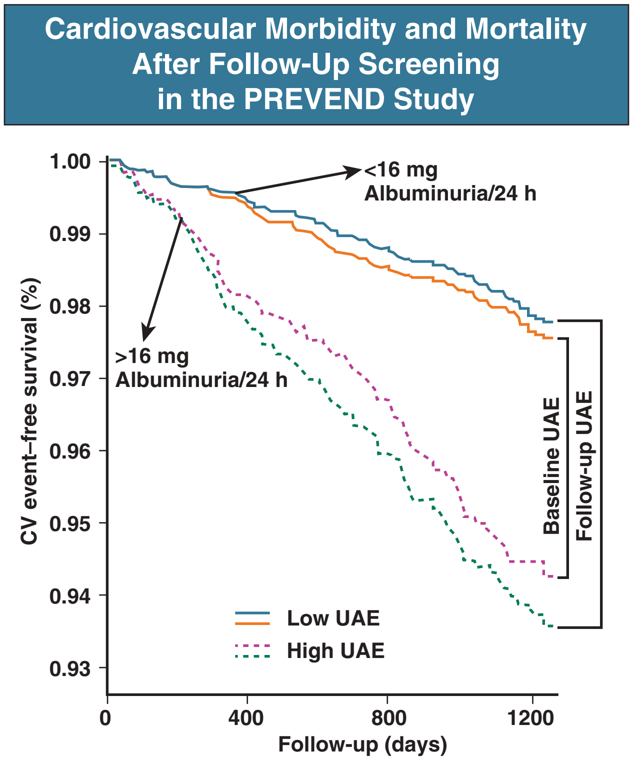

Fig. 30.12 Event-free survival for cardiovascular *(CV)* morbidity and mortality after follow-up screening in the PREVEND study. Individuals are stratified according to the presence of a high or low urinary albumin excretion *(UAE)*. High and low UAE are defined by either the UAE measurement from the baseline screening *(orange and violet lines)* of approximately 4.2 years before follow-up screening or the repeated UAE measurement at time of the follow-up screening *(blue and green lines)*. To allow comparison, the survival curves for the 6800 individuals with either the baseline or follow-up measurement of UAE are plotted in the same graph. A high UAE *(dashed lines)* is defined as a UAE ≥ 16.2 mg/24 h, being the 75th percentile of UAE with use of the UAE measurement of the baseline screening. (From reference 69.)

Nodular glomerular intercapillary lesions in advanced DKD were described in 1936 by Kimmelstiel and Wilson (Fig. 30.14C).[72] The nodules are located in the central regions of peripheral glomerular lobules as well-demarcated eosinophilic and periodic acid–Schiff-positive masses (see Fig. 30.14C and D). When they are not acellular, nodules contain pyknotic nuclei. It is suggested that nodules result from microaneurysmal dilation of the associated capillary followed by mesangiolysis and laminar organization of the mesangial debris with lysis of the center of the lobule. Foam cells often surround the nodules. These appearances, reported in only 10% to 50% of biopsy specimens in both type 1 and type 2 diabetes, are also seen in membranoproliferative glomerulonephritis (see Chapter 21), in amyloidosis and light-chain deposition disease (see Chapter 27), and specific stains and immunofluorescence findings, respectively, will clarify the diagnosis.

The diffuse glomerular lesion occurs more often than the nodular lesion, with an incidence of more than 90% in patients with type 1 diabetes longer than 10 years and an incidence of 25% to 50% in patients with type 2 diabetes. Diffuse glomerular lesions consist of an increase of mesangial matrix extending to involve the capillary loops (see Fig. 30.14B). In contrast to nodular lesions, which are of little functional significance, the degree of diffuse glomerulosclerosis correlates with the clinical manifestations of worsening renal function. Accumulation of mesangial matrix is the feature most consistently associated with progression.[73] In more severe disease, the capillary wall thickening and mesangial expansion lead to capillary narrowing (see Fig. 30.13B) and hyalinization, with accompanying periglomerular fibrosis.

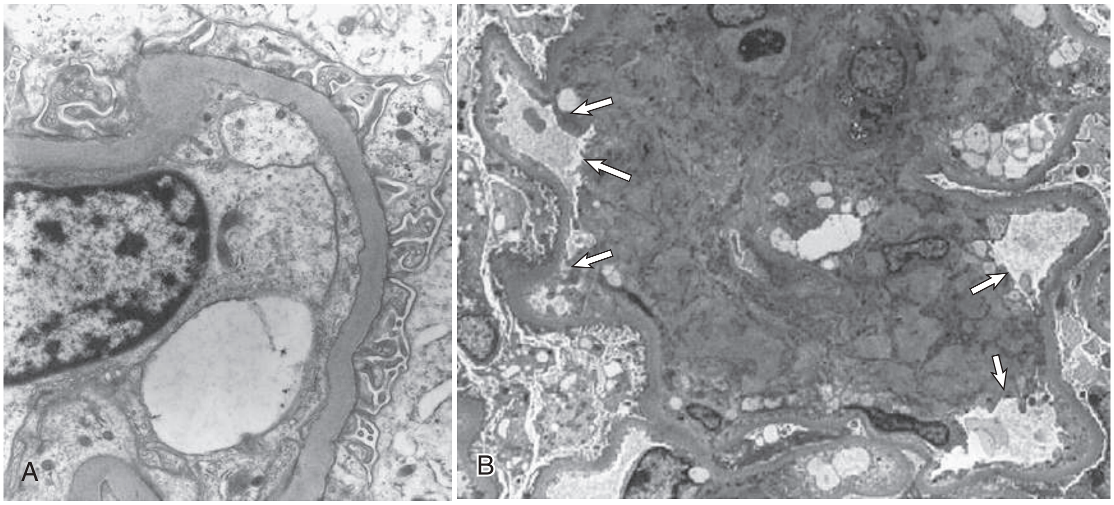

Fig. 30.13 **Electron microscopy of structural changes in diabetic nephropathy.** (A) Glomerular basement membranes are diffusely thickened. (B) The expanded mesangium encroaches on the capillary spaces *(arrows)*.

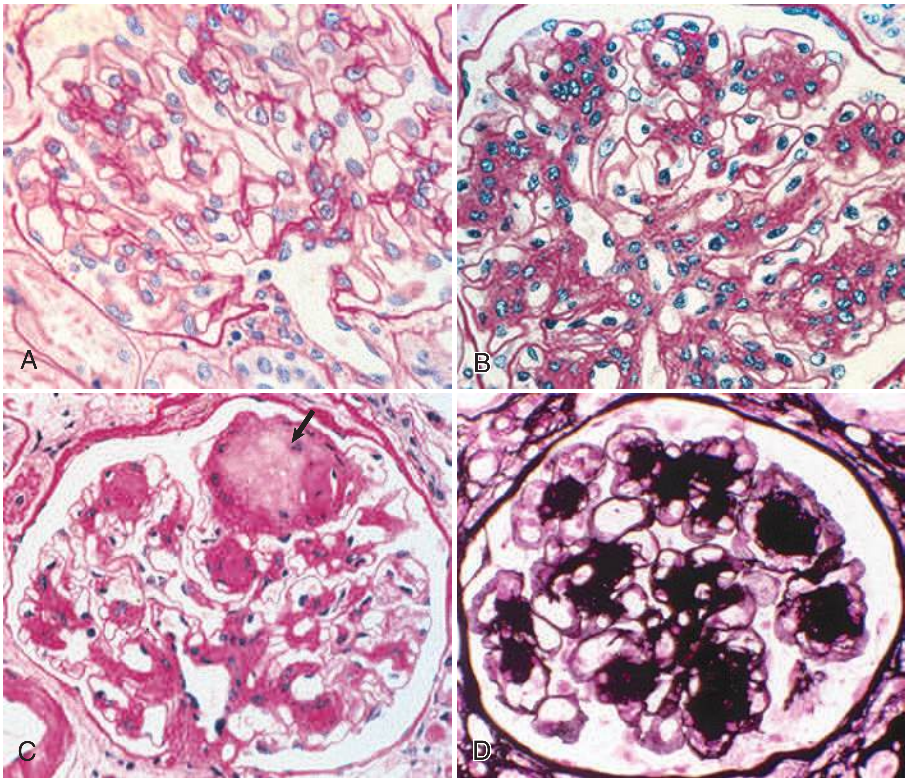

Fig. 30.14 **Light microscopy of glomerular changes in diabetic kidney disease (DKD).** (A) Normal glomerulus. (B) Diffuse glomerular lesion. Widespread mesangial expansion. (C) Nodular lesion as well as mesangial expansion. There is a typical Kimmelstiel-Wilson nodule at the top of the glomerulus *(arrow)*. (*A*, *B*, and *C*, Periodic acid–Schiff reaction). (D) Nodular lesion. Methenamine silver staining shows the marked nodular expansion of mesangial matrix.

Podocytes are involved early in the course of DKD in type 1 and type 2 DM (Fig. 30.15), and an increase in foot process width is already observed with only slight increases in albuminuria.[74,75] Longitudinal studies in DKD demonstrated a reduction in podocyte number that closely correlated with proteinuria.[74] Renal biopsy specimens from Pima Indians with type 2 diabetes showed a broadening in podocyte foot processes and a concomitant reduction in the number of podocytes per glomerulus.[76]

Arteriolar lesions are prominent in diabetes. Hyaline material progressively replaces the entire wall structure and involves both the afferent and efferent vessels, which is highly specific for diabetes.

A new classification of DN was introduced in 2007. This classification considers not only glomerular changes (Fig. 30.16) but also pathologic alterations of the tubulointerstitium and vasculature.[77] Immunohistologic examination is usually negative, but linear immunoglobulin G (IgG) can be seen occasionally because of passive trapping in the GBM (Fig. 30.17).

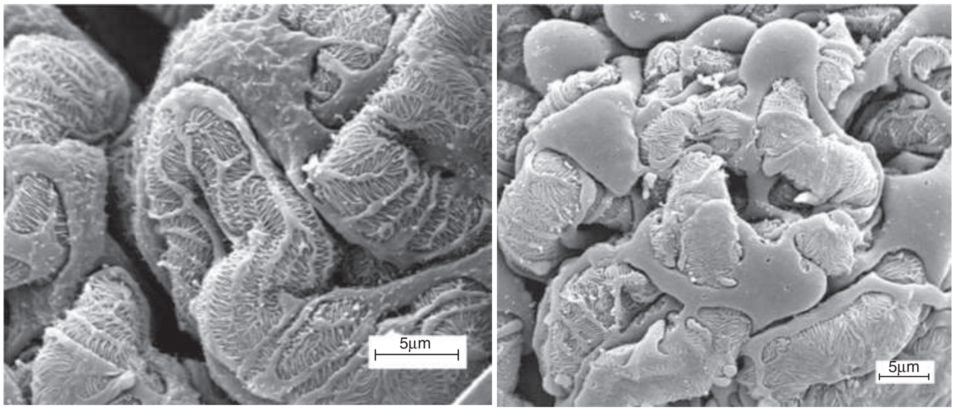

Fig. 30.15 Electron micrograph of external surface of glomerular tufts from rats after removal of the Bowman capsule by freeze-fracture. (Left) Normal rat kidney with podocyte cell body; the primary processes and terminal foot processes resting on the glomerular capillary basement membrane are clearly seen. (Right) In diabetic rat kidney, the decrease in the density of foot processes and the denuded glomerular capillary basement membrane are apparent. (From reference 75.)

Tubulointerstitial fibrosis and tubular atrophy may be the best pathologic correlates for the progressive decline in GFR. Tubulointerstitial fibrosis and renal arteriosclerosis are more prevalent in type 2 than type 1 diabetes. In fact, renal structure is heterogeneous in patients with type 2 diabetes; only a subset of patients with type 2 have typical diabetic glomerulopathy, whereas a substantial proportion have more advanced tubulointerstitial and vascular rather than glomerular lesions or have normal or near-normal renal structure.[77] Some patients with type 2 diabetes have a kidney appearance more suggestive of glomerular ischemia or tubulointerstitial disease.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of DKD is based on the detection of proteinuria. In addition, most patients also have hypertension and retinopathy. The main evaluation procedures in the patient with suspected DKD include the following:

- Measurement of urinary albumin or protein
- Measurement of serum creatinine concentration and estimation of GFR
- Measurement of BP
- Ophthalmologic examination

Measurement of Albuminuria or Proteinuria

As alluded to earlier, moderately increased albuminuria (previously microalbuminuria) is arbitrarily defined as excretion of 30 to 300 mg albumin/24 h in at least two of three consecutive urine samples (Table 30.1). There is substantial individual day-to-day variation in albumin excretion (coefficient of variation, 30% to 50%) and also between day and night collections (Fig. 30.18). Even in the upper quantiles of so-called normoalbuminuria, the risk for progression and cardiovascular events is elevated. At concentration of 30 to 300 mg/24 h, albumin is normally not detected by nonspecific tests for protein (e.g., Biuret reaction). Albumin can be detected, however, by use of specific techniques such as dipstick, enzyme-linked immunosorbent assay, nephelometry, and radioimmunoassay. Instead of difficult-to-obtain 24-hour urine collections, the albumin concentration can be determined in spot urine or, better, first-void morning urine samples. The normal range is less than 20 µg/ml.

The detection of urinary albumin is a specific indicator of DN only if confounding factors such as fever, physical exercise, urinary tract infection, nondiabetic renal disease, hematuria from other causes, heart failure, uncontrolled hypertension, and uncontrolled hyperglycemia have been excluded.[78]

TABLE 30.1 Urinary Albumin Excretion Rate Levels of 24-Hour and Overnight Urinary Albumin Excretion Rate (Uae) Are Diagnostic for Microalbuminuria and Overt Diabetic Nephropathy

	UAER	
Condition	**24 hr (mg/day)**	**Overnight (µg/min)**
Normoalbuminuria	<30	<20
Microalbuminuria	30-300	20-200
Overt nephropathy	>300	>200

As noted in the text, the terms for microalbuminuria and macroalbuminuria have been replaced by new terminology. These historical terms are still widely used and are presented here for clarity.

The main advantage of searching for microalbuminuria early in the course of diabetes is that it predicts a high renal and cardiovascular risk and thus allows targeted intervention. The American Diabetes Association (www.diabetes.org) and other societies recommend annual testing of all diabetic patients.

By definition, there is clinically overt DKD (severely increased albuminuria; formerly macroalbuminuria) if the rate of albumin excretion exceeds 300 mg/day. At this point, serum proteins other than albumin are usually excreted in the urine as well (nonselective proteinuria).

Although there are few guidelines regarding repeated measures of albuminuria or proteinuria after a diagnosis of diabetic kidney disease has been established, Kidney Disease: Improving Global Outcomes (KDIGO) recommends using the albumin-to-creatinine ratio or protein-to-creatinine ratio annually to determine if there is disease progression,[78] although assaying the urine ratio of albumin to creatinine can be much more expensive in certain countries.

Measurement of Blood Pressure

When measuring the BP in a diabetic patient, the following issues should be taken into account:

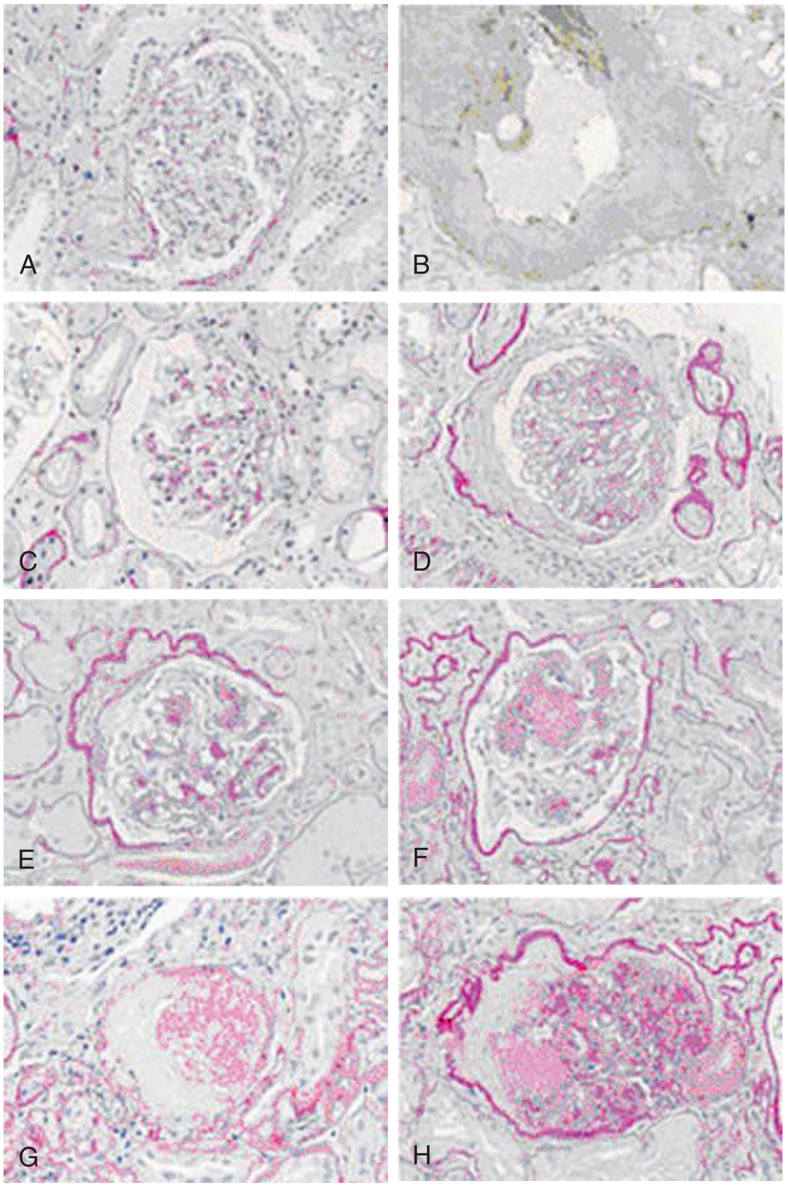

Fig. 30.16 **Pathologic classification of diabetic kidney disease (DKD; according to Tervaert et al).** Representative examples of the morphologic lesions in DKD. (A) Glomerulus showing only mild ischemic changes, with splitting of the Bowman capsule. No clear mesangial alteration. (B) Electron micrograph of this glomerulus. The mean width of the GBM was 671 nm (mean taken over 55 random measurements). Electron microscopy provides the evidence for classifying the biopsy with only mild light microscopy changes into class I. (C and D) Class II glomeruli with mild and moderate mesangial expansion, respectively. In C, the mesangial expansion does not exceed the mean area of a capillary lumen (IIa), whereas in D it does (IIb). (E and F) A class III Kimmelstiel-Wilson lesion is seen in F. The lesion in E is not a convincing Kimmelstiel-Wilson lesion; therefore, on the basis of the findings in this glomerulus, the finding is consistent with class IIb. For the purpose of the classification, at least one convincing Kimmelstiel-Wilson lesion (as in F) needs to be present. (H) Signs of class IV DKD consist of hyalinosis of the glomerular vascular pole and a remnant of a Kimmelstiel-Wilson lesion on the opposite site of the pole. (G) Example of glomerulosclerosis that does not reveal its cause (glomerulus from same biopsy as H). For the purpose of the classification, signs of DKD should be histopathologically or clinically present to classify a biopsy with global glomerulosclerosis in more than 50% of glomeruli as class IV. (From reference 77.)

- In overweight patients with type 2 diabetes, the size of the cuff has to be adapted to the upper arm circumference. When this exceeds 32 cm, cuffs of 18-cm width are indicated.
- Patients with severe autonomic neuropathy tend to develop orthostatic hypotension, defined as a decrease of systolic BP by more than 20 mm Hg in the upright position. It is therefore advisable to measure BP after being in the upright position for a defined period (e.g., 30 minutes). However, such an approach may not always be feasible in a primary care setting.
- The circadian BP profile tends to be abnormal in the early stages, and even a paradoxical increase in the nighttime BP is not rare. In the diabetic patient with nephropathy, it has been shown that a

nighttime increase in BP is independently associated with a 20-fold higher mortality and a higher risk for renal failure. Occasional measurements of ambulatory BP are particularly useful to assess the efficacy of antihypertensive treatment.

- In diabetic patients with sclerosis or calcification of the radial and brachial arteries, occasionally there may be pseudohypertension, or "white-coat hypertension," may occasionally occur, that is, spuriously elevated BP values despite normotension established by intraarterial BP measurements. This condition should be suspected if a discrepancy is found between modest target organ damage (e.g., left ventricular hypertrophy) and very high measured BP values. Such patients tend to develop marked hypotension even with relatively modest antihypertensive therapy.

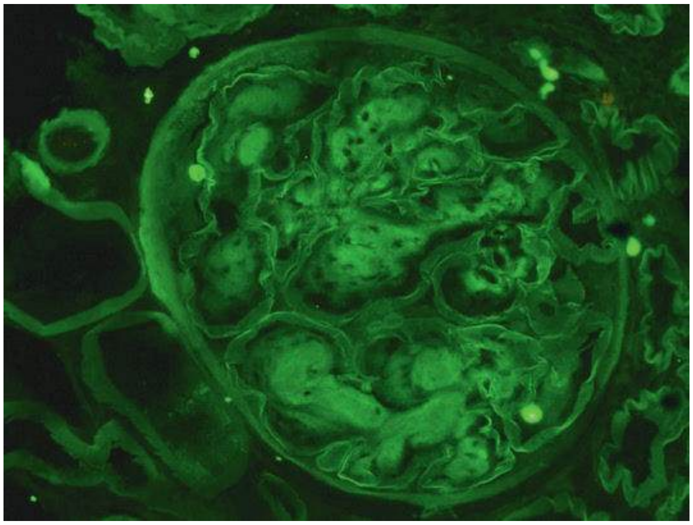

Fig. 30.17 **Immunofluorescence for glomerular immunoglobulin G (IgG) in diabetic nephropathy.** Faint staining of the glomerular basement membrane (GBM) for IgG results from passive trapping of IgG in the expanded GBM. (Courtesy Prof. Peter Furness, Leicester, UK.)

Measurement of Serum Creatinine and Estimation of Glomerular Filtration Rate

In clinical practice, the serum creatinine concentration is most frequently used to assess renal function, but it may be grossly misleading in wasted patients when muscle mass is low. This problem is particularly frequent in elderly female patients with type 2 diabetes. KDIGO recommends reporting estimated GFR in adults using the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation.

Differential Diagnosis

Although hematuria has been considered one of the atypical features indicating the presence of nondiabetic renal disease in patients with diabetes, it may be present in DKD. Moreover, a study identified hematuric patients with pathologically defined DKD, who had significantly lower renal function than nonhematuric patients with DKD.[79] The prevalence of nephrotic syndrome and retinopathy was significantly higher in hematuric patients than in nonhematuric patients with diabetic glomerulosclerosis.

On the other hand, other forms of kidney disease may be found in patients with type 2 diabetes. Younger patients with diabetes, shorter duration of diabetes, and proteinuria in the absence of retinopathy strongly suggest nondiabetic renal disease.[80] Membranous nephropathy,

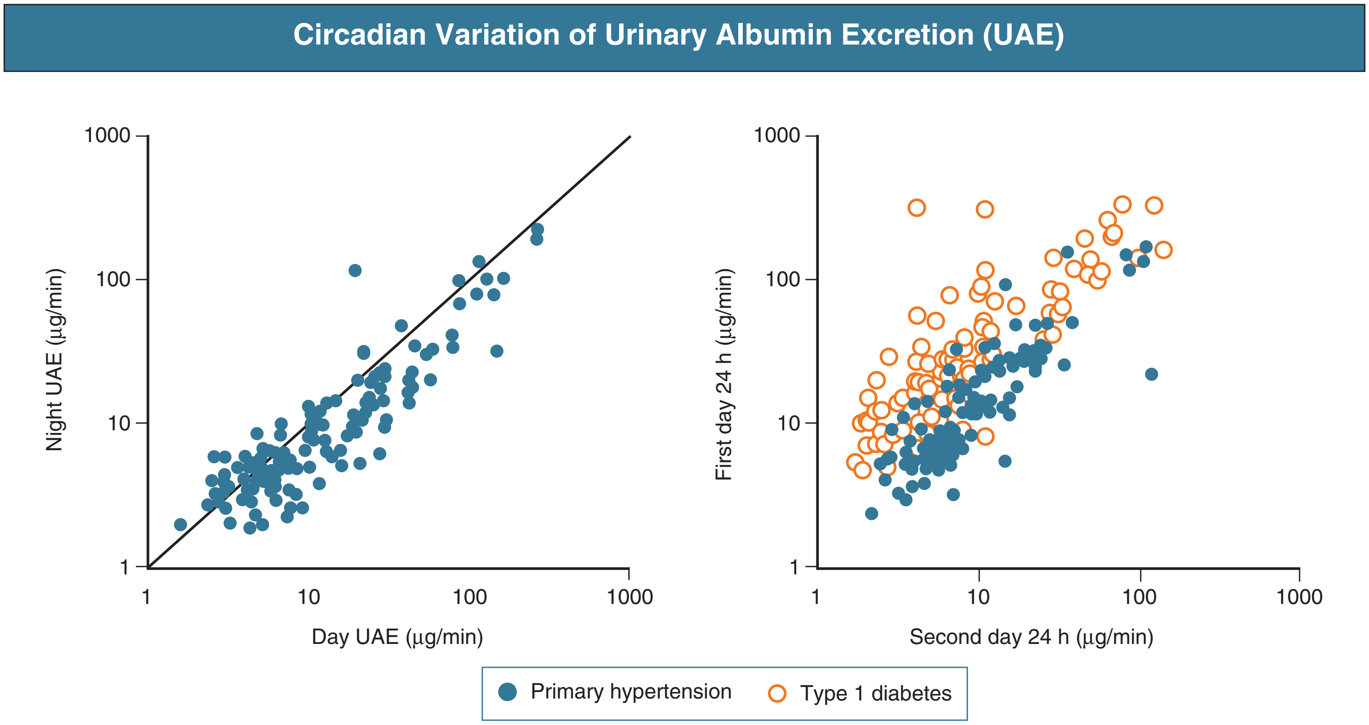

Fig. 30.18 **Circadian variation of urinary albumin excretion *(UAE).*** UAE is lower in resting conditions at night than during daytime activity. Relationship between UAE assessed on two different days 1 week apart in patients with type 1 diabetes *(open circles)* and primary hypertension *(closed circles).* There is substantial individual day-to-day variation of albumin excretion and also between day and night collections. (From reference 78.)

FSGS, acute interstitial nephritis, postinfectious GN, and IgA nephropathy have all been described in patients with type 2 diabetes in whom DKD was clinically suspected (Fig. 30.19).

Indications for Renal Biopsy

Further investigation, including renal biopsy, should be considered in the following situations (Fig. 30.20):

- If retinopathy is not present in type 1 diabetes with proteinuria or moderately impaired renal function (absence of retinopathy does not exclude DKD in type 2 diabetes).
- If the onset of proteinuria has been sudden and rapid, particularly in type 1 diabetes, and if the duration of type 1 diabetes has been less than 5 years. Alternatively, if the evolution has been atypical, for example, without transition through the usual stages,

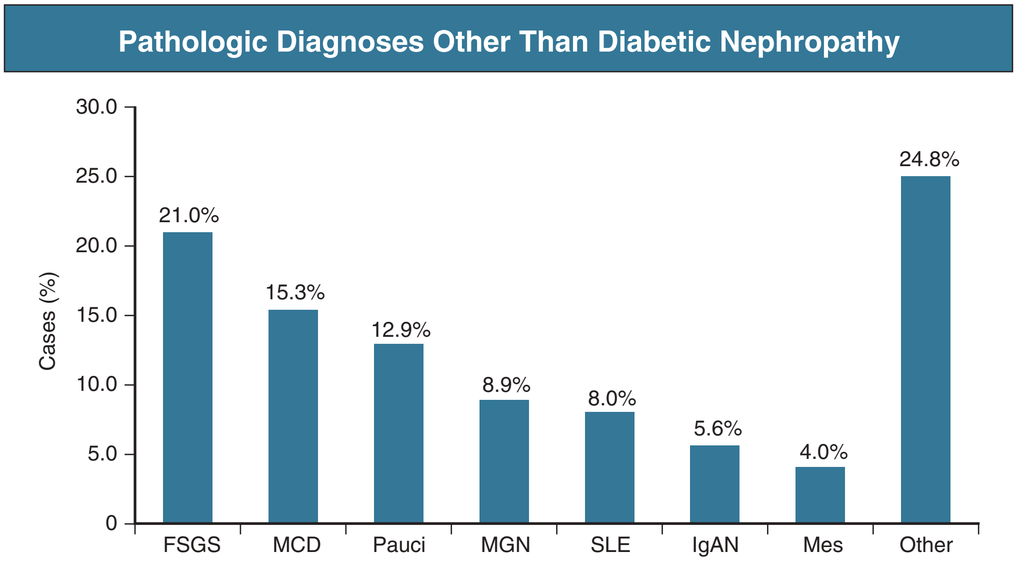

Fig. 30.19 **Pathologic diagnoses other than diabetic nephropathy are found in more than half of patients with type 2 diabetes with proteinuria.** A total of 233 patients were studied; 53.2% (124 patients) had a diagnosis of nondiabetic renal disease. *FSGS,* focal segmental glomerulosclerosis; *IgAN,* IgA nephropathy; *MCD,* minimal change disease; *Mes,* mesangial immune complex glomerulonephritis; *MGN,* membranous nephropathy; *Pauci,* ANCA-positive pauci-immune glomerulonephritis; *SLE,* systemic lupus erythematosus. (From reference 80.)

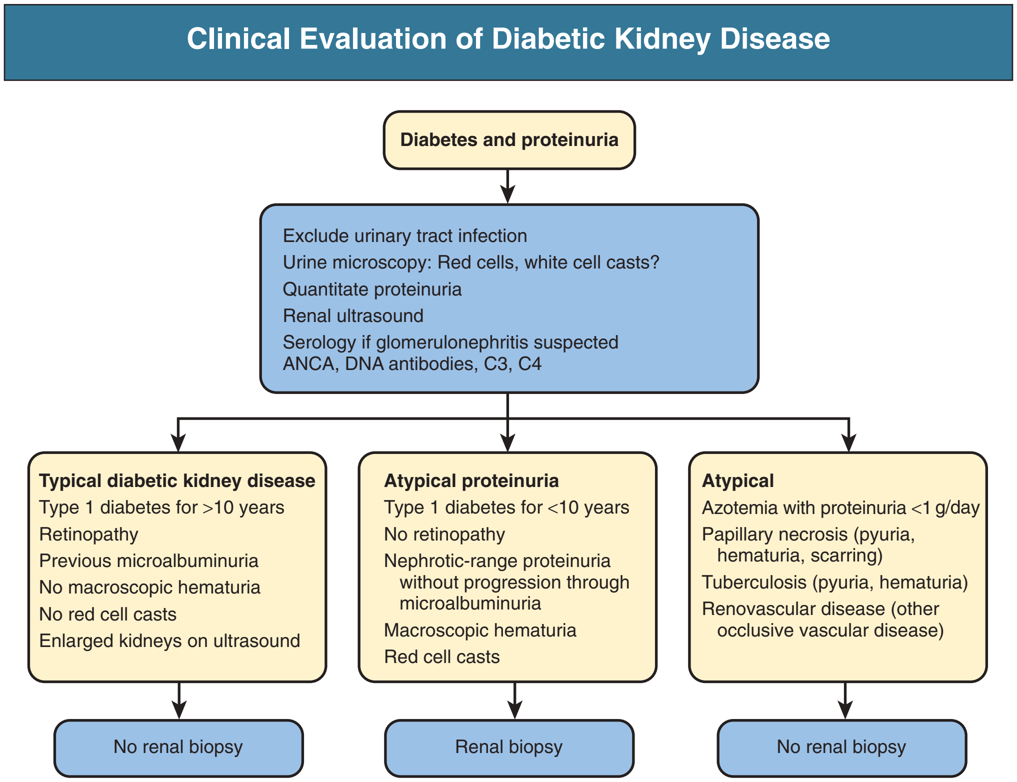
Clinical Evaluation of Diabetic Kidney Disease
Diabetes and proteinuria
Exclude urinary tract infection
Urine microscopy: Red cells, white cell casts?
Quantitate proteinuria
Renal ultrasound
Serology if glomerulonephritis suspected
ANCA, DNA antibodies, C3, C4
Typical diabetic kidney disease
Type 1 diabetes for >10 years
Retinopathy
Previous microalbuminuria
No macroscopic hematuria
No red cell casts
Enlarged kidneys on ultrasound
Atypical proteinuria
Type 1 diabetes for <10 years
No retinopathy
Nephrotic-range proteinuria without progression through microalbuminuria
Macroscopic hematuria
Red cell casts
Atypical
Azotemia with proteinuria <1 g/day
Papillary necrosis (pyuria, hematuria, scarring)
Tuberculosis (pyuria, hematuria)
Renovascular disease (other occlusive vascular disease)
No renal biopsy
Renal biopsy
No renal biopsy

Fig. 30.20 **Clinical evaluation of diabetic kidney disease.** *ANCA,* Antineutrophil cytoplasmic autoantibody.

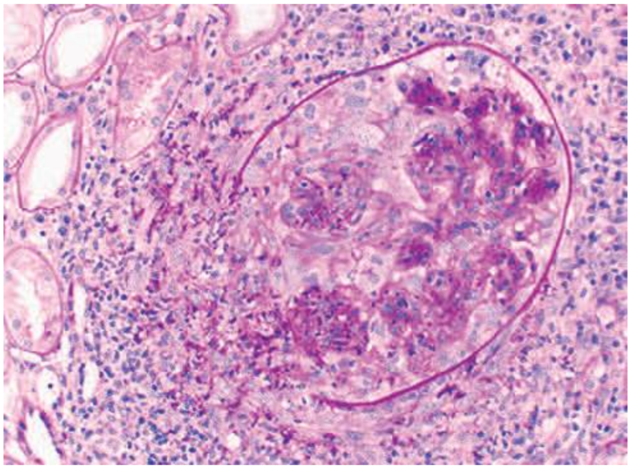

Fig. 30.21 **Glomerulonephritis superimposed on diabetic kidney disease (DKD).** A glomerulus showing a cellular crescent with rupture of the Bowman capsule superimposed on nodular DKD. The patient, known to have DN, presented with rapidly deteriorating renal function and red cell casts in the urine.

particularly the development of nephrotic syndrome without previous microalbuminuria.

- If there is macrohematuria or an active nephritic urinary sediment including acanthocytes or red blood cell casts suggesting GN; the sediment in DKD typically is unremarkable apart from some occasional erythrocytes.
- If the decline in renal function is exceptionally rapid, or if renal dysfunction is found without significant proteinuria (first, renovascular disease must be excluded) (Fig. 30.21).

If renal ultrasound reveals small kidneys or a significant size difference, it is prudent not to perform a renal biopsy. With the recognition of molecular tools to better classify kidney disease, there may be benefit for increased use of renal biopsies to better characterize the heterogeneity of disease in the future.

Approach to the Diabetic Patient With Impaired Renal Function

When seeing a diabetic patient with CKD, the nephrologist should do the following:

- Assess the cause of CKD (acute vs. chronic renal impairment; DKD vs. alternative causes of renal damage).
- Assess the magnitude of proteinuria and the rate of progression.
- Search for evidence of the typical extrarenal microvascular and macrovascular complications of diabetes.

The majority of diabetic patients with heavy proteinuria or renal failure have DKD. Renal ischemia (atherosclerotic renal artery stenosis or cholesterol embolism) is common in diabetic patients, and a substantial proportion of patients with type 2 diabetes have small kidneys and low GFR without albuminuria, possibly the result of macrovascular disease.

If urinary tract infection occurs, it is more severe in the diabetic than the nondiabetic patient. Purulent papillary necrosis and intrarenal abscess formation, however, have now become rare.

Diabetic patients with nephropathy are particularly prone to development of AKI after administration of NSAIDs or radiocontrast media or after cardiovascular events or septicemia. Preventive measures for AKI are discussed in Chapter 70. AKI superimposed on preexisting DKD carries a very poor renal prognosis.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements about diabetic nephropathy is correct?
   - **A.** The pathophysiology for diabetic nephropathy is different in type 1 and type 2 diabetes.
   - **B.** Glomerulosclerosis, tubular atrophy, and tubulointerstitial lesions are typical pathologic findings in diabetic nephropathy.
   - **C.** Development of diabetic nephropathy is always associated with microalbuminuria.
   - **D.** Development of diabetic nephropathy is always associated with hypertension.
2. Which of the following is *not* a risk factor for the development of diabetic kidney disease?
   - **A.** Genetic background
   - **B.** Hyperglycemia
   - **C.** Smoking
   - **D.** Anemia
   - **E.** Type of diabetes
3. Which of the following findings may suggest a nondiabetic origin of the renal disease?
   - **A.** Proteinuria greater than 2 g/day
   - **B.** Large kidneys on ultrasound
   - **C.** Increased serum creatinine
   - **D.** Acanthocytes in urine sediment
4. Which of the following observations suggests inflammation is a feature in diabetic kidney disease?
   - **A.** Increased transforming growth factor-β levels
   - **B.** Inflammasome activation in the diabetic kidney
   - **C.** Markedly elevated C-reactive protein and ferritin levels
   - **D.** Peripheral leukocytosis
   - **E.** Presence of urinary red and white cell casts

31

Prevention and Treatment of Diabetic Kidney Disease

Li-Li Tong, Sharon Adler, Christoph Wanner

In diabetic patients, the development of diabetic kidney disease (DKD) signifies the presence of a generalized microvascular syndrome that is frequently accompanied by macrovascular disease. (see Chapter 30). The terms DKD and diabetic nephropathy (used in previous editions of this chapter) are synonymous, and encompasses the spectrum of vascular, glomerular, and tubulointerstitial components of chronic kidney disease (CKD) attributed to diabetes. Classically, DKD evolves through several clinical stages based on urine albumin excretion (UAE) values: normoalbuminuria, moderately increased albuminuria (previously called microalbuminuria), and severely increased albuminuria (previously called macroalbuminuria, or overt nephropathy).[1] Furthermore, a substantial proportion of diabetic patients have a nonproteinuric phenotype with progressive loss of glomerular filtration rate (GFR). There is consensus that both the level of UAE and GFR have predictive importance for both renal outcome and cardiovascular (CV) morbidity and mortality. Normoalbuminuria is arbitrarily defined by a UAE of less than 30 mg/24 h, a threshold far above the normal albumin excretion in most healthy individuals. Thus, even in patients with normoalbuminuria, an incremental elevation of UAE is associated with increased cardiorenal risk.

In patients with established DKD, regression of albuminuria and preservation of renal function, although difficult, is the ideal treatment goal. Strict blood pressure (BP) and glycemic control early in the disease course is vital. Aggressive lipid-lowering and lifestyle modifications, including adherence to low-protein and low-sodium diet, exercise, weight loss, and smoking cessation all are beneficial and likely to improve renal and CV outcomes. Such multifactorial therapy has been shown to result in impressive lowering of the risk for cardiovascular disease (CVD), nephropathy, retinopathy, and autonomic polyneuropathy in the Steno 2 trial in patients with type 2 diabetes, and even a delayed reduction of mortality was seen.[2] Most patients with advanced-stage diabetic kidney disease, however, are likely to die from CVD or progress to end-stage renal disease (ESRD), even though treatment may slow this progression.

This chapter reviews the current preventive and therapeutic strategies that promote renoprotection and cardioprotection in diabetic patients (Fig. 31.1). In general, the treatment principles for established DKD are similar to those adopted for the prevention of DKD, although multiple and more intensive strategies may be required for treatment and the magnitude of benefit tends to be greater at earlier stages of disease. Patients with DKD often require multiple antihypertensive agents (including renin-angiotensin system [RAS] blocking agents) to achieve BP goal, insulin therapy in type 1 diabetes, two or more drugs for glucose control in type 2 diabetes, at least one lipid-lowering agent, and aspirin or other antiplatelet agents for CV protection. One obstacle to achieving adherence is the complexity of these regimens. Therefore prevention and treatment of patients with DKD needs to be individualized and requires consideration of the cost, side effects, and convenience of the drug regimen measured against the anticipated benefits. Special considerations are indicated in the management of the diabetic patient with advanced CKD (see Chapter 32). Many therapeutic issues discussed here are not specific for DKD and thus are also relevant for CKD in general (see Chapter 79).

GLYCEMIC CONTROL

In patients with type 1 diabetes, strict glycemic control decreases the risk for albuminuria and impaired glomerular filtration rate (GFR). The Diabetes Control and Complications Trial (DCCT) compared the effects of intensive glucose control with conventional treatment on the long-term complications of type 1 diabetes (Fig. 31.2). During a 9-year period, patients with mean hemoglobin A_{1c} (HbA_{1c}) of 7% who received intensive therapy had a 35% to 45% lower risk for development of moderately increased albuminuria compared with the control group (mean HbA_{1c} 9%).[3] Furthermore, the DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) trial data indicated that the long-term risk for developing impaired GFR was lower by 50% in patients treated for an average of 6.5 years with intensive glucose control than among those treated with conventional therapy. This effect was not evident until more than 10 years after randomization, beyond the period of the DCCT treatment intervention.[4]

For patients with type 2 diabetes, several major studies have also demonstrated a lower risk for nephropathy with stricter glycemic control. In a study design similar to the DCCT, the Kumamoto study found a 60% reduction in moderately increased albuminuria in relatively young, nonobese patients with type 2 diabetes receiving intensive glycemic treatment (HbA_{1c} 7.1%) compared with conventional treatment (HbA_{1c} 9.4%).[5] In the United Kingdom Prospective Diabetes Study (UKPDS) trial, newly diagnosed patients with type 2 diabetes were assigned to intensive management (HbA_{1c} 7.0%) with a sulfonylurea or insulin or to conventional management (HbA_{1c} 7.9%) with diet alone. After 9 years of intensive therapy, relative risk reduction for the development of moderately increased albuminuria was 24%.[6] After termination of the study, patients were observed for a further 10 years. The differences in HbA_{1c} were lost within 1 year, but a 24% lower risk of microvascular disease and myocardial infarction (−15%) persisted. All-cause mortality was also reduced (−13%). This phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycemic control even if followed by a return to less intensive metabolic control has been termed “metabolic memory” or “legacy effect.” It underlines the importance of early glycemic control in the primary prevention of microvascular and macrovascular complications in diabetic patients.

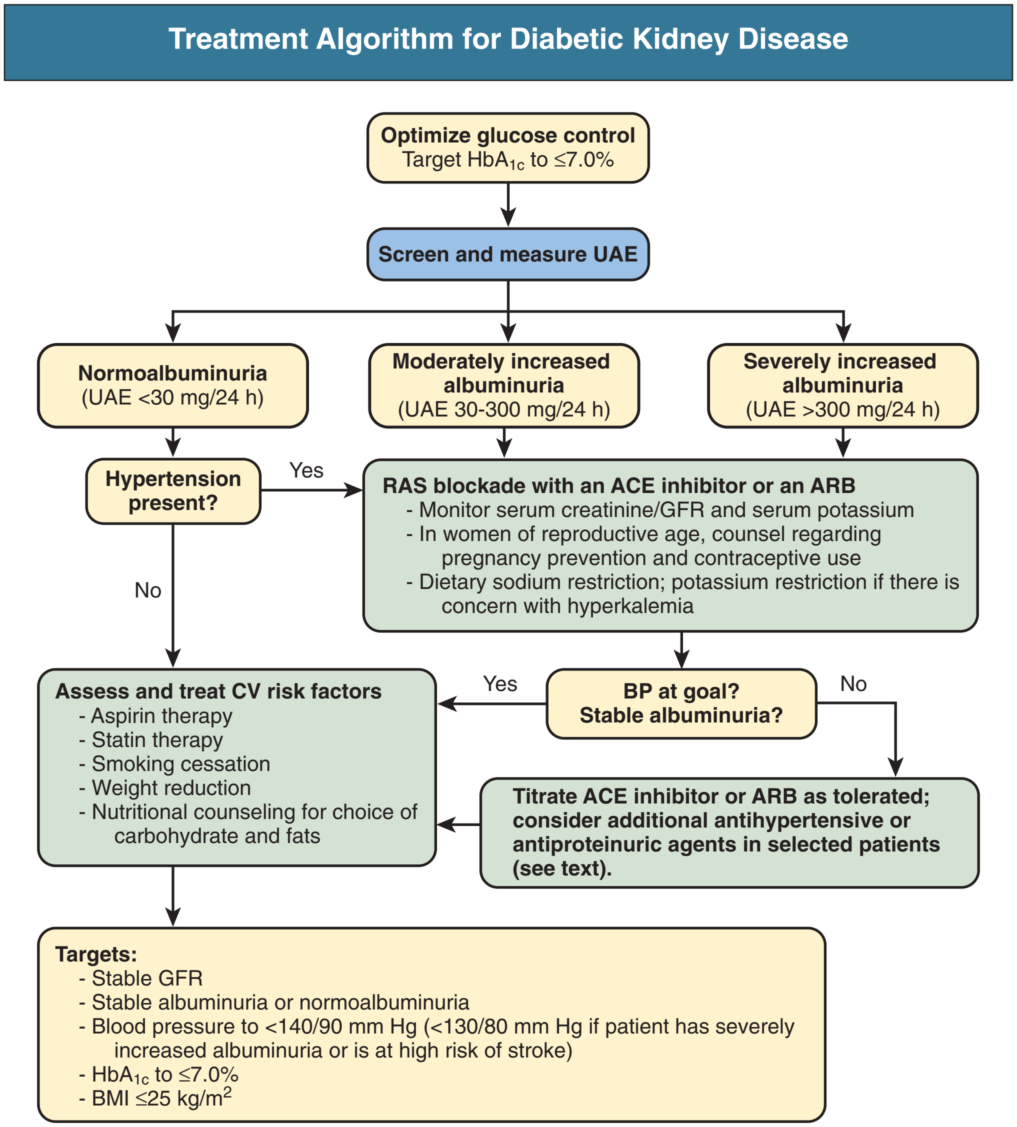
Treatment Algorithm for Diabetic Kidney Disease
Optimize glucose control
Target HbA1c to ≤7.0%
Screen and measure UAE
Normoalbuminuria
(UAE <30 mg/24 h)
Moderately increased albuminuria
(UAE 30-300 mg/24 h)
Severely increased albuminuria
(UAE >300 mg/24 h)
Hypertension present?
Yes
No
RAS blockade with an ACE inhibitor or an ARB
- Monitor serum creatinine/GFR and serum potassium
- In women of reproductive age, counsel regarding pregnancy prevention and contraceptive use
- Dietary sodium restriction; potassium restriction if there is concern with hyperkalemia
Assess and treat CV risk factors
- Aspirin therapy
- Statin therapy
- Smoking cessation
- Weight reduction
- Nutritional counseling for choice of carbohydrate and fats
Yes
BP at goal?
Stable albuminuria?
No
Titrate ACE inhibitor or ARB as tolerated; consider additional antihypertensive or antiproteinuric agents in selected patients (see text).
Targets:
- Stable GFR
- Stable albuminuria or normoalbuminuria
- Blood pressure to <140/90 mm Hg (<130/80 mm Hg if patient has severely increased albuminuria or is at high risk of stroke)
- HbA1c to ≤7.0%
- BMI ≤25 kg/m2

Fig. 31.1 Treatment algorithm for diabetic kidney disease. In considering the management of patients with diabetes and chronic kidney disease (CKD), a global perspective is required, which includes therapy that retards progression of kidney disease as well as therapy that minimizes cardiovascular risk and addresses other major diabetic complications, including coronary artery disease, peripheral artery disease, retinopathy, neuropathy, gastroparesis, and dyslipidemia. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CV,* cardiovascular; *GFR,* glomerular filtration rate; *Hb,* Hemoglobin; *HTN,* hypertension; *RAS,* renin-angiotensin system; *UAE,* urine albumin excretion.

Most of the evidence favoring strict glycemic control comes from studies of patients with normoalbuminuria or early stages of DKD. Fewer studies addressed intensive glycemic control in patients with more advanced stages of DKD, in whom it may be difficult to show a benefit because the results are confounded by the effects of concomitant hypertension and CVD. Even so, there is evidence to support glycemic control in reducing the risk for worsening albuminuria and renal functional decline.[4,7] Furthermore, in patients with type 1 diabetes with DKD, glycemic control also may improve renal histology. Renal biopsy specimens from pancreatic transplant recipients in whom true euglycemia is restored showed stabilized glomerular structure at 5 year follow-up and improved glomerular and tubular structure at 10 years after transplantation.[8]

Glycemic Targets

Several major trials tested whether strict glycemic control reduced CVD risk in type 2 diabetics. The Action in Diabetes and Vascular Disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE) study showed that intensive blood glucose control (HbA_{1c} 6.5% vs. 7.3%) yielded a 10% relative reduction in major macrovascular and microvascular events, in particular a 21% relative reduction in nephropathy.[9] However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, very tight glycemic control (lowering of HbA_{1c} to median of 6.4% vs. 7.5% with conventional control) was associated with 22% increase in mortality from any cause and did not significantly reduce major CV events.[10] A third major study of tight glucose control in

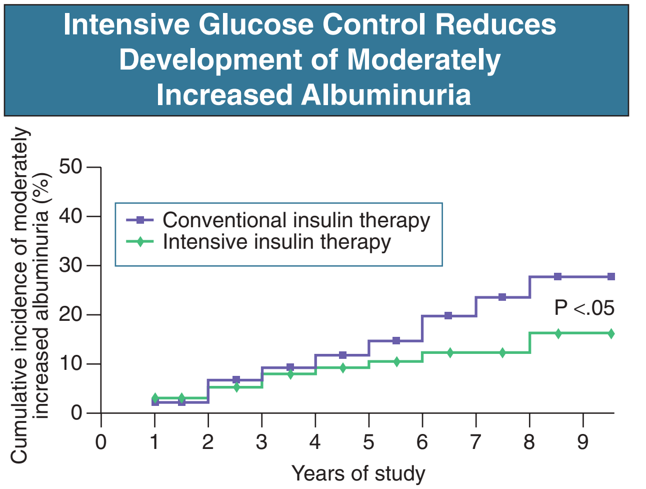

Fig. 31.2 **Moderately increased albuminuria risk reduction with intensive versus conventional insulin therapy.** Intensive glucose control was associated with a decreased risk for the subsequent development of moderately increased albuminuria in patients with type 1 diabetes. (Modified from reference 3.)

patients with type 2 diabetes, the Veterans Affairs Diabetes Trial (VADT), found no significant reduction in CV deaths or events over 7.5 years in high-risk patients treated aggressively for glycemic control (median HbA_{1c} 6.9%) compared with standard therapy (median HbA_{1c} 8.4%).[11]

It is apparent that glycemic control must be individualized and take into account the patient's age, duration of diabetes, presence of CVD, presence of CKD, and microvascular risks and complications, as well as previous glycemic control and susceptibility to and awareness of hypoglycemia. In younger patients with short duration of diabetes, high life expectancy, low risk for hypoglycemia, and no prior CV events, strict glycemic control can reduce the risk for nephropathy and other microvascular complications. Major guidelines, including the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), recommend lowering HbA_{1c} levels to a goal of approximately 7.0% for most patients with type 1 and type 2 diabetes.[12] This roughly translates to maintaining a fasting glucose of 80 to 130 mg/dl (4.4 to 7.2 mmol/l) and a postprandial glucose of less than 180 mg/dl (10 mmol/l). However, a more cautious approach to glycemic control is sensible in the frail or elderly patient with long-standing diabetes or preexisting CV problems or who is susceptible to hypoglycemic episodes. In these patients, the HbA_{1c} goal may be set higher (e.g., <8.0%). Accordingly, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) endorse tight glycemic control at the onset of diabetes in patients with few comorbidities as a preventive strategy and less stringent control in patients with more advanced comorbidities.[13]

Antihyperglycemic Therapeutic Options in Type 2 Diabetic Kidney Disease

The choice of antihyperglycemic therapy in patients with type 2 diabetes is a highly individualized decision, with consideration of medication-associated adverse events, degree of renal impairment, patient preference, cost, and convenience of therapy (see Chapter 32). Recent trials of novel antihyperglycemic therapies such as sodium glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 inhibitors (DPP4i), and glucagon-like peptide-1 (GLP-1) analogues have expanded the options to control glycemia and BP in patients with type 2 diabetes and improve CV and/or renal outcomes.

SGLT2 Inhibitors

Empagliflozin, dapagliflozin, and canagliflozin, are now widely approved antihyperglycemic therapies with a glycosuric mechanism. SGLT2 inhibitors induce osmotic diuresis and have natriuretic effects contributing to plasma volume contraction. They decrease systolic and diastolic BP by 4 to 6/1 to 2 mm Hg, respectively. They also decrease weight. SGLT2 inhibition is associated with an acute, dose-dependent reduction in eGFR by approximately 5 ml/min/1.73 m^2 and approximately 30% to 40% reduction in albuminuria. These effects mirror preclinical observations suggesting that proximal tubular natriuresis activates renal tubuloglomerular feedback through increased macula densa sodium and chloride delivery, leading to afferent vasomodulation.[14] Glycosuric effects are attenuated in patients with CKD (eGFR <60 ml/min/1.73 m^2) but BP, eGFR, and albuminuria lowering effects are preserved.

With regard to long-term clinical outcomes, the Empagliflozin Cardiovascular Outcome Event (EMPA-REG OUTCOME) trial, using empagliflozin 10 or 25 mg/day in patients with type 2 diabetes and established CVD reported a 14% reduction in the primary composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, and more than 30% reductions in CV mortality, overall mortality, and heart failure hospitalizations.[15] The recently published Canagliflozin Cardiovascular Assessment Study (CANVAS) showed a similar magnitude of CV events reduction using canagliflozin in patients with type 2 diabetes and a high risk of CVD. Therefore some guidelines now recommend that SGLT2 inhibitors with proven CV benefit be prioritized in patients with type 2 diabetes with insufficient glycemic control and who have atherosclerotic CVD. Furthermore, the EMPA-REG OUTCOME study reported a 39% reduction in incident or worsening nephropathy that included doubling of serum creatinine (relative risk reduction, 44%) and renal-replacement therapy (relative risk reduction, 55%) in the empagliflozin group, while the CANVAS-Renal trial similarly reported an impressive 40% reduction in the composite renal outcome (defined as a sustained 40% reduction in the rate of eGFR decline, need for renal replacement therapy, or death from renal causes).[15a,16] However, one concern with the use of SGLT2 inhibitors is an increase incidence of acute kidney injury, which has been reported in up to 6% of cases, especially with canaglifozin.

Analogues of Human Glucagon-Like Peptide-1

Several GLP-1 analogues, including liraglutide and semaglutide, have been approved for the treatment of type 2 diabetes. They effectively lower glucose levels and slightly reduce weight and BP. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial showed that fewer patients in the liraglutide group (relative risk reduction, 22%) died from CV causes, and the rate of death from any cause was lower (15%) as well. Fewer patients experienced a nephropathy end-point (−23%), which consisted mainly in a reduction of severely increased albuminuria.[17] Similar results were obtained in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) study.[18]

Dipeptidyl Peptidase-4 Inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitors (i.e., gliptins) represent another new class of antihyperglycemic therapy for patients with type 2 diabetes and can be used even in patients with advanced CKD. Treatment with DPP-4 inhibitors reduce albuminuria, although it is unclear whether this is a valid marker of renal protection. So far, clinical trials of DPP-4 inhibitors have demonstrated no additional CV outcome benefit compared with placebo.[19]

Blood Pressure Control

In patients with type 1 diabetes the appearance of moderately increased albuminuria typically precedes hypertension. In patients with type 2 diabetes, however, as many as 40% have known hypertension before the diagnosis of DKD. Once overt nephropathy develops, hypertension is an almost universal finding and is associated with volume expansion and salt sensitivity. The absence of hypertension in an untreated patient with overt nephropathy should raise suspicion for underlying cardiac problems. In both patients with type 1 and 2 diabetes, higher BP is associated with increasing albuminuria, with more rapid progression, and increased risk for kidney failure, as well as increased risk for fatal and nonfatal CV events.[20] Thus effective treatment of systemic hypertension is arguably the single most important strategy in the treatment of established DKD (Fig. 31.3). Antihypertensive therapies, regardless of agent used, reduce UAE, delay progression of nephropathy, postpone renal impairment, and improve survival in both patients with type 1 and type 2 diabetes with DKD.

The optimal BP target in DKD remains unclear. Guidelines published before the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial suggested a BP target in diabetic patients of less than 130/80 mm Hg. However, this BP target was challenged by findings of the ACCORD BP trial. Among diabetic patients with high CV risk randomized to goal systolic BP of less than 120 mm Hg or standard therapy aiming for under 140 mm Hg, there was no difference in the risks for composite major CV events, but the risks for hyperkalemia and renal dysfunction were increased at lower BP goals.[21] A cross-sectional analysis of patients in the Swedish National Diabetes Registry also failed to show a reduction in mortality in patients with systolic BP below 130 versus 130 to 139 mm Hg.[22] In the Irbesartan Diabetic Nephropathy Trial (IDNT), progressive lowering of systolic BP to 120 mm Hg was associated with improved renal and patient survival, an effect independent of baseline renal function.[23] Mortality increased with systolic BP below 120 mm Hg, although a cause-and-effect relationship cannot be inferred from the data. From a safety perspective, low diastolic pressure is poorly tolerated, and the incidence of myocardial infarction and mortality increases at values below 70 mm Hg, at least in patients with coronary heart disease, presumably because coronary perfusion occurs only during diastole. Indeed, in the IDNT study, CV mortality increased not only with higher systolic pressure but also with low diastolic pressure.

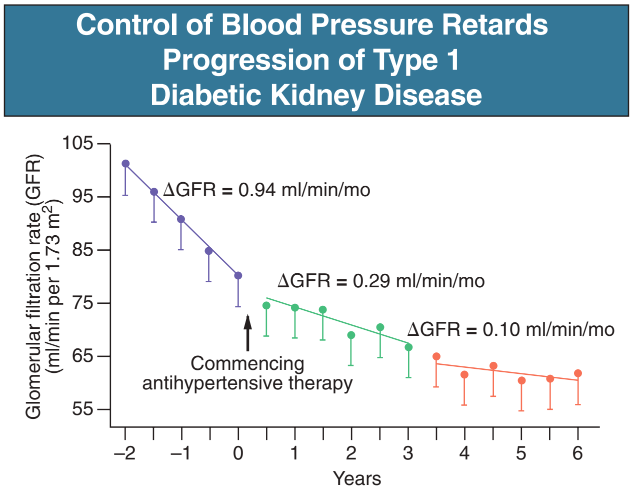

Fig. 31.3 Control of blood pressure reduces the risk for progression in type 1 diabetic kidney disease. (Modified from reference 20.)

Our recommendation for BP goals is consistent with the 2012 KDIGO guideline for BP control in diabetic patients, aiming for a target BP of less than 140/90 mm Hg for all diabetic patients and less than 130/80 mm Hg for patients with CKD and/or UAE of greater than 30 mg/24 h.[24] The 2016 American Diabetes Association (ADA), the 2014 Joint National Committee (JNC) 8, and the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines advocate similar targets. For diabetic patients at highest risk for cerebrovascular accident, the ACCORD BP trial showed that lower systolic BP goals (i.e., <120 mm Hg) may provide greater protection against stroke, but the potential risks for and burdens of serious adverse events attributable to antihypertensive therapy must be considered with such treatment goals.

Renin-Angiotensin System Blockade in the Prevention of Diabetic Kidney Disease

We do not recommend the use of RAS blockade in normotensive, normoalbuminuric diabetic patients for the primary prevention of DKD. Most patients with diabetes do not develop DKD, even after long periods of uncontrolled hyperglycemia, and there are hazards in the use of RAS blockers, including their potential teratogenicity. In a post hoc analysis of the multicenter Diabetic Retinopathy Candesartan Trials (DIRECT) program, which included patients with normotensive and normoalbuminuric type 1 diabetes and normoalbuminuric type 2 diabetes with or without hypertension, the ARB candesartan was found to have no effect on the development of moderately increased albuminuria.[25]

In hypertensive, normoalbuminuric diabetic patients, an ACE inhibitor or ARB are both effective as a first-line antihypertensive agent. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), which randomized patients with hypertension, normoalbuminuria, and type 2 diabetes to placebo, verapamil, trandolapril, or a combination of verapamil plus trandolapril, showed less progression to moderately increased albuminuria in patients receiving trandolapril either alone or with verapamil.[26] Results with verapamil alone was no different from that with placebo. There were similar findings in smaller studies with other RAS blockers, implicating a class effect. Longer term studies would be required to demonstrate the effects of RAS blockade on the clinically important outcomes of death, dialysis, and doubling of serum creatinine level in normoalbuminuric patients.

Renin-Angiotensin System Blockade in the Treatment of Diabetic Kidney Disease

In diabetic patients with established DKD, RAS blockade with ACE inhibitors, or ARBs confers renoprotection that is independent of BP reduction. Intraglomerular hemodynamic and nonhemodynamic renal effects of angiotensin II best explain the observed renoprotection. Supporting this hypothesis, in vitro models of DKD show cellular effects of RAS inhibition that are consistent with benefits independent of BP effects (see Chapter 30).

Type 1 Diabetic Patients

In patients with type 1 diabetes with moderately increased albuminuria, ACE inhibitors reduce the risk for progression to overt nephropathy. In a meta-analysis in normotensive patients with type 1 diabetes and moderately increased albuminuria treated with ACE inhibitors, the majority for more than 2 years, treatment was associated with a 60% reduction in progression to severely increased albuminuria and a threefold increase in regression to normoalbuminuria.[27] Changes in BP cannot entirely explain the antiproteinuric effect of ACE inhibitors.

In patients with severely increased albuminuria or overt nephropathy, the Collaborative Study Group trial demonstrated that captopril reduced albuminuria, slowed loss of GFR, and delayed the onset of kidney failure compared with placebo.[28] The beneficial effect of captopril was greater in patients with reduced GFR at baseline largely because one of the components of the composite end-point, a doubling of baseline serum creatinine level, was achieved more quickly in these patients.

Data are insufficient to demonstrate the efficacy of ARBs in type 1 DKD. Nevertheless, based on the shared properties of ACE inhibitors and ARBs in inhibiting the RAS, there is reason to believe that both are effective in the treatment of type 1 DKD.

Type 2 Diabetic Patients

In patients with type 2 diabetes, more data are available on the renoprotective effect of ARBs compared with ACE inhibitors. In the stage of moderately increased albuminuria, the IRMA 2 study showed that irbesartan reduced progression to overt nephropathy by 70% in patients with hypertension and type 2 diabetes during a 2-year follow-up period.[29] In the MARVAL trial, valsartan produced a greater reduction in UAE than did amlodipine (44% vs. 8%), with the same degree of BP reduction, suggesting that the antiproteinuric effect of ARBs is BP independent.[30]

In patients with type 2 diabetes with severely increased albuminuria and decreased GFR, large RCTs (IDNT and RENAAL) have demonstrated that ARBs are effective in lowering proteinuria and decreasing the relative risk for reaching the composite end-point of death, dialysis, and doubling of serum creatinine level.[31,32] However, the risk reduction for reaching the composite end-point was only 18% to 20% in these studies in patients with type 2 diabetes and nephropathy, compared with the more robust risk reduction of about 50% in patients with type 1 diabetes receiving captopril. ARBs did not decrease CV death in these trials but did decrease the incidence of heart failure.

Compared with ARBs, data on the efficacy of ACE inhibitors in type 2 DKD are less strong, largely because available studies had a small sample size or short follow-up. Nevertheless, some studies did show that ACE inhibitor use results in greater reduction in albuminuria and slower decrease in GFR compared with other antihypertensive agents. Whereas both ACE inhibitors and ARBs are probably effective for treatment of DKD in patients with type 2 diabetes, few studies have directly compared their efficacy. In a small RCT of patients with type 2 diabetes with early DKD and 5-year follow-up, telmisartan was not inferior to enalapril in providing long-term renoprotection.[33]

Aldosterone Blockade in Diabetic Kidney Disease

Although many studies have demonstrated a beneficial effect of ACE inhibitors and ARBs in retarding progressive renal disease, these studies did not differentiate between the relative contributions of the RAS blockade versus aldosterone system blockade (see Chapter 7). In fact, plasma aldosterone levels are elevated in a subset of patients despite ACE inhibitor and ARB therapy (also known as aldosterone breakthrough; see Chapter 79). In studies that defined aldosterone breakthrough as any increase from an individual's baseline serum aldosterone level (i.e., before RAS blockade), the incidence ranged from 40% over 10 months to 53% over 12 months.[34] In addition to its classic effects of promoting sodium retention and enhancing potassium and magnesium excretion, aldosterone promotes tissue inflammation and fibrosis.[35] Small studies have demonstrated considerably faster decline in GFR in patients who experienced aldosterone breakthrough (median, –5.0 ml/min/yr) than in those who did not (median, –2.4 ml/min/yr).

Aldosterone blockade using a mineralocorticoid receptor antagonist (MRA) such as spironolactone or eplerenone has been shown to reduce proteinuria when used alone and has an additive effect on proteinuria when combined with ACE inhibitor or ARB.[36] However, the risk for hyperkalemia frequently limits the use of combined MRA with ACE inhibitors or ARBs, especially in patients with reduced GFR. Current evidence is not strong enough to support widespread screening for aldosterone breakthrough. In select patients, the addition of a MRA with close monitoring of serum potassium levels may represent optimal therapy for patients with aldosterone breakthrough who no longer show maximal antiproteinuric effects with RAS blockers, although there is no definitive evidence that this will improve clinical outcomes. In addition to diuretic therapy, resins for chronic use that lower serum potassium can reduce the incidence of hyperkalemia in patients with CKD. Aggressive use of resins may offer the potential to enhance the therapeutic impact of renin-angiotensin-aldosterone inhibition while modulating hyperkalemia, but additional randomized trials are required.

Combination Therapy With Renin-Angiotensin System Antagonists

Combination therapy with RAS antagonists is not recommended in the treatment of DKD. Although earlier small trials suggested combined therapy with an ACE inhibitor and an ARB is more effective in reducing BP and proteinuria than is either drug alone,[37] results of several large trials failed to show improved clinical outcome. The Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial (ONTARGET), which included diabetic and nondiabetic patients with CV risk, failed to show improved CV outcomes from a combination of an ACE inhibitor and an ARB. Instead, it showed more rapid loss of kidney function in some patients, a trend toward an increase in the development of ESRD that fell just short of statistical significance, and a possible increase in mortality.[38] The more recent Veterans Affairs Nephropathy in Diabetes study (VA NEPHRON-D)[39] tested combination therapy with ACE inhibitor and ARBs in patients with type 2 diabetes with overt nephropathy and found no difference in the primary end-point of CKD progression or death. There was, however, an impressive increase in hyperkalemia (6.3 vs. 2.6 events/100 person-years; $P < .001$) and doubling of the risk for acute kidney injury (12.2 vs. 6.7 events/100 person-years; $P < .001$) with combination therapy compared with ARB alone.

ACE inhibitors or ARBs have been studied in combination with a direct renin inhibitor (aliskiren). Further reductions in proteinuria have been reported with these combinations compared with the ACE inhibitor or ARB alone. However, as was seen in ONTARGET and VA NEPHRON-D studies, an incremental antiproteinuric effect is not automatically translated into clinical outcome benefits. The large Aliskiren Trial in Type 2 Diabetics Using Cardio-Renal End-points (ALTITUDE) was terminated prematurely because of findings that a combination of aliskiren and ACE inhibitors or ARBs caused considerable increase in nonfatal stroke, hypotension, hyperkalemia, and renal complications after 1.5 to 2 years.[40] Thus aliskiren could be considered as an alternative RAS blocker for its antiproteinuric and BP effects, but more research is needed to demonstrate that it is as effective as ACE-inhibitors or ARBs.

Dosing and Adverse Effects Associated With Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

In individual patients, proteinuria may continue to respond to ACE inhibitor or ARB dose escalations beyond those recommended for BP control.[41] Unfortunately, maximal dosing of ACE inhibitors or ARBs may be limited by side effects, including hyperkalemia, hypotension, and reduced GFR. In women of reproductive age, counseling about pregnancy prevention and contraceptive use should begin before a RAS blocker is started.

Serum creatinine concentration may increase up to 30% in proteinuric patients with renal impairment after starting a RAS blocker. This rise in creatinine is associated with long-term renoprotection, and therapy should not necessarily be stopped in these patients. Increases in serum creatinine concentration above 30% after initiation of a RAS blocker should raise the suspicion of renal artery stenosis. Aggressive dose increments of ACE inhibitors or ARBs, especially in conjunction with diuresis, can precipitate acute kidney injury. In advanced CKD and aggressive sodium restriction, although RAS blockers are not contraindicated, the de novo introduction of these agents or injudicious dose increments may precipitate the need for dialysis prematurely, so some caution is appropriate.

Other Antihypertensive and Antiproteinuric Agents

Diuretics and Low Sodium Intake

The antiproteinuric effects of RAS blockers are enhanced by a low-sodium diet (e.g., <2 g sodium/day) and diuretic use. In patients with DKD, a loop diuretic or a thiazide diuretic is frequently necessary as part of the antihypertensive regimen. Combination of a diuretic with a RAS blocker is more effective than either type of treatment alone for lowering BP and proteinuria.

Calcium Channel Blockers

Dihydropyridine calcium channel blockers (dCCBs; e.g., nisoldipine, nifedipine, amlodipine) may be used as additional antihypertensive agents, but they have not been shown to reduce albuminuria or slow the progression of renal disease.[42]

Nondihydropyridine calcium channel blockers (ndCCBs; e.g., diltiazem, verapamil) have been shown in some studies to have beneficial antiproteinuric effects. A meta-analysis of randomized trials of ndCCB and dCCB in hypertensive patients with proteinuric renal disease found that at comparable BP control, ndCCB reduced proteinuria by approximately 30% compared with baseline, whereas dCCB had no appreciable effects on proteinuria.[43] These findings suggest ndCCBs are reasonable agents for BP control and can be used in combination with a RAS blocker in patients with DKD.

β-Blockers

Classic β-adrenergic blockers have adverse metabolic effects and are therefore undesirable in diabetic patients, but this is no longer true for the novel β-blockers (e.g., carvedilol, nebivolol). Despite insufficient controlled evidence, β-blockade appears to be useful because of the extremely high CV risk in patients with DKD and can be used in combination with a RAS blocker to achieve optimal BP control.

Treatment of Dyslipidemia

Most patients with DKD have dyslipidemia characterized by low levels of high-density lipoprotein (HDL) cholesterol, high triglyceride (TG) levels, and a shift from larger toward smaller LDL cholesterol. Dyslipidemia in diabetic patients may contribute to the development of glomerulosclerosis and progressive renal disease.[44] In the Diabetes Atherosclerosis Intervention Study (DAIS), patients with type 2 diabetes taking fenofibrate had a significantly lower rate of progression from normoalbuminuria to moderately increased albuminuria at 3 years compared with the placebo group.[45]

The 2013 KDIGO guidelines for Lipid Management in CKD recommend treatment with a statin in adult diabetic patients with CKD who are not treated with chronic dialysis. Because treatment with statins provides substantial CV benefit, emphasis is now placed on assessing a patient's global risk for CVD and using maximum tolerated statin intensity for primary and secondary prevention of CVD. Furthermore, existing evidence does not support a specific on-treatment LDL cholesterol target.[46] Once a patient is placed on a maximum tolerated dosage of statin, follow-up measurement of lipid levels is usually unnecessary except in instances in which the results would modify management. In contrast, once a patient has ESRD and is placed on dialysis, statin therapy may come too late to translate into improved CV outcomes (see Chapter 32).[47]

In diabetic patients, LDL cholesterol is not the sole lipid that defines CV risk. As major statin trials have demonstrated, lowering of LDL cholesterol does not prevent the majority of adverse CV events and does not bring the CV risk in diabetics down to the level of nondiabetic patients (referred to as residual CV risk). Atherogenic dyslipidemia, specifically elevated TG, low HDL cholesterol, elevated apolipoprotein B, and elevated apolipoprotein C III, are thought to be key factors associated with residual CV risk in diabetic patients.[48] In the UKPDS, elevated TG was independently associated with albuminuria in patients with type 2 diabetes. Thus interventions aimed at improving all lipid targets are recommended. However, it is not clear whether this is best achieved by intensification of statin therapy or supplementation of statin therapy with a fibrate or omega-3 fatty acids. In the ACCORD Lipid trial, routine use of combination therapy with a statin plus a fibrate did not reduce CV risk in patients with type 2 diabetes.[49]

Nonpharmacologic Interventions

For all diabetic patients, emphasis should be placed on lifestyle modification to lower the risk for diabetic kidney disease and CV events, including dietary restriction of salt and saturated fat, weight reduction and exercise as appropriate, and smoking cessation.

Dietary protein restriction may alleviate uremic symptoms in patients at or approaching ESRD. However, it is of uncertain benefit in the treatment of DKD. Small trials have shown low-protein diets (0.8 g/kg/day) reduce proteinuria significantly with increased plasma albumin in patients with type 2 diabetes with severely increased albuminuria.[50] A meta-analysis concluded that although low-protein diet improved proteinuria; it was also associated with lower serum albumin concentrations and was not associated with a significant improvement of renal function in patients with either type 1 or type 2 DKD.[51] Nutritionist counseling is advised for all patients with advanced CKD to avoid protein-energy malnutrition and receive education on salt, potassium, and phosphate restriction, as well as choice of carbohydrates and fats (see Chapter 86).

Lifestyle modifications such as smoking cessation and weight reduction can provide additive renal benefits and lower the risk for CV events in patients with established DKD. Smoking in particular is an independent risk factor for the development of nephropathy in type 2 diabetes and is associated with an accelerated loss of renal function. Smoking cessation ameliorates progression of moderately increased albuminuria to severely increased albuminuria and improves renal prognosis.[52] Weight reduction also may improve renal outcome. In a small RCT of obese (body mass index, >27 kg/m^2) diabetic and nondiabetic patients with proteinuric renal disease, patients who lost weight through dieting had marked improvement in proteinuria compared with those who lost no weight.[53]

EMERGING TREATMENTS FOR DIABETIC KIDNEY DISEASE

A number of therapeutic agents, some experimental and others in clinical use for other indications, have been tried with the goal of preventing or treating DKD. Unfortunately, a high rate of attrition has been observed with many investigational drugs due to failure to meet primary clinical end-points or unacceptable side effect profiles. Bardoxolone methyl (an inducer of the Nrf2 pathway), ruboxistaurin (a protein kinase C inhibitor), pirfenidone (an antifibrotic agent), pimagedine/aminoguanidine/pyridoxamine (advanced glycation end-product formation inhibitors), palosuran (a vasopeptidase inhibitor), probucol (an antioxidant), and sulodexide (a glycosaminoglycan), have all failed in various phases of

TABLE 31.1 Selected Investigational Drugs for Diabetic Kidney Disease

Drug	Mechanism of Action	Clinical Trials and Comments
Finerenone,	MRAs	In phase 2 trials, the addition of finerenone to RAS blockers improved UAE, with a low incidence of hyperkalemia.[54] Phase 3 trials (FIDELIO-4800 pts., FIGARO-6400 pts.) are underway.
Atrasentan	Endothelin A receptor blocker	In phase 2 trials, atrasentan reduced albuminuria when used with RAS blocker in patients with type 2 diabetes; significant risk for peripheral edema noted in a subgroup of patients receiving a higher dose of atrasentan (1.75 mg).[56] A phase 3 trial (SONAR-4148 pts.) was stopped early due to lower than anticipated incidence of primary end-points.
Paricalcitol,	Vitamin D receptor activators	A RCT ($n = 281$) found that addition of paricalcitol to RAS blocker lowered albuminuria in type 2 patients with DKD.[57]
Allopurinol, febuxostat, topiroxostat	Purine analogue and inhibitor of xanthine oxidase that decreases uric acid formation	Limited short-term studies have shown improved blood pressure control and slowing of CKD progression after serum uric acid lowering with allopurinol.[59]
Pentoxifylline, CTP-499	Nonselective phosphodiesterase inhibitors	In a small trial ($n = 169$) of patients with type 2 diabetes, the addition of pentoxifylline to a RAS blocker had additive antiproteinuric effect and slowed renal disease progression after the first year of treatment and maintained statistical significance with placebo after 24 mo.[60]
CCX-140	C-C Chemokine receptor 2 antagonist	A phase 2 trial of patients with type 2 diabetes with DKD on a stable RAS blocker showed a statistically significant improvement in albuminuria compared with placebo.
Baricitinib	Selective JAK1/JAK2 inhibitor	A phase 2 trial to evaluate the safety and efficacy of baricitinib in reducing UAE in patients with type 2 diabetes with DKD was completed in 2014. Official results not published yet.
Selonsertib (GS-4997)	Selective apoptosis signal-regulating kinase 1 inhibitor	A phase 2 trial evaluating the efficacy and safety of GS-4997 on top of a RAS blocker in patients with type 2 diabetes with DKD was completed in August 2016. Outcome measurements include change in UAE and eGFR. Official results not published yet.
ASP-8232	Vascular adhesion protein 1 inhibitor	Ongoing phase 2 trial to evaluate the efficacy and safety of ASP-8232 in patients with type 2 diabetes with DKD.
Bardoxolone methyl (RTA-402)	Inducer of Nrf2 pathway	A phase 3 trial of bardoxolone methyl in DKD was halted because of excess serious adverse events in the treated group. There is an ongoing phase 2 trial to assess the safety and efficacy of RTA-402 in Japanese patients with type 2 diabetes with CKD.

CKD, Chronic kidney disease; *DKD,* diabetic kidney disease; *eGFR,* estimated glomerular filtration rate; *MRA,* mineralocorticoid receptor antagonist; *RAS,* renin-angiotensin system; *RCT,* randomized controlled trial; *UAE,* urine albumin excretion.

clinical development. Ongoing trials exploring new treatments in DKD include newer, selective MRAs, endothelin receptor antagonists, drugs that target oxidative stress, xanthine oxidase inhibitors, and other anti-inflammatory and antifibrotic agents (Table 31.1).

MINERALOCORTICOID RECEPTOR ANTAGONISTS

The use of available steroidal MRAs such as spironolactone and eplerenone is often limited because of adverse side effects arising from poor selectivity for mineralocorticoid receptors and hyperkalemia. Finerenone, a newer nonsteroidal MRA, improves markers of kidney function when added to a RAS blocker in patients with DKD. Unlike the steroidal MRAs, finerenone has greater receptor selectivity and affinity in vitro. In phase 2 trials, the addition of finerenone to a RAS inhibitor improved UAE with a very low incidence of hyperkalemia compared with placebo at 90 days.[54] Phase 3 trials of finerenone in patients with DKD are underway. Several additional novel MRAs (CS-3150, MT-3995, KBP-5074) with undisclosed molecular structures are in phase 2 trials.

ENDOTHELIN RECEPTOR ANTAGONISTS

The renal endothelin system is activated in experimental DKD and in patients with DKD. The antiproteinuric effect of an endothelin A receptor blocker was shown in the Avosentan on Doubling of Serum Creatinine, End stage Renal Disease and Death (ASCEND) phase 3 clinical trial. However, avosentan-related adverse events such as fluid retention led to early termination of the ASCEND trial.[55] Another endothelin A receptor blocker, atrasentan, is more selective than avosentan, and was shown in a phase 2 trial to reduce albuminuria when used in conjunction with a RAS inhibitor in patients with type 2 diabetes.[56] Significant weight gain was noted in patients receiving atrasentan, suggesting volume overload. A large phase 3 trial (SONAR) is underway assessing the effect of atrasentan versus placebo in type 2 diabetes mellitus with DKD. It has strict entry criteria that exclude patients at risk for fluid overload.

Vitamin D Receptor Activators

Vitamin D receptor activation has been shown to reduce proteinuria in small trials of DKD. A cross-sectional analysis of the 2001 to 2006 National Health and Nutrition Examination Survey (NHANES) data showed that there was an independent association between vitamin D deficiency and insufficiency with the presence of nephropathy. The largest phase 2 RCT investigating the effect of paricalcitol (a vitamin D analogue) 1 or 2 μg/day in patients with type 2 diabetes failed to meet its primary end-point (change in UAE), but post hoc analysis showed lowered albuminuria compared with placebo in patients with high sodium intake and on a higher dose of paricalcitol.[57] The study has many limitations, however. Only 58% of the patients assigned to 2 μg/day of paricalcitol received the full dose during the study, and the follow-up period of 24 weeks was brief. A meta-analysis of pooled data from five small and heterogeneous clinical trials ($n = 219$) suggested no significant change in UAE after vitamin D supplementation.[58]

Xanthine Oxidase Inhibitors

Epidemiologic studies suggest an independent association between asymptomatic hyperuricemia and increased risk for arterial hypertension, CKD, albuminuria, CV events, and mortality. Several open-label clinical trials have shown improvements in BP control and slowing of CKD progression after serum uric acid lowering with allopurinol. In a meta-analysis of RCTs in patients with stage 3 to 5 CKD, allopurinol was found to have a small but statistically significant improvement in eGFR, as well as a tendency toward benefit for proteinuria.[59] Clinical trials of allopurinol and its novel analogues, febuxostat and topiroxostat, are underway to assess the impact of these drug in DKD.

Phosphodiesterase Inhibitors

Pentoxifylline (PTF) is a nonselective phosphodiesterase (PDE) inhibitor currently used for symptomatic relief of claudication. It has vasodilatory and antihypertensive effects and may have beneficial hemodynamic effects in the kidney. PTF also inhibits synthesis of inflammatory cytokines. In a small trial in patients with type 2 diabetes, the addition of PTF to RAS blockade had additive antiproteinuric effects and slowed kidney disease progression after the first year of treatment and maintained statistical significance compared with placebo after 24 months.[60] Based on this and several other positive outcomes of PTF trials, more selective PDE inhibitors (CTP-499, PF-489791) have been developed, though there are insufficient data on these agents at this time.

Novel Therapeutic Approaches

Several novel investigational agents, including CCX-140 (chemokine inhibitors), baricitinib (a selective JAK1/JAK2 inhibitor), selonsertib (a selective apoptosis signal-regulating kinase 1 inhibitor), ASP-8232 (a vascular adhesion protein 1 inhibitor), SER150 (a thromboxane A2 receptor antagonist), and several drugs currently in clinical use for other indications (e.g., N-acetylcysteine, colchicine), are being evaluated for treatment of proteinuric renal disease, including DKD. A new formulation of bardoxolone methyl, RTA 402 (an inducer of Nrf2 pathway), is being tested for safety and efficacy in Japanese patients with type 2 diabetes with CKD. The role of micro-RNAs in the pathogenesis of DKD is an emerging field and may also provide additional novel treatment approaches. New insights into the molecular mechanisms that underlie the origin and progression of DKD are emerging from large-scale genetic and molecular studies in experimental models and humans.

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32

Management of the Diabetic Patient With Chronic Kidney Disease

Rosa M. Montero, David J. A. Goldsmith

Diabetes mellitus (DM) type 2 (T2DM), and to a lesser extent type 1 (T1DM), are rapidly increasing in incidence, with more than 642 million people predicted to be affected worldwide by 2040 (Fig. 32.1).[1] In this chapter we refer to the management of both types of DM and specify where differences in management arise between the two. DM is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the Western world, with current therapeutic strategies often slowing but rarely completely halting the disease in all cases.

DIAGNOSTIC CONSIDERATIONS

Few people with known DM and slowly evolving CKD undergo renal biopsy to diagnose diabetic nephropathy (DN).[2] Those who undergo renal biopsy are usually selected in the context of atypical presentations of DN, such as those with frank hematuria (requiring renal and bladder imaging, cystoscopy, and, if no cause found, a renal biopsy) or those with nephrotic range albuminuria in the presence of a normal glomerular filtration rate (GFR) or a rapid increase in the severity of albuminuria.

GENERAL MANAGEMENT CONSIDERATIONS

It is well established that not everyone with DN progresses (in terms of more severe albuminuria and/or declining estimated GFR [eGFR]); in some cases this is due to premature mortality from cardiovascular (CV) disease or other comorbidity.[3,4] CKD stages 1 to 3a DN are usually managed in the community or by diabetologists whose treatment strategies require little modification until renal function deteriorates further. Those referred to a nephrologist tend to be CKD stage 3b to 5, with some requiring dialysis and/or transplantation. Therefore the remainder of this chapter will focus on how to manage this group guided by current evidence and practice guidelines.[5] We also mention newer tools and treatments that may soon become available in clinical practice.

MONITORING DIABETIC RENAL DISEASE (STAGE CKD3B-5)

The mainstay of treating DM with CKD and monitoring its progression is based on successfully controlling the product of two assays; glycosylated hemoglobin A_{1c} (HbA_{1c}) and albuminuria (typically quantified by albumin-to-creatinine ratio [ACR]).

Hemoglobin A_{1c}

HbA_{1c} is a measure that arises from a nonenzymatic Maillard reaction, in which condensation of the aldehyde group of glucose and the N-terminal amino group of the β-chain of HbA0 [N-(1-deoxyfructosyl)Hb] occurs.[6] Approximately 6% of adult hemoglobin is glycated with HbA_{1c}, forming the majority of all glycohemoglobin in human blood. Fifty percent of HbA_{1c} value arises from the previous 30 days of glucose exposure, 40% from 31 to 90 days and 10% from 91 to 121 days; hence HbA_{1c} has evolved as a marker of medium-term glycemic control. An advantage of using HbA_{1c} is its low inter-subject biologic variability that is unaffected by diurnal variation or stress.[7] The disadvantages, however, include the discrepancy in its levels with short-term mean serum glucose levels because of the longer time span that forms the result. Age, ethnicity, pregnancy, and underlying disease also may affect HbA_{1c} values.[8] The life span of red blood cells directly affects the HbA_{1c}, which is also affected by erythropoietin, iron, folic acid, and/or vitamin B_{12} deficiency; hence the limitations in CKD are profound. Despite these limitations a raised HbA_{1c} (>8% [>64 mmol/mol]) has been shown to be associated with higher all-cause and CV mortality in advanced diabetic CKD, including in patients on dialysis and transplant recipients.[9-13] Lower HbA_{1c} levels (<5.4% [<36 mmol/mol]) have been associated with increased mortality in patients with poor nutritional status. DM patients with advanced CKD, including dialysis patients, have a U- or J-shaped curve of HbA_{1c} and mortality. Too high or too low HbA_{1c} levels are therefore detrimental and (<6.5% [<48 mmol/mol]) or (>8% [>64 mmol/mol]) should be avoided.[14]

In view of the risks for hypoglycemia in patients with advanced CKD, physicians should individualize glycemic targets based on the risks and benefits in such patients.[15] Table 32.1 shows a comparison of biomarkers available to determine glycemic control. Numerous clinical trials, however, have used HbA_{1c} as a reference, and thus until further studies are conducted specifically assessing any of the novel glycemic markers in the CKD population, HbA_{1c} will continue to be used.[14] Fig. 32.2 shows a flow chart for management targets of HbA_{1c} in DM CKD3b-5. Table 32.2 shows the current standard care and target values proposed for patients with DM CKD3b-5. In dialysis patients a target HbA_{1c} of less than 8.5% (<69 mmol/mol) is recommended[16]; however, continuous glucose measurements are likely to be increasingly used in the future.

Albuminuria

Detection of albuminuria in DM CKD has been the mainstay of monitoring progression through normoalbuminuria (<30 mg albumin/24 h), microalbuminuria (30 to 300 mg albumin/24 h; now often termed *moderately increased albuminuria*) and macroalbuminuria (>300 mg albumin/24 h; now often termed *severely increased albuminuria*). Previously it has been thought that most survivors with DM will eventually develop progressive DN, with increasing albuminuria, morbidity, and mortality.[17] However, this paradigm is being challenged as people with T2DM with nonproteinuric DM CKD have been described as

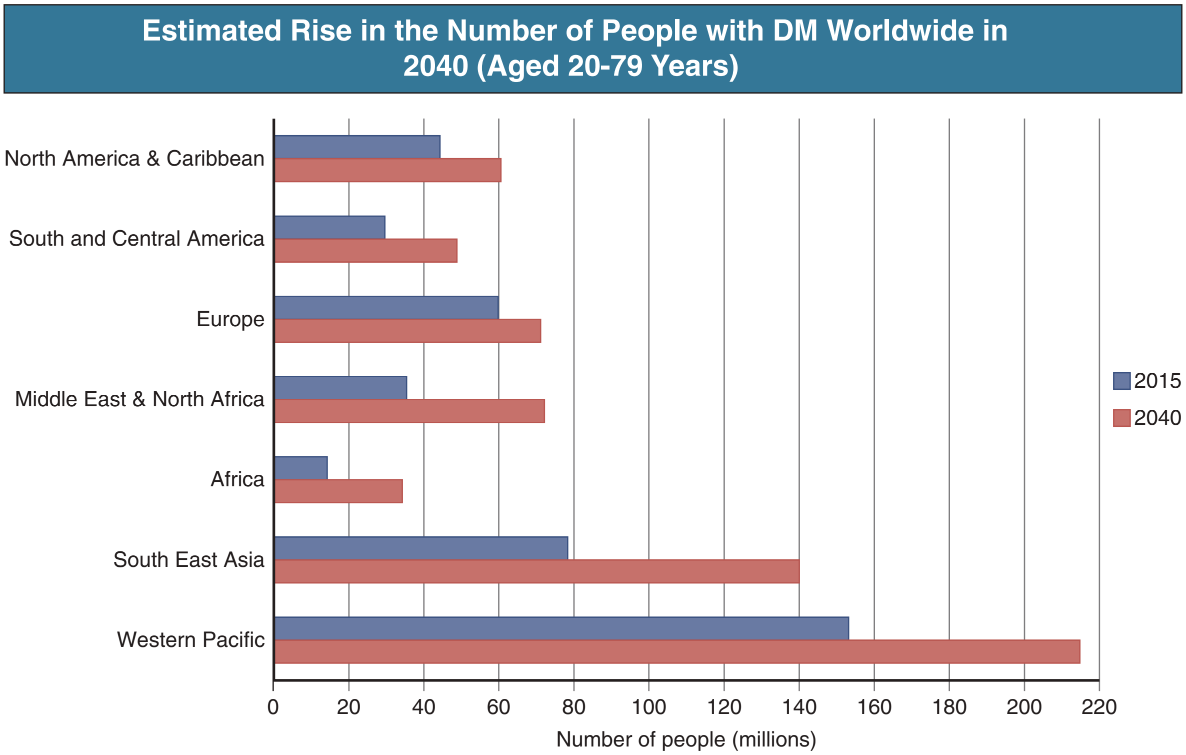

Fig. 32.1 Worldwide estimated rise in the prevalence of diabetes mellitus from 2015 to 2040. (Data from reference 1.)

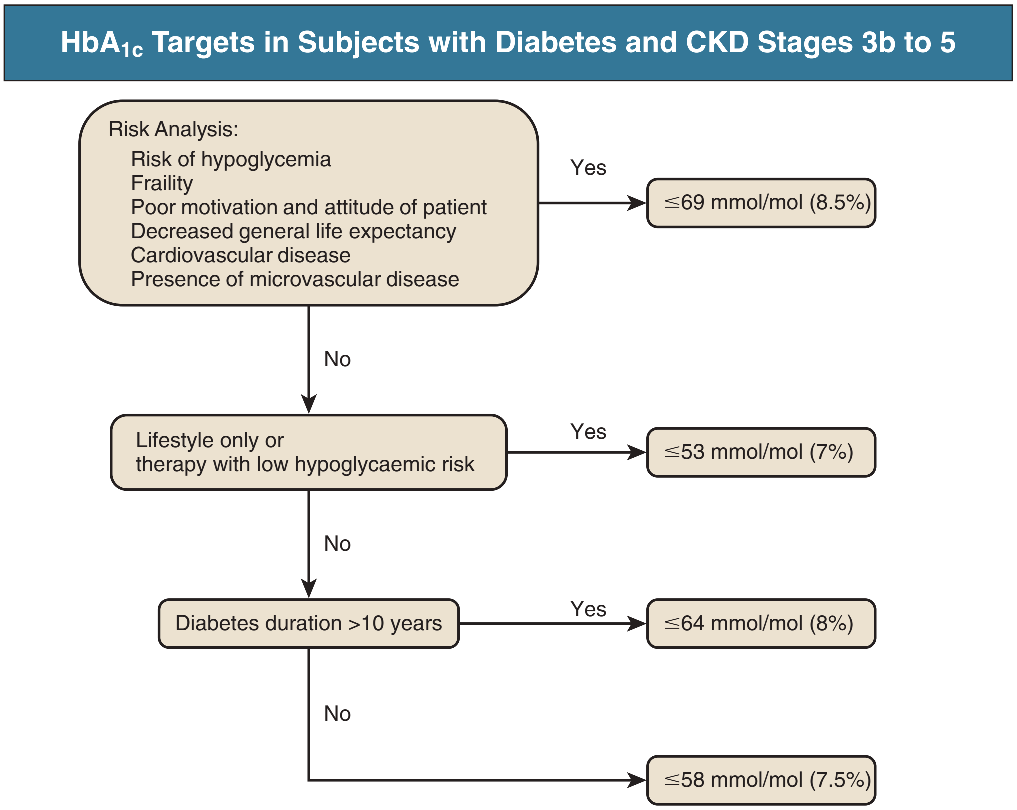
HbA1c Targets in Subjects with Diabetes and CKD Stages 3b to 5
Risk Analysis:
Risk of hypoglycemia
Fraility
Poor motivation and attitude of patient
Decreased general life expectancy
Cardiovascular disease
Presence of microvascular disease
Yes
≤69 mmol/mol (8.5%)
No
Lifestyle only or therapy with low hypoglycaemic risk
Yes
≤53 mmol/mol (7%)
No
Diabetes duration >10 years
Yes
≤64 mmol/mol (8%)
No
≤58 mmol/mol (7.5%)

Fig. 32.2 Management targets for HbA_{1c} in patients in DM CKD3b-5. Modified from ERBP guidelines(5).

TABLE 32.1 Comparison of the Different Glycemic Markers in Diabetes Associated with Chronic Kidney Disease

Marker	Advantages	Disadvantages
HbA$_{1c}$	Long-term glycemic marker. Standardization of HbA$_{1c}$ assays. In comparison with blood glucose, less sensitivity to preanalytical variables, lower within-subject biologic variability, little/no diurnal variations, little/no influence from acute stress, and little/no influence from common drugs known to influence glucose metabolism. Excellent separation of the HbA$_{1c}$ fraction from other Hb adducts and with no interference from carbamylated Hb.	Falsely *increased* values with iron and/or vitamin B$_{12}$ deficiency, decreased erythropoiesis, alcoholism, CKD, decreased erythrocyte pH, increased erythrocyte life span, splenectomy, hyperbilirubinemia, carbamylated Hb, intake of high-dose aspirin, chronic opiate use. Falsely *decreased* values after administration of; erythropoietin, iron, vitamin B$_{12}$; with reticulocytosis, chronic liver disease, ingestion of aspirin, vitamin C, vitamin E, hemoglobinopathies, increased erythrocyte pH, decreased erythrocyte life span, splenomegaly, rheumatoid arthritis, drugs; antiretrovirals, ribavirin and dapsone, hypertriglyceridemia. Variable changes with fetal Hb, hemoglobinopathies, methemoglobin, genetic determinants.
Glycated albumin	Short-term glycemic marker (2-3 wk). Independent of gender, erythrocyte life span, erythropoietin therapy, or serum albumin concentration. Associated with vascular injury markers.	Values can be influenced by lipemia, hyperbilirubinemia, hemolysis, increased uric acid, uremia, intake of high-dose aspirin, poor nutrition, age, albuminuria, cirrhosis, thyroid dysfunction, and smoking. Concentration inversely affected by body mass index, body fat mass, and visceral adipose tissue. Different reference ranges depending on applied methods. Limited data. Expensive, time-consuming, currently not widely available.
Fructosamine	Marker of average glucose levels in the previous 10-14 days. Simple, automated analysis.	Contradictory results concerning the correlation between fructosamine and glucose concentrations in CKD. Values can be influenced by nephrotic syndrome, thyroid dysfunction, glucocorticoid administration, liver cirrhosis. Concentration influenced by uremia, glycemia, hypoalbuminemia, hyperuricemia. Within-subject variation is higher than that for HbA$_{1c}$.
1,5 Anhydroglucitol	Marker of day-to-day changes in glucose levels. Retained metabolic inertness, steady-state levels in all tissues and negligible influence of sampling conditions such as collection time, body weight, age, sex, and food intake of subjects.	Poor diagnostic for diabetes in comparison to other glycemic markers. Contained in traditional Chinese herbal medicines. Limitations for use in subjects with renal tubular acidosis, advanced CKD or ESRD. Not widely available, limited data on its clinical everyday value.

Modified from European Best Practice guideline.
CKD, Chronic kidney disease; *ESRD,* end-stage renal disease; *Hb,* hemoglobin.

a subgroup developing ESRD.[18] Cross-sectional studies have reported T2DM without proteinuria and GFR less than 30 ml/min/1.73 m^2, illustrating that renal insufficiency may occur without albuminuria and thus reduce the benefit of using albuminuria as a marker for this subgroup. The metabolic syndrome has frequently been associated with nonproteinuric GFR decline with insulin resistance, obesity, and systolic hypertension. This phenotype of T2DM may progress with loss of GFR to ESRD without detection if albuminuria alone were to be used as the marker of progression. Not all people with moderately increased albuminuria progress to severely increased albuminuria[19]; and some patients with moderately increased albuminuria undergo spontaneous remission. The introduction of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) also may cause regression of albuminuria,[20] thus rendering albuminuria an unreliable marker of progression as people continue to develop ESRD.

Albuminuria arises from glomerular and/or tubular damage and typically occurs after 10 years of T1DM. T2DM is commonly diagnosed by the presence of albuminuria, and thus the time for its development is unclear. Thirty percent of people with retinopathy will develop albuminuria and therefore should be monitored for development of CKD to allow for early intervention.[21] Some patients with T2DM may present with retinopathy before being diagnosed with DM CKD, hence the importance of screening. Albuminuria also can be affected by exercise, fever, hypertension, heart failure, pregnancy and menstruation, urinary tract infection, marked hyperglycemia, and sepsis and in these instances should be interpreted with caution. Nevertheless, the presence and severity of albuminuria continue to be used as outcomes in clinical trials and have yet to be compared with new biomarkers entering the field.[22]

MANAGEMENT OF DIABETES IN SUBJECTS WITH STAGE 3B-5 CKD

A multidisciplinary approach is pivotal to successful management of DM CKD and its complications and should include nephrologists, diabetologists, cardiologists, renal/diabetes nurse specialists, podiatrists, ophthalmologists, and dieticians. The primary goal of current management is to slow the progression of kidney disease; however, the future

TABLE 32.2 **Standard Care and Target Values Proposed for Patients With Diabetes Mellitus Who Have Chronic Kidney Disease**

Parameter	Stage 3 and 4 CKD	Stage 5 CKD (Including Dialysis)
Metabolic Control		
HbA_{1c}	>6.5%-7.5%	>7.0%-8.0%
Preferred agents	Meglitinides, sulfonylureas, insulin	Insulin
Blood Pressure		
Systolic/diastolic BP	130/80 mm Hg	140/90 mm Hg
Preferred agents	ACEs/ARBs	β-blockers
Lipid Treatment		
LDL cholesterol	<100 mg/dl	?
Preferred agents	Statins	Statins in CKD stage 5, no agents to be commenced in dialysis as primary prevention
Anemia Treatment		
Hemoglobin level	11-12 g/dl (avoid >13)	11-12 g/dl (avoid >13)
Preferred agents	Iron/ESA	Iron/ESA
Vitamin D Supplements*		
	Vitamin D_3/1,25-OH D_3	1,25-OH D_3/vitamin D_3
Supportive Treatment		
Smoking cessation	++	++
Hypoglycemia awareness	++	+++
Low-dose aspirin	++	+
Exercise (daily/weekly)	++	++
Foot care	+++	+++
Prevention of falls	+	+++

*In case of vitamin D supplements, the therapeutic approach should be reversed from native vitamin D first in CKD3-4 to vitamin D analogues first in CKD5.

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *ESA,* erythropoiesis-stimulating agent; *LDL,* low-density lipoprotein; *?,* benefit unknown; +/++/+++, moderately/very/highly indicated.

aim is to halt the disease process and reverse any damage. The remission clinics experience[23] illustrated the benefits of regular follow-up in CKD patients, with current recommendations for follow-up ranging from yearly to quarterly that is determined by the level of GFR and its rate of decline.

Hypoglycemia and Hyperglycemia

Hypoglycemia becomes increasingly frequent with advancing CKD because of changes in insulin, carbohydrate metabolism, and renal gluconeogenesis. As GFR declines to less than 60 ml/min/1.73 m^2, regular review of the oral antidiabetic regimen or insulin dosing is essential. These medications may need to be reduced or stopped to prevent the accumulation of the drugs and their metabolites that can cause various adverse effects, including hypoglycemia. Life-threatening episodes of hypoglycemia are more common in patients receiving dialysis. The onset of a hypoglycemic episode may result in 27% mortality 2 days after the hypoglycemic event, emphasizing the importance of monitoring and reviewing medications.[24] Elderly patients in particular who have a hypoglycemic episode have been shown to have increased mortality. The use of any hypoglycemic agents in dialysis patients should therefore be closely monitored and reviewed. The following agents may be used to effectively treat hyperglycemia to avoid the development of DM-related complications.

Oral Hypoglycemic Agents

Several currently available oral agents require dose adjustments in stage CKD3b-5 (Table 32.3). As renal function deteriorates there will be an increase in drug-drug interactions together with further complications of DM, for example, gastroparesis that can affect the pharmacokinetics of these oral medications.

Biguanides

Metformin is an insulin sensitizer that decreases hepatic glucose production, increases insulin sensitivity and insulin-mediated utilization of glucose in peripheral tissues while decreasing glucose intestinal absorption. Metformin is recommended as the first-line agent in T2DM when lifestyle measures alone are insufficient to reduce HbA_{1c} into range. It reduces all-cause and CV mortality in this population.[5] The dose of metformin should be reduced according to renal function and an information card or leaflet be given to those with CKD3b or higher (GFR <45 ml/min/1.73 m^2) that instructs patients to temporarily stop metformin in states of dehydration, before the administration of radiocontrast media and other situations in which there is an increased risk for acute kidney injury (AKI). The use of metformin historically has not been recommended with GFR less than 30 ml/min/1.73 m^2 because of the risk for lactic acidosis. However a recent Cochrane review[25] found no evidence that CKD3b or higher enhanced the risk for lactic acidosis in patients receiving appropriate doses of metformin.[5,26]

Sulfonylureas

Sulfonylureas are a class of insulin secretagogues that stimulate pancreatic insulin secretion and close K-ATP channels on β-cell plasma membranes. First-generation sulfonylureas are long-acting and almost exclusively excreted by the kidneys. These are best avoided in CKD or require dose adjustments (see Table 32.3). Second-generation agents are short-acting and primarily metabolized by the liver, with most metabolites undergoing renal clearance. Their use carries the risk for hypoglycemia as GFR declines and insulin clearance decreases. Sulfonylureas are highly protein-bound but can be displaced into circulation by other drugs used in patients with DM (e.g., salicylates, β-blockers), further contributing to hypoglycemia. Sulfonylureas may become ineffective over time as a result of islet cell exhaustion; thus glycemic control with these agents in advancing CKD should be monitored. The metabolites of gliclazide and glipizide are inert or weakly active and may be used in patients with ESRD on dialysis.

Thiazolidinediones

Thiazolidinediones are peroxisome proliferator-activated receptor (PPAR) modulators, which work to increase insulin sensitivity. Their use is limited by causing weight gain and fluid retention through transcriptional upregulation of tubular amiloride-sensitive sodium channels. This is problematic in subjects with CKD who are prone to cardiovascular disease (CVD) and congestive heart failure. Rosiglitazone was withdrawn from the market because of increased risk for myocardial infarction reported with its use, although pioglitazone remains in use. Higher rates of bone fractures also have been reported in patients treated with these agents.

TABLE 32.3 Daily Dosing for Oral Hypoglycemic Agents*

Class	Drug	CKD1 and 2	CKD3	CKD4	CKD5	Dialysis
Biguanide	Metformin	No adjustment	850-1500 mg	500 mg	Awaiting further data	Awaiting further data
Sulfonylureas:						
First generation	Tolazamide	Avoid	Avoid	Avoid	Avoid	Avoid
	Tolbutamide	250 mg daily-tid	250 mg daily-tid	250 mg daily-tid	Avoid	Avoid
Second generation	Gliclazide	Low dose and titrate every 1-4 wk	Low dose and titrate every 1-4 wk	Low dose and titrate every 1-4 wk	Low dose and titrate every 1-4 wk	Low dose and titrate every 1-4 wk
	Glipizide	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
	Glimeprimide	Reduce to 1 mg	Reduce to 1 mg	Reduce to 1 mg	Avoid	Avoid
α-Glucosidase inhibitors	Acarbose	No adjustment	No adjustment	Lowest dose <50 mg	Lowest dose <50 mg	Lowest dose <50 mg
Meglitinides	Repaglinide	No adjustment	No adjustment	No adjustment	Limited experience	Limited experience
	Nateglinide	No adjustment	No adjustment	No adjustment	Start at 60 mg	Avoid
Gliptins (DPP-4 inhibitors)	Linagliptin	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
	Sitagliptin	No adjustment	Reduce to 50 mg	Reduce to 25 mg	25 mg	25 mg
	Saxagliptin	No adjustment	Reduce to 2.5 mg	2.5 mg	2.5 mg	2.5 mg
Thiazolidinediones	Pioglitazone	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Amylin analogue	Pramlintide	No adjustment	No adjustment	No adjustment	Dose reduction, awaiting further data	Awaiting further data
Incretin mimetics (GLP-1 analogues)	Exenatide	No adjustment	Reduce to 5 mcg	Avoid	Avoid	Avoid
	Liraglutide	Limited experience	Limited experience	Limited experience	Limited experience	Limited experience
SGLT-2 inhibitors	Canagliflozin	Reduced efficacy	Careful monitoring	Careful monitoring	Avoid	Avoid
	Empagliflozin/ Dapagliflozin	Limited experience	Limited experience	Limited experience	Limited experience	

Modified from ERBGP.

*Those awaiting further data require careful consideration.

CKD1 and 2, stages 1-2 CKD; *CKD 3,* stage 3 CKD; *CKD4,* stage 4 CKD; *CKD5,* stage 5ND CKD.

Meglinitides

Meglinitides are primarily metabolized in the liver and act as insulin secretagogues similar to sulfonylureas. Repaglinide is converted to inactive metabolites that are mainly excreted in bile, with less than 10% renal excretion, and therefore is commonly used in patients with DM CKD. In contrast, more than 80% of nateglinide is excreted in the urine, and thus should be used cautiously with advancing CKD.

Incretin Mimetics: Glucagon-Like Peptide-1 Analogues

GLP-1 analogues promote glucose-mediated insulin secretion by pancreatic β-cells in response to food entering the gut and suppress glucagon secretion. The GLP-1 analogues help stimulate weight loss by appetite suppression, both centrally and by affecting gastric motility. European Renal Best Practice (ERBP) guidelines do not recommend these agents in advancing CKD; however, a recent systematic review and meta-analysis reports incretin-based therapies (e.g., GLP-1 agonists, DPP-4 inhibitors) effectively reduce HbA_{1c} levels in T2DM CKD3-5. No increased hypoglycemia, CV events, increased mortality, or progression to ESRD were reported.[27] However, there were wide confidence intervals, thus currently precluding any definitive conclusions.

Gliptins: Dipeptidyl Peptidase-4 Inhibitors

The gliptin class inhibits the effect of DPP-4, a cellular membrane protein expressed in a variety of tissues that function to rapidly degrade endogenous incretin hormones (e.g., GLP-1). Agents such as linagliptin are primarily metabolized by the liver and excreted in the bile, thus not requiring dose adjustments in CKD. Gliptins are advantageous because they do not cause weight gain.

α-Glucosidase Inhibitors

α-Glucosidase is an intestinal enzyme needed to digest carbohydrates. It hydrolyses complex starches to oligosaccharides in the lumen of the small intestine, releasing glucose. Inhibition of this enzyme maintains the integrity of complex carbohydrates, thereby allowing less glucose absorption, and thus should be taken at the start of meals. These agents may be maintained but require dose adjustment with advancing CKD.

Amylin Analogues

Amylin analogues regulate glucose levels according to food intake and control gastric emptying and postprandial glucagon secretion. They increase satiety and thus reduce food intake. It is unclear how effective these drugs are in subjects with stage CKD5 or those on dialysis and further studies are required.

SGLT-2 Inhibitors

Sodium glucose cotransporter protein subtype-2 (SGLT-2) in the renal proximal convoluted tubule is blocked by SGLT-2 inhibitors, thereby increasing renal excretion of glucose. There are increased risks for genital mycotic infections and, rarely, urinary tract infections; thus patients taking these should be cautioned. In the EMPA-REG OUTCOME trial,[28] patients with T2DM and GFR greater than 90 to 45 ml/min/1.73 m^2 were recruited. Empagliflozin was seen to reduce the risk for CV mortality, all-cause mortality, and hospitalization for congestive heart failure with favorable effects on weight, systolic blood pressure (BP), and serum uric acid.[29] This is consistent with previous reports of SGLT-2 inhibitors on reducing CV and all-cause mortality.[30] EMPA-REG OUTCOME also reported a reduction in doubling of serum creatinine and renal replacement therapy (RRT) while reducing progression to macroalbuminuria[28]; however, the perceived renal benefits cannot be fully explained by the moderate reduction in HbA_{1c}, BP, or serum uric acid. It has been postulated that SGLT-2 inhibitors decrease proximal tubular reabsorption of sodium that increases distal sodium delivery to the macula densa that in turns activates tubuloglomerular feedback, resulting in afferent vasodilatation and a reduction of hyperfiltration. There is a reduction in intraglomerular pressure, BP, blood glucose, and blood volume. In addition, the increase in ketone body metabolism is thought to induce an energy-efficient oxygen consumption state at the mitochondrial level that reduces hypoxic stress in the kidney, reducing renal progression of DN.[29] A risk for euglycemic ketoacidosis and bone fractures in those with CKD3-5 taking SGLT-2 inhibitors has been raised that requires further investigation. Recently, more than 100 cases of AKI have been reported with this class of drug, with many cases occurring in the first few weeks of use, in addition to reports of irreversible renal failure and death. The mechanism of this is unknown, although it may relate to volume depletion and hypernatremia from the osmotic diuresis. Despite these concerns, SGLT-2 combined with metformin, sulfonylureas, or DPP-4 inhibitors, as a second agent for glycemic control, is gathering momentum in the general diabetic population, and this practice will likely become increasingly common in those with early DM CKD.[31] The effectiveness of SGLT-2 inhibitors in advancing CKD is currently unknown, and future studies need to address this.

Insulin

Endogenously secreted insulin undergoes first-pass metabolism in the liver, leaving approximately half available to enter the systemic circulation and be used by peripheral tissues. Thirty to eighty percent of insulin is removed by the kidney: 40% via proximal tubular reabsorption and intracellular degradation and 60% via glomerular filtration. Exogenous insulin is destroyed in the gastrointestinal tract and therefore is given parenterally, usually subcutaneously. After absorption, insulin is inactivated via enzymatic process in the liver and kidney and is excreted in the urine; thus with a falling GFR the risk for hypoglycemia is high and insulin dosing should be continuously reviewed with advancing CKD.[5]

Normally insulin sensitivity detects a raised blood glucose causing insulin secretion. This sensitivity is lost with the development of DM, and thus a loss of insulin secretion in response to glycemia is termed *insulin resistance*. In contrast, CKD progression in nondiabetic patients results in the loss of renal gluconeogenesis and a decline in insulin renal excretion that in itself may result in episodes of hypoglycemia because of the continued presence of insulin. Poor insulin degradation secondary to uremia, inflammation, and a raised catabolic rate seen in CKD also contribute to hypoglycemia and insulin resistance, and thus insulin must be dosed with caution.[32] The combination of progressive CKD and DM results in further insulin resistance and loss of sensitivity where regulatory mechanisms are unable to compensate, with studies therefore recommending a halving of insulin doses when GFR is less than 45 ml/min/1.73 m^2.[33]

Types of insulin. Limited data in patients with DN favor the use of analogues, in which the insulin molecule has been modified to rapid or long-acting forms so as to possess pharmacokinetics similar to physiologic insulin secretion, in contrast to traditional human insulins.

Insulin lispro maintains a similar metabolic profile, regardless of whether DN is present. Insulin aspart, a rapid-acting analogue, and long-acting analogues (e.g., glargine, detemir), also have been found to have a metabolic profile largely unaffected by CKD. Currently no specific insulin regimen is recommended in the setting of CKD. For T1DM, however, the basal bolus regimen of 3 daily injections of short-acting insulin with meals combined with 1 or 2 injections of long-acting insulin, as used in the Diabetes Control and Complications Trial (DCCT), is the standard treatment regimen. In T2DM, patients requiring insulin, the regimen usually starts on once-daily or twice-daily, long-acting, or intermediate-acting insulin. Mixed formulations (fixed percentages of short- to long-acting insulins) or the basal bolus regimen as in T1DM may be necessary if glycemic control is not achieved and requires regular review and adjustment as CKD progresses.

Future Therapeutics

New agents continue to be developed to prevent patients with diabetes developing CKD and progressing to ESRD. Alongside these treatment avenues is the development of more sensitive biomarkers that may aid the decision of when to commence new therapies. Table 32.4 shows potential new therapeutics for DN and their current stage of trial development that in the future may be introduced at variable stages of DM CKD.

MANAGEMENT OF HYPERTENSION IN THE DIABETIC SUBJECT WITH CHRONIC KIDNEY DISEASE

Blood Pressure Goals

The ERBP have recently recommended that BP targets in diabetic patients with stages CKD3b-5 should be the same as the general population, that is, a target of less than 140/90 mm Hg. In this way the risk for exacerbating autonomic dysfunction that is commonly seen in advanced DM CKD and may prejudice coronary perfusion, further exacerbating the risk for CV complications, is reduced. A Cochrane review[34] of five randomized control trials reported a reduced risk for stroke with a reduction in BP to less than 120/70 mm Hg, but this has not been reproduced in other studies, which found an increase in adverse events with no improvement in all-cause mortality or morbidity.[5] In contrast, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) and other major societies recommend a BP less than 130/80 mm Hg in DM CKD,[35] with the cut-off derived from observational studies (Multiple Risk Factor Intervention Trial [MRFIT], the Okinawa Screening Programme). Despite this, there is a lack of strong evidence from randomized controlled trials (RCTs) to support this target in secondary prevention of renal disease, with systematic review of relevant trials showing no benefit on renal outcomes (e.g., the rate of decline of GFR, progression to ESRD) but an increase in adverse events with tight BP control less than 120/70 mm Hg and are not recommended. The Action to Control Cardiovascular Risk in Diabetes (ACCORD), in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), African American Study of Kidney Disease and Hypertension (AASK), and Modification of Diet in Renal Disease (MDRD) studies recommend a target systolic BP less than 130/80 mm Hg in patients with DM; however, there is no consistent recommendation in DM CKD that represents a benefit in CV or all-cause mortality with this target.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend targets of less than 140/90 mm Hg in CKD3 without albuminuria that are based on the conclusion that insufficient high-quality evidence from RCTs are available to recommend a lower target based on observational studies.[36] A target of less than 130/80 mm Hg in DM CKD with albuminuria is given with caution to adjust treatment to the individual due to the enhanced risk for CVD. The Australian Kidney Health Australia–Caring for Australasians with Renal Impairment (KHA-CARI) guidelines similarly recommend a less than 140/90 mm Hg target in those with CKD, unless CKD occurs with macroalbuminuria, and then a target of less than 130/80 mm Hg is adopted, but again with caution to tailor treatments to the individuals in view of adverse events.

TABLE 32.4 Potential New Therapeutics for Treatment of Diabetic Nephropathy

Agent	Target	Studies	Effect
Pyridoxamine dihydrochloride (vitamin B_6)	Advanced glycation end-product (AGE) inhibitor	Human: Phase 3	Decreases AGE levels and ACR, and improves creatinine
Nrf-2 activator (triterpenoid RTA dh404)	Nrf-2	Animal Human: Phase 2	Restores Nrf-2 activity and decreases oxidative stress. Japan phase 2 with careful selection of patients in view of adverse heart failure events leading to previous trial cessation
Endothelin 1A antagonist (atrasentan)	Endothelin 1A receptor	Animal and human: Phase 3	Reduction in ACR, BP, and lipids in DN and nondiabetic CKD. Dose-related adverse effects fluid overload
Thromboxane A2 receptor antagonist/ thromboxane synthase inhibitor (SER150)	Thromboxane receptor and thromboxane synthase	Human: Phase 2 trial	Reduction in ACR, improvement in GFR—results pending
Daglutril	Endothelin converting enzyme and neutral endopeptidase inhibitor	Animal Human: RCT	Antifibrotic in animals. Reduction in BP irrespective of A2RB in humans
Pentoxifylline	TNF-α blockade	PREDIAN: Human phase 3 trial	Reduction of albuminuria in addition to ACE inhibitor/ARB
LY3016859 monoclonal antibody	Epiregulin/ Anti-TNF-α	Human: Phase 2	Reduction in ACR
Baricitinib	JAK1/JAK2 selective inhibitor	Human: Phase 2	Reduction in ACR
GKT137831	NOX1/4inhibitor	Human: Phase 2	Reduction in ACR
Doxycycline	Metalloproteinase inhibitor, tetracycline	Human: Small RCT	Reduction in ACR while on treatment
Allopurinol	Xanthine oxidase inhibitor	Human: RCT	Reduction in ACR and serum creatinine, improves GFR
Silymarin (milk thistle)	Antioxidant, TGF-β	Human: Small RCT	Reduction in ACR, urinary TNF-α and malondialdehyde
Pirfenidone	TGF-β	Small RCT Animal studies	Improved GFR at 1 year, gastrointestinal side effects
Anti-CTGF monoclonal Antibody (FG-3019)	CTGF	Animal Human: Phase 1	Reduction in ACR in microalbuminurics
Paracalcitriol (vitamin D)	Vitamin D	Small RCT: VITAL study	Reduction in ACR in DN, no effect on overall mortality
RS102895	Chemokine receptor CCR2 antagonist	Animal Human: Phase 2 (CCX140-B)	Animal: Reduction in ACR, improved histologic features, decrease oxidative stress with improved glucose tolerance
Emapticap pegol (NOX-E36)	CCL2 antagonist	Human: Phase 2	Reduction in ACR
Vascular endothelial growth factor (VEGF) antibody antagonist	VEGF	Animal	Decrease glomerular hypertrophy, hyperfiltration, and albuminuria
VPI-2690B monoclonal antibody	Anti-αVβ3 integrin	Human: Phase 2	Reduction in ACR
Octreotide	Somatostatin agonist	Animal Human	Improved GFR, reduction in ACR, normal renal volume
Sarpogrelate (Anplag)	$5HT_{2A}$ receptor antagonist	Human: Phase 4 (SONATA)	Reduction in ACR and urinary MCP-1 levels
Adrenocorticotropic hormone (ACTH) gel	ACTH	Human	Reduction in ACR, no effect on renal function
Finerenone	Mineralocorticoid receptor antagonist	Human: Phase 3	Reduction in ACR

Modified from reference 22.

5-HT2A, Serotonin 2A; *ACE,* angiotensin-converting enzyme; *ACR,* albumin-to-creatinine ratio; *BP,* blood pressure; *CKD,* chronic kidney disease; *DN,* diabetic nephrology; *GFR,* glomerular filtration rate; *MCP,* monocyte chemoattractant protein. *RCT*, randomized controlled trial.

The Systolic Blood Pressure Intervention Trial (SPRINT) trial reported a significantly lower risk for CVD outcomes and all-cause mortality in nondiabetic CKD populations with hypertension with systolic BP less than 120 mm Hg versus less than 140 mm Hg[37] (Chapter 79). In contrast, reports of increased all-cause mortality and CV morbidity have been reported in DM with systolic BP less than 130 mm Hg; thus these inconclusive studies require trials to be conducted in large DM cohorts to specifically address this. On the basis of current evidence we would therefore recommend a target BP of less than 130/80 mm Hg in CKD3b-4 and less than 140/90 mm Hg in CKD5 and dialysis.

What Agents Should Be Used?

Diabetic subjects with stages CKD3-5 without albuminuria have been shown to benefit from all BP-lowering medications. Patients with DM CKD usually will require more than one antihypertensive agent to achieve BP targets. Selective β-blockers are recommended as primary prevention in patients with DM stages CKD3b-5, and these should continue through advancing CKD if tolerated. Lipophilic (e.g., bisoprolol) rather than hydrophilic agents are advised because studies have shown these to decrease the risk for hospitalization, all-cause mortality, and sudden death.[5] Aldosterone antagonists can reduce target organ damage as well as albuminuria and left ventricular hypertrophy (LVH). The addition of spironolactone to an ACE inhibitor further reduces albuminuria; however, the risk for hyperkalemia limits their use and, if used, must be done so cautiously and considered in conjunction with a loop diuretic.[38] Other antihypertensive agents, such as calcium channel antagonists and thiazide-like diuretics, also have been shown to reduce the risk for CVD in DM, with some evidence of benefit in the DM CKD population.[39] In addition, salt restriction should be advocated to 5 to 6 g/day (<100 mmol/day Na^+) to improve BP control.[40]

Renin-Angiotensin-Aldosterone System Blockade

Numerous studies have illustrated the benefits of renin-angiotensin-aldosterone (RAAS) blockade specifically with ACE inhibitors/ARBs in DM[41,42]; however, the benefits of these agents alone or combined in advancing CKD have been debated in view of the risks for hyperkalemia and other adverse renal outcomes. ERBP recommends CKD3b-5 or those on dialysis with DM and CV indications (congestive cardiac failure, coronary heart disease [CHD]) should be treated with an ACE inhibitor. In instances in which patients are intolerant of ACE inhibitors the ARB should be substituted. Substantial evidence has shown that dual ACE inhibitor and ARB (or ACE inhibitor or ARB plus aliskirin) is potentially harmful and not recommended. The risk for hyperkalemia is reported to be 6.8 times higher with RAAS blockade in CKD with GFR less than 30 ml/min/1.73 m^2 compared with GFR greater than 50 ml/min/1.73 m^2.[5] Introduction of a loop diuretic or correction of metabolic acidosis may limit hyperkalemia; however, dual RAAS blockade is no longer recommended.

ERBP guidelines currently suggest discussion with patients with DM CKD5 regarding the advantages and disadvantages of stopping RAAS blockade to delay RRT. Discussion with patients is essential to their understanding the unpredictable rate of renal function decline with cessation of RAAS blockade. Some patients may accelerate toward RRT with cessation, whereas others may maintain the stability of their function and thus the importance of discussing options with the patient.

CARDIOVASCULAR COMPLICATIONS

The DCCT and Epidemiology of Diabetes Intervention (EDIC) trial in T1DM and the Steno-2 population reported an increase of CV death occurring before DM CKD patients reached ESRD.[43,44] ERBP guidelines recommend that formal workup of coronary heart disease in DM CKD to be the same as that in nondiabetic CKD patients (Chapter 81). Arguably, more patients with DM CKD should have more aggressive workup similar to those undergoing transplantation, because the latter have shown underlying silent CVD, yet further studies are required to determine which patients with DM CKD would benefit from aggressive workup and intervention.

Coronary Heart Disease

Patients with DM CKD3b-5 should have coronary angiograms and intervention if indicated irrespective of the radiocontrast agent risk in view of improved cardiac outcomes. In contrast, in patients with stable CAD, optimal medical management should be adhered to with β-blocker, statin, and aspirin or clopidogrel unless large areas of ischemia or significant left main/proximal left anterior descending coronary artery lesions are seen. Coronary artery bypass grafting (CABG) is preferred over percutaneous coronary intervention (PCI) in patients with multivessel or complex CAD (SYNTAX Score II; www.syntaxscore.com/). Studies show CABG reduces the risk from cardiac death more than PCI in DM CKD, including in patients on dialysis. In the event of an acute coronary event, those with DM CKD3b-5 should be treated the same as patients with CKD3b-5 without DM or patients with DM without CKD3b-5.

Peripheral Vascular Disease

Peripheral vascular disease occurs regularly in patients with DM CKD; thus regular clinical examination with investigations as directed by the diabetes vascular foot team should be undertaken. This will add to early revascularization to try and prevent amputation where possible.

Erectile Dysfunction

Erectile dysfunction frequently occurs in DM CKD as a combination of vasculopathy and medication side effects for treating CHD and hypertension. Phosphodiesterase inhibitors may be used unless the patients is taking nitrates or has uncontrolled CHD.

Antiplatelet Agents

Hyperglycemia has a procoagulant effect on platelet aggregation independent of insulin levels, and hyperinsulinemia itself carries an inhibitory effect on fibrinolysis and thus significantly increases the risk for thrombosis. Platelet reactivity is known to increase with advancing CKD (Chapter 83). Post hoc analyses of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) and Clopidogrel for the Reduction of Events During Observation (CREDO) trials found no benefit in adding clopidogrel to aspirin in patients with DN because this may lead to worse outcomes independent of bleeding risk. ERBP advises glycoprotein IIb/IIIa inhibitors should not be added to standard care in DM CKD3b-5. The addition of a thienopyridine or ticagrelor is not recommended in DM CKD3b-5, especially if there are additional risk factors for bleeding. Aspirin should be started as secondary prevention in DM CKD3b-5 unless contraindicated or intolerant, in which case clopidogrel may be considered as an alternative. Aspirin should be started only as primary prevention in DN patients without risk factors for major bleeding.

Dyslipidemia

Given the elevated risk for CVD in DM it is generally recommended that hyperlipidemia be treated (Chapter 81). KDOQI recommends that all patients with DM CKD1-4 should receive treatment if low-density lipoprotein cholesterol (LDL-C) is greater than 100 mg/dl, with a target of less than 70 mg/dl. The National Institute for Health and Care Excellence (NICE) UK guidelines stipulate a total cholesterol of less than 155 mg/dl and LDL-C less than 77 mg/dl for optimal prevention of microvascular and macrovascular complications of diabetes.[35,45] Statins decrease the risk for cardiac mortality with no effect on kidney outcomes. In view of the increased risk for CV mortality, ERBP recommends a statin should be commenced in DM CKD3-4 and considered in stage 5 but not be commenced in patients with diabetes on dialysis.

In nondialysis CKD patients, a beneficial effect on lowering cholesterol was confirmed in the Study of Heart and Renal Protection (SHARP), which included more than 9000 patients with a wide range of CKD and no history of CVD, randomized to simvastatin and ezetimibe or placebo. A 17% reduction in adverse CV outcomes was seen for every 33 mg/dl reduction in LDL-C, whether the CKD subject was diabetic or nondiabetic, with no impact on mortality.[46] However, in DM dialysis patients the AURORA, SHARP, and 4D trials did not show significant reductions in CV events or mortality despite LDL-C falling by up to 42%. No consensus has been reached as to whether a statin commenced in early DM CKD should be stopped when reaching dialysis, and ERBP guidelines recommend continuation or cessation should be determined by the patients' condition and preference. Fibrates can reduce the risk for increased albuminuria and can replace statins in DM CKD3b patients who are intolerant of statins.[5] Dose reductions in statins are not normally required for advancing CKD because these drugs are safe to use in CKD, and, once commenced, subsequent lipid monitoring is not required.

MICROVASCULAR COMPLICATIONS OF DIABETES

Retinopathy

Annual screening is recommended to ensure prompt intervention.

Neuropathy

Gabapentin is commonly used to treat neuropathic pain associated with diabetes, but requires dose reduction with advancing CKD. Dosing may require alternate days or administration after hemodialysis sessions to avoid the known sedative and motor (myoclonus) effects of gabapentin accumulation that occur in individuals with reduced eGFR. Pregabalin is an alternative that is predominantly excreted by the kidneys and should be used cautiously with advancing CKD. Regular diabetic foot care is required because peripheral neuropathy masks the development of ulcers that may subsequently lead to amputation in view of the added burden of vascular disease seen with CKD.

Autonomic Neuropathy

Gastroparesis is common in diabetes and can affect the absorption of oral medication. It may be treated with endoscopically administrated Botox injections that can be used in DM CKD3b-5; however, hydration throughout the procedure should be maintained to avoid development of AKI. Optimizing the management of gastroparesis is extremely difficult but should be considered before transplantation in view of the potential effects on immunosuppressant absorption. Involving local gastroenterology and diabetologists allows new therapies to be trialed in this population.

Postural hypotension may pose difficulties with hemodialysis and thus agents such as midodrine have been used with variable success. Midodrine is contraindicated in patients with arrhythmias and previous cardiac events and, if used, should be done so with caution. Other measures such as adjustments to dialysis prescriptions together with consideration of peritoneal dialysis (PD) may improve patient symptoms; however, there is currently no evidence to advocate a specific treatment strategy in this area.

Diabetic Foot Disease

DM CKD3b-5 patients have a high risk for diabetic foot disease that is a major cause of hospitalization and nontraumatic amputation. Yearly inspection of the feet and examination of peripheral pulses and sensation is an essential part of the diabetic patient's consultation, along with general foot care (Chapter 86). Education on appropriate footwear and monitoring for signs of early infection are fundamental to prevention. DM CKD3b-5 patients and those on RRT should be seen regularly by their local podiatry services.

COMPLICATIONS FROM CHRONIC KIDNEY DISEASE

Anemia

Anemia occurs commonly in DN and acts as a risk multiplier for all-cause mortality in patients with DM CKD and an independent risk factor for LVH, CVD, and congestive cardiac failure (Chapter 82). Diabetic patients have lower hemoglobin (Hb) levels at every CKD stage than patients with CKD from other causes. One study found a prevalence of 41% in diabetic versus 17% in nondiabetic CKD patients, occurring before renal function begins to decline.[47] Therefore DM CKD3 should be screened for anemia. Patients with DN have increased levels of proinflammatory cytokines from low-grade systemic inflammation, causing resistance to the effects of erythropoietin in various tissues of the body that impairs the efficient use of iron in the generation of new erythrocytes. Other factors causing resistance include autonomic neuropathy, ACE inhibitors/ARBs, and microvascular damage in the bone marrow.

The Trial to Reduce Cardiovascular Events with Aransep Treatment (TREAT) was a landmark study in the use of erythropoiesis-stimulating agents ESAs for correcting anemia secondary to CKD in T2DM with a median follow-up of 29 months, GFR 20 to 60 ml/min/1.73 m^2, and Hb 11 g/dl or less. Patients were randomized either to darbepoetin-alfa (Hb 13g/dl) or control with rescue darbepoetin treatment if Hb was less than 9 g/dl. The treatment group had fewer CV revascularization procedures but significantly increased risk for fatal and nonfatal nonhemorrhagic strokes.[48] Of the TREAT cohort, 31% progressed to dialysis and death despite good BP, glycemic, and lipid control.

Mineral Bone Disease

Imbalance in mineral metabolism increases CV risk and is associated with renal bone disease in DM CKD. Targets for parathyroid hormone (PTH), calcium, and phosphate levels should be aligned to those with non-DM CKD (Chapter 84). Vitamin D insufficiency (<75 nmol/l concentration for plasma 25(OH)D_3) is common in CKD and DM. Routine repletion of native vitamin D, though likely not to be harmful, is not recommended unless levels are in the "depletion" range (<20 nmol/l for 25(OH)D concentrations). The use of pharmacologic therapies for the suppression of PTH is the same for non-DM CKD patients.

Diet and Malnutrition

DM CKD patients are often severely catabolic and tend to develop malnutrition (Chapter 86). This risk is particularly high during periods of intercurrent illness and fasting but also may arise from ill-advised recommendations to restrict protein intake. Anorectic obese patients with T2DM and advanced CKD often undergo massive weight loss, leading to normalization of fasting glucose concentration and even of hyperglycemia after a glucose load. Low muscle mass because of wasting is an important reason for misjudging the severity of CKD, resulting in a delayed start of RRT. Therefore weight loss recommendations in DM CKD patients who are overweight should be supervised by a dietician to avoid malnutrition. Physical exercise can be promoted, and DM CKD3b-5 patients should perform additional physical exercise at least three times per week for 30 to 60 minutes to decrease fat mass and improve quality of life according to ERBP.

Electrolytes and Fluid Retention

Salt restriction and diuretics are the mainstay treatment of fluid retention in DM CKD. Metabolic acidosis can be treated with bicarbonate supplementation; in patients with hyperkalemia, diet and RAAS blockade should be reviewed.

END-STAGE RENAL DISEASE

According to ERBP, patients with DM CKD5 should be given the choice of RRT because no evidence exists to suggest one modality is better than another. The increase in mortality seen in DM continues and is at its highest on RRT.[22] Decisions regarding the preferred modality of RRT should begin at DM CKD4-5. Education should be given on the different treatment options, and transplant workup investigations should be started in potentially suitable candidates. Hepatitis B vaccinations should be given early in patients with DM CKD3b to increase immunity.

Dialysis

Hemodialysis

Mortality is unchanged whether hemodialysis (HD) or hemodiafiltration is used; however, it is recommended that high flux rather than low flux dialysis be performed. The IDEAL study comparing early to late initiation of HD (with 34% of both groups having diabetes as the primary cause of ESRD), found no significant survival benefit[49] (Chapter 80). Considerations for the timing of RRT initiation in DN are similar to those in patients without DM and include the speed of renal function decline, the probability of functioning vascular access, and the projected life expectancy of patients.

Vascular Access

Evidence recommends avoiding tunneled central venous catheters as a primary access in patients with DM starting HD because of the higher risk for associated infection[5] (Chapter 91). The advantages and disadvantages of each access should be discussed with patients. Vascular mapping may increase the likelihood of successful arteriovenous fistula (AVF) creation in those with DM (especially in females and the elderly). Proximal AVFs have been reported to be more successful than distal AVF as the high calcific atherosclerosis commonly found in DM CKD causes difficulty in creation and maturation of AVF.

Peritoneal Dialysis

PD may be used in DM CKD requiring RRT and as a result of the slower ultrafiltration rate compared with HD may lower risks for precipitating CV events or hypotension (Chapter 97). Glucose intake from PD contributes 400 to 800 kcal/day (100 to 200 g/day of glucose). Intraperitoneal insulin (soluble human insulin) can be injected through the connecting tubing before starting dialysis or added to dialysate. Intraperitoneal insulin is adsorbed onto plastic surfaces of the delivery systems and bioavailability depends on the solution, therefore insulin requirements are often higher using this administrative method than subcutaneous injections. Intraperitoneal insulin is absorbed through the portal circulation, with decreased amplitude of glucose excursions and improved mean plasma glucose, resulting from inhibition of hepatic gluconeogenesis. However, soluble human insulin increases the risk for subcapsular hepatic steatosis that is linked to the dosage of intraperitoneal insulin used and there is a lack of high-quality evidence demonstrating its effects on risk for infection and quality of glucose control, as compared with subcutaneous insulin.

Non–glucose-containing solutions (e.g., icodextrin) avoid the risk for hyperglycemia and the potentially harmful effects of glucose degradation products, while resulting in better ultrafiltration volume, BP control, and preservation of residual function (Chapter 97). Some metabolites of icodextrin also can act as a substrate for the glucose dehydrogenase present in blood glucose meters, resulting in potential overestimation of blood glucose levels.

Transplantation

The U.S. Renal Data System data showed 5-year survival rates of 29% in diabetic patients starting dialysis compared with those undergoing kidney transplants (75% deceased-donor, 85% living-donor).[50] Ideally, the transplant should be preemptive to avoid an interim period of dialysis in which uremic symptoms are minimal. For patients with T1DM, the ideal form of transplantation is simultaneous pancreas and kidney transplantation or living-donor kidney transplant[5] (Chapter 110). Other options are sequential living-donor kidney transplantation, followed by deceased-donor pancreas transplant or islet transplantation prior to living donor kidney transplant. Initially there were concerns with this approach because of possible worse outcomes in terms of survival and the pancreas graft itself; however, outcomes have improved in recent years.[5]

Islet after kidney transplantation does not improve survival and is not recommended. In contrast, kidney transplantation alone is recommended by the ERBP for T2DM CKD requiring RRT. Providing patients meet the inclusion criteria for transplantation, DM CKD patients should not be denied kidney transplantation on the basis of their DM. Pancreas alone or simultaneous pancreas and kidney transplantation is not recommended in T2DM in view of insulin resistance.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following falsely increases hemoglobin A_{1c} readings?
   - **A.** Antiretrovirals
   - **B.** β-Thalassemia
   - **C.** Rheumatoid arthritis
   - **D.** Alcoholism
   - **E.** Erythropoietin
2. Which of these antidiabetic medications are safe to use in end-stage kidney disease (ESRD)?
   - **A.** Empagliflozin
   - **B.** Exenatide
   - **C.** Gliclazide
   - **D.** Metformin
   - **E.** Tolbutamide
3. Which of the following statements are *true* in diabetic chronic kidney disease (CKD)?
   - **A.** T2DM should be given pancreas alone transplants.
   - **B.** Hemodialysis should be introduced in preference to peritoneal dialysis in diabetic patients with ESRD.
   - **C.** There is clear evidence that statin therapy improves cardiovascular mortality in the dialysis population.
   - **D.** Anemia in diabetic patients can occur even with normal renal function.
   - **E.** Coronary artery bypass grafting is contraindicated in patients with diabetic CKD.
4. Which of the following is *not* an underlying mechanism or pathology of hypoglycemia in diabetic CKD?
   - **A.** Loss of renal gluconeogenesis
   - **B.** Increasing plasma concentrations of oral antidiabetic agents
   - **C.** Reduced renal clearance of insulin
   - **D.** Loss of insulin sensitivity
   - **E.** Formation of renal calculi

33

Normal Blood Pressure Control and the Evaluation of Hypertension

*William J. Elliott, William J. Lawton**

NORMAL BLOOD PRESSURE CONTROL

Systemic arterial blood pressure (BP), or the pressure of the blood within the arteries exerted against the arterial wall, is produced by the contraction of the left ventricle (producing blood flow) and the resistance of the arteries and arterioles. *Systolic* blood pressure (SBP), or *maximum* BP, occurs during left ventricular systole. *Diastolic* blood pressure (DBP), or *minimum* BP, occurs during ventricular diastole. The difference between SBP and DBP is the pulse pressure.[1] The mean arterial pressure (MAP) is calculated clinically as the DBP plus one third of the pulse pressure.

Blood flow, Q, as defined by the hydraulic analogy of Ohm's law, varies directly with the change in pressure, P, across a blood vessel, and varies inversely with the resistance, R, defined as $Q = P/R$. Rearrangement shows that pressure varies directly with blood flow and resistance, $P = QR$. Ohm's law suffices for an overall view of the circulation. However, the flow within a vessel is governed by the Hagen-Poiseuille equation:

$$Q = \Delta P \times (\pi r^4/8L) \times (1/\eta)$$

where r is the radius of the pipe, L is its length, and η is the coefficient of viscosity. Thus, as the lumen of a vessel decreases, the pressure increases by the fourth power of the radius, to maintain the same blood flow.

Normal BP is controlled by cardiac output and the total peripheral resistance and is dependent on the heart, the blood vessels, the extracellular volume, the kidneys, the nervous system, humoral factors, and cellular events at the membrane and within the cell (Fig. 33.1). Cardiac output is determined by the stroke volume in liters per minute (l/min) and the heart rate. In turn, stroke volume is dependent on intravascular volume (regulated by the kidneys) and myocardial contractility. Myocardial contractility involves sympathetic and parasympathetic control of heart rate, intrinsic activity of the cardiac conduction system, complex membrane transport and cellular events requiring influx of calcium that lead to myocardial fiber shortening and relaxation, and effects of humoral substances (e.g., catecholamines) on increasing heart rate and myocardial fiber tension.

Total peripheral resistance is regulated by baroreflexes and sympathetic nervous system (SNS) activity, response to neurohumoral substances and endothelial factors, myogenic responses, and intercellular events mediated by receptors and mechanisms for signal transduction.[2] Baroreflexes are derived from (1) high-pressure baroreceptors in the aortic arch and carotid sinus and (2) low-pressure cardiopulmonary baroreceptors in ventricles and atria. Aortic baroreceptor nerve fibers travel via the vagus nerve (cranial nerve X); carotid sinus fibers travel via the glossopharyngeal nerve (cranial nerve IX). These receptors respond to stretch (high pressure) or filling pressures (low pressure) and send tonic inhibitory signals to the brainstem. If BP and tonic inhibition increase, inhibition of sympathetic efferent outflow occurs, decreasing vascular resistance and heart rate. However, if BP decreases, less tonic inhibition occurs, and heart rate and peripheral vascular resistance (PVR) increase, thereby increasing BP.

The brainstem cardiovascular (CV) centers are localized in the dorsomedial medulla. Neural afferents from cranial nerves IX and X are integrated in the nucleus tractus solitarius (NTS). From here, vasoconstriction and increased heart rate are mediated through the caudal and rostral ventrolateral medulla by the SNS. Efferents from the NTS communicate with the nucleus ambiguus (vagal nucleus) to decrease heart rate via the vagus nerve. Also, the central neural control of renal function modulates renal blood flow, glomerular filtration rate (GFR), excretion of sodium and water, and renin release. These factors in turn regulate intravascular volume, vascular resistance, and BP.[3] This complex physiology has taken on greater clinical relevance recently, given the mixed results of pivotal trials of percutaneous, catheter-based renal denervation.[4,5]

Inhibitory reflexes also originate in the kidney. Increases in urine flow rate increase renal pelvic pressure, which stretches the renal pelvic wall, leading to activation of mechanosensory nerves in the renal pelvic wall. Activation of these sensory nerves decreases renal sympathetic nerve activity and induces diuresis and natriuresis, an inhibitory renorenal reflex response. The responsiveness of the renal sensory nerves is modulated by dietary sodium. A high sodium intake enhances the responsiveness of the afferent renal mechanosensory nerves; conversely, renal denervation increases urinary flux and fractional excretion of sodium.[6]

Numerous vasoactive substances have effects on blood vessels, the heart, the kidneys, and the central nervous system (CNS) to regulate BP (Table 33.1). The renin-angiotensin-aldosterone system (RAAS) regulates volume and PVR (Fig. 33.2), particularly in the long term (hours to weeks, Fig. 33.3). Angiotensin II (Ang II) constricts vascular smooth muscle; stimulates aldosterone secretion; potentiates SNS activity; stimulates salt and water reabsorption in the proximal tubule;

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*The authors thank Drs. DiBona, Kopp and Luft for their contributions to previous editions of this chapter.

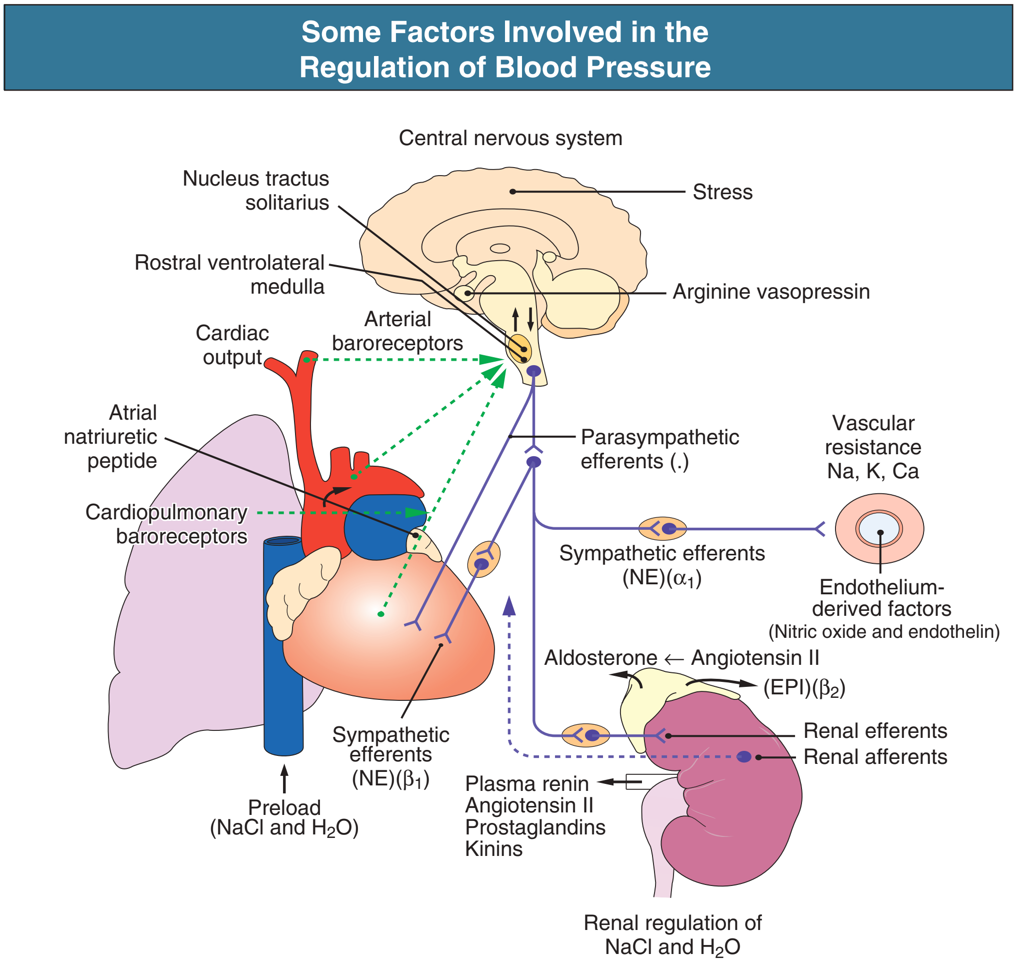
Some Factors Involved in the Regulation of Blood Pressure
Central nervous system
Nucleus tractus solitarius
Stress
Rostral ventrolateral medulla
Arginine vasopressin
Cardiac output
Arterial baroreceptors
Atrial natriuretic peptide
Parasympathetic efferents (.)
Vascular resistance Na, K, Ca
Cardiopulmonary baroreceptors
Sympathetic efferents (NE)(α_1)
Endothelium-derived factors (Nitric oxide and endothelin)
Aldosterone ← Angiotensin II
(EPI)(β_2)
Renal efferents
Renal afferents
Sympathetic efferents (NE)(β_1)
Preload (NaCl and H_2O)
Plasma renin
Angiotensin II
Prostaglandins
Kinins
Renal regulation of NaCl and H_2O

Fig. 33.1 Some factors involved in regulation of blood pressure. *Dashed lines* refer to feedback to the central nervous system from cardiovascular *(green dash)* or renal *(purple dash)* sites. *ACh,* Acetylcholine; *EPI,* epinephrine; *NE,* norepinephrine; α_1, β_1, β_2, adrenergic receptors.

stimulates prostaglandin, nitric oxide (NO), and endothelin release; increases thirst; and stimulates vascular remodeling and inflammation. Aldosterone stimulates sodium channels in distal renal tubular epithelium, leading to sodium retention and potassium excretion. It also exerts inflammatory and fibrotic effects through the mineralocorticoid receptor in vascular cells and in the heart.[7] Plasma concentrations of renin and aldosterone are both inversely related to salt intake and are influenced by many antihypertensive medications.

The second major effector system, working primarily over seconds to minutes (see Fig. 33.3), is the SNS. Sympathetic nerve endings release the vasoconstrictor (norepinephrine) that binds the α-adrenergic receptor (adrenoceptor) on vascular cells, renal cells, and other cells (e.g., adipocytes). Epinephrine increases heart rate, stroke volume, and SBP through α- and β-adrenoceptors. The hormone is released from the adrenal medulla. Increased sympathetic tone has long-term influences on CV regulation and may cause hypertension and contribute to chronic kidney disease (CKD).[8] In the kidneys, sympathetic nerves mediate renin release. Furthermore, innervation of each individual nephron affects sodium reabsorption. In doing so, the SNS regulates both effective circulating fluid volume and PVR.

The kallikrein-kinin system counters the RAAS and produces vasodilator kinins, which stimulate prostaglandin and NO production (see Fig. 33.2). Prostaglandin E and prostacyclin block the vasoconstriction by Ang II and norepinephrine. Two endothelium-derived factors have opposite effects on the blood vessels: NO is a vasodilator, whereas the endothelins are vasoconstrictors. Natriuretic peptides, of the atrial, brain, or C-types, induce vasodilation and natriuresis and inhibit other vasoconstrictors (RAAS, SNS, endothelin). See Chapter 36 for a detailed discussion of all the drugs that affect the previously discussed physiologic systems that regulate BP.

Other physiologic systems that control BP can be used as investigative tools, but not yet therapeutically in humans. Renalase is a flavin adenine dinucleotide–dependent amine oxidase that is secreted by the kidney, circulates in the blood, and modulates cardiac function and systemic BP by metabolizing catecholamines; there is currently debate about whether mutations in the gene coding for renalase are associated with hypertension.[9] Heme oxygenase-1 is an intrarenal and systemic BP modulator that inhibits oxidants, resulting in decreased BP; in one study, individuals with an unfavorable gene promoter for this enzyme had a higher prevalence of hypertension and increased mortality.[10] Endogenous digitalis-like factors, which inhibit cell surface Na^+,K^+-ATPase and include an ouabain-like factor and marinobufagenin, also appear to regulate BP, CV, and renal function.[11] Urotensin II is a locally expressed vasoconstrictive cyclic vasoactive peptide that stimulates proliferation of vascular smooth muscle cells and fibroblasts, inhibits insulin release, and modulates GFR. Nonetheless, high plasma urotensin II levels were associated with reduced CV complications and death in 122 patients with CKD, stages 2 to 5, and in an earlier cohort of 191 hemodialysis patients from the same center.[12,13] In obese persons, leptin may increase

TABLE 33.1 **Some Vasoactive Substances That Modulate Blood Pressure**

Group	Compound	Cellular Effects
Catecholamines	Norepinephrine, epinephrine, dopamine	Adrenergic receptors (α_1, α_2, β_1, β_2) causing protein phosphorylation and increased intracellular calcium through G proteins linked to ion channels or second messengers (cyclic nucleotides, phosphoinositide hydrolysis)
Renin-angiotensin system (RAS)	Angiotensin II (Ang II)	Angiotensin receptors (AT_1, AT_2, AT_4) causing increased intracellular calcium and protein phosphorylation through second messenger, phosphoinositide hydrolysis, and activated protein kinases Aldosterone stimulation
Mineralocorticoids	Aldosterone	*Genomic:* Binds to cytoplasmic mineralocorticoid receptor, translocates to nucleus, modulates gene expression, and signal transduction and effectors (S_gK, CHIF, K_i-Ras), which increases transport proteins (increasing ENaC number and open probability) *Nongenomic:* Effects through separate membrane or cytosolic proteins
Kallikrein-kinin system	Bradykinin	Bradykinin receptors (B_1, B_2), B_2-G protein coupling causes activation of phospholipase C, increased inositol phosphates, and intracellular calcium
Arachidonic acid oxidation products	Prostaglandins: Prostaglandin E (PGE), prostacyclin, thromboxanes Lipoxygenase enzyme products: Leukotrienes, hydroxyeicosatetraenoates	Nine prostaglandin receptors coupled to G proteins: (e.g., PGI_2 [receptor IP], PGE_2 [receptors EP_1, EP_2]); $PGF_{2\alpha}$ (receptor FP)
Endothelium-derived factors	Endothelium-derived relaxing factor (nitric oxide) Endothelins (ET-1, ET-2, ET-3)	Increased levels of cyclic guanosine monophosphate cause activation of protein kinases G proteins activate phospholipase C and l-type calcium channels Class 2 G protein–coupled receptor
Natriuretic peptides	Atrial, brain, and C-type	Activation of three receptor types; further effects mediated by cGMP
Posterior pituitary hormones	Arginine vasopressin	Vasopressin receptors (AVPR 1A; AVPR 1B) mediated by second messenger system, phosphatidyl inositol/calcium; AVPR2 effects via adenylate cyclase (cAMP)
Cyclic vasoactive peptides	Urotensin II (UT II)	UT II binds to G protein receptor GPR 14
Other substances	Acetylcholine, adenosine, insulin, neuropeptide Y, serotonin, sex hormones (estrogens, progesterone, androgens), glucocorticoids, other mineralocorticoids, substance P, vasopressin, renalase, heme oxygenase 1, uric acid	

ENaC, Amiloride-sensitive epithelial sodium channel.

BP by activating the CNS through a melanocortin pathway.[14] Although its clinical importance is hotly debated, higher serum uric acid levels have been associated with BP and CV outcomes in some (but not all) cohort studies, and at least two hypouricemic drugs have lowered BP in pilot studies. Intracellular urate also may activate the renin-angiotensin system (RAS), induce intrarenal oxidative stress, block endothelial NO, and directly affect the vasculature.[15] T cells also may be involved in primary hypertension, possibly via heat shock protein 70 and/or interleukin-17, because they invade target organs and lead to release of Ang II and oxidants.[16] Chemoreceptors in the brain medulla and the carotid and aortic bodies respond to changes in carbon dioxide and oxygen tension, resulting in renal vasoconstriction and dilation of the CNS and coronary vasculature.[17] The small guanosine triphosphatase, Rho, and its kinase, stimulate vasoconstriction and may have a role in cerebral artery spasm, hypertension, heart failure, and other CV conditions.[18]

The kidney has long been recognized as a source of hypertension, based on renal cross-transplantation experiments,[19] and the hypotensive effects of bilateral nephrectomy in patients with end-stage renal disease (ESRD) and severe hypertension. However, activation of CNS and renal SNS pathways are now recognized as important in long-term BP control, in part by delayed effects on the kidneys.[20] Renal sympathetic denervation by radiofrequency ablation through the renal arteries has led to substantial reduction in BP in patients with resistant hypertension, but the large U.S. trial did not achieve significantly better BP control at 6 months, compared with sham-operated controls.[21,22] This negative result more likely stemmed from technical issues in the conduct of the trial than a nonsignificant contribution to the pathophysiology of hypertension.

DEFINITION AND CLASSIFICATION OF HYPERTENSION

In the general population, BP is nearly normally distributed, with a shift to the left in the young and the opposite in older people and those with CKD. Thus any definition of hypertension is arbitrary. Hypertension is often asymptomatic, with symptoms more commonly attributed to sequelae of hypertension or its treatment. Hypertension may be classified by its associated morbidity and mortality, as increases over arbitrary cut points, or by thresholds defining therapeutic benefit.

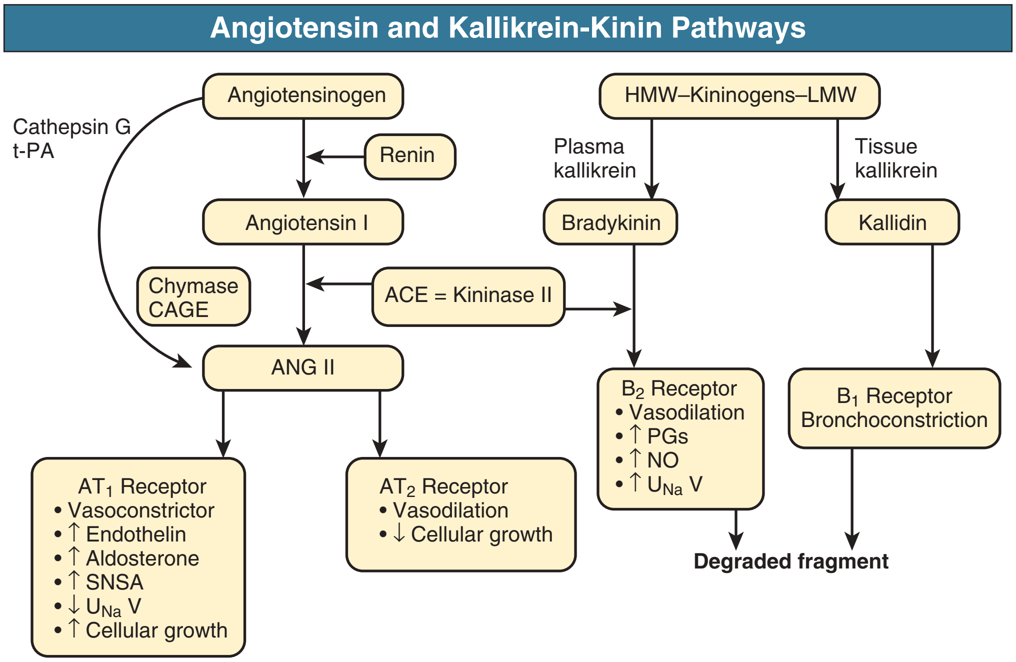
Angiotensin and Kallikrein-Kinin Pathways
Angiotensinogen
Cathepsin G
t-PA
Renin
Angiotensin I
Chymase
CAGE
ACE = Kininase II
ANG II
AT$_1$ Receptor
• Vasoconstrictor
• ↑ Endothelin
• ↑ Aldosterone
• ↑ SNSA
• ↓ U$_{Na}$ V
• ↑ Cellular growth
AT$_2$ Receptor
• Vasodilation
• ↓ Cellular growth
HMW–Kininogens–LMW
Plasma kallikrein
Tissue kallikrein
Bradykinin
Kallidin
B$_2$ Receptor
• Vasodilation
• ↑ PGs
• ↑ NO
• ↑ U$_{Na}$ V
B$_1$ Receptor
Bronchoconstriction
Degraded fragment

Fig. 33.2 **Interactions and functions of renin-angiotensin and kallikrein-kinin systems.** *ACE,* Angiotensin-converting enzyme; *ANG II,* angiotensin II; *AT$_1$, AT$_2$,* angiotensin receptors; *B$_1$, B$_2$,* bradykinin receptors; *CAGE,* chymostatin-sensitive angiotensin II–generating enzyme; *HMW,* high molecular weight; *LMW,* low molecular weight; *NO,* nitric oxide; *PGs,* prostaglandins; *SNSA,* sympathetic nervous system activity; *t-PA,* tissue plasminogen activator; *U$_{Na}$ V,* urinary sodium excretion.

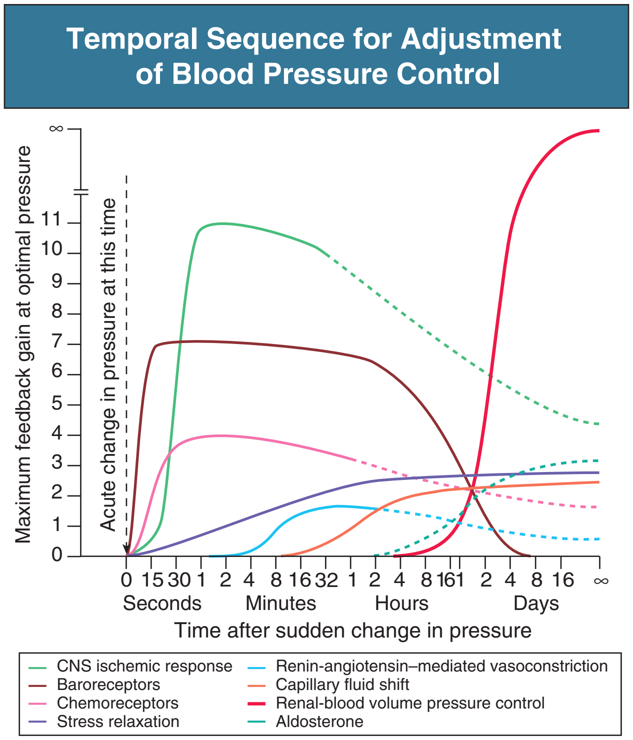

Fig. 33.3 **Temporal sequence for adjustment of blood pressure control.** Degree of activity, expressed as feedback gain, of several arterial blood pressure (BP) control systems at various times after a sudden change in arterial BP. Note the infinite gain of the renal-volume mechanism for BP control. *CNS,* Central nervous system. (From reference 1.)

Blood Pressure in Relation to Morbidity and Mortality

The first approach defines hypertension by relating BP levels to the risk for morbidity and mortality. The association of SBP and DBP with CV and renal complications is continuous over the entire BP range.[23] Death from both heart disease and stroke increases progressively and linearly from BP as low as 115/75 mm Hg upward in all age groups from 40 to 89 years (Figs. 33.4 and 33.5). In observational studies an increase in SBP of 20 mm Hg or DBP of 10 mm Hg was associated with a doubling of mortality from heart disease or stroke. Several interventional trials have observed a J-shaped curve (suggesting that mortality increases below a threshold SBP), yet this phenomenon is also seen in the bottom decile in both individual and pooled observational studies of untreated subjects (see Figs. 33.4 and 33.5), indicating that those in the lowest decile have a higher risk, irrespective of treatment. Elevated SBP has been identified by the Global Burden of Disease study to be the leading contributor to disability-adjusted life-years worldwide in 2013 and again in 2015. In both reports, these investigators characterized a SBP between 110 and 115 mm Hg as the "theoretical minimum risk level" for BP. Although all national and international hypertension guidelines agree about the continuous relationship between risk and BP, as well as a recommendation for lifestyle modifications in people with BP 120/80 mm Hg or greater, many differ regarding how BP should be classified, especially if the BP is between 120 and 139/80 and 89 mm Hg. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) introduced the term *prehypertension* for individuals with SBPs from 120 to 139 mm Hg, or DBPs between 80 to 89 mm Hg[24]; this term was also recommended for these BP values by the American Society of Hypertension/International Society of Hypertension 2013 guidelines. The 2013 European Society of Hypertension/European Society of Cardiology guidelines distinguished BPs between of 120 and 129/80 and 84 mm Hg

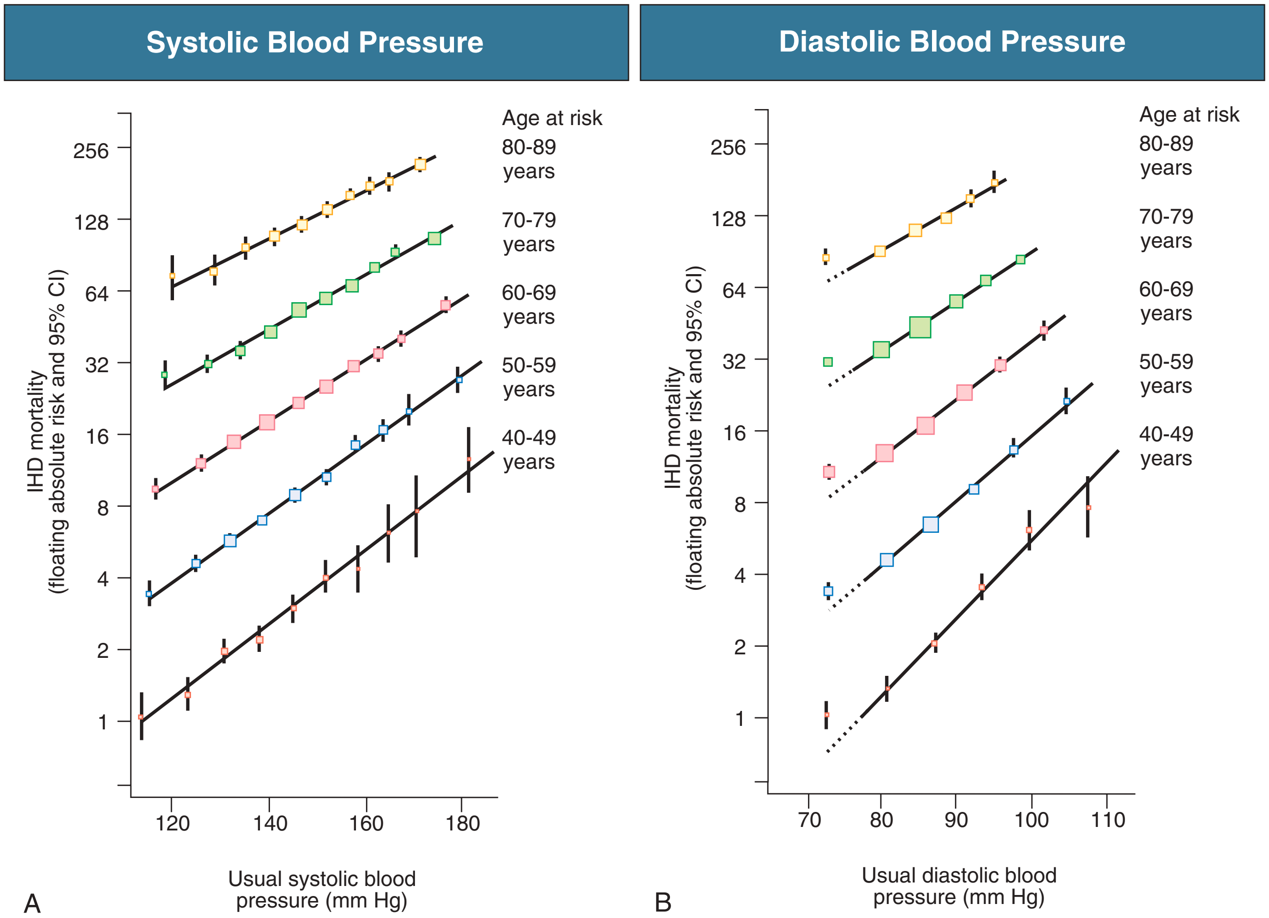

Fig. 33.4 **Ischemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at start of that decade.** (A) Systolic blood pressure. (B) Diastolic blood pressure. Floating absolute risk is a relative risk score that adjusts for the absolute death rate within a particular age group. The size of the squares correlates inversely with the variance of the data collected for that data point. *CI,* Confidence interval. (From reference 23.)

TABLE 33.2 Working Group–American Society of Hypertension Definition and Classification of Hypertension

Class	BP Elevation		CV Disease*	CV Risk Factors	Early Disease Markers	Target Organ Disease
Normal	Normal or rare	or	None	None or few	None	None
Hypertension						
Stage 1	Occasional intermittent	or	Early	Several	Usually present	None
Stage 2	Sustained	or	Progressive	Many	Overtly present	Early signs present
Stage 3	Marked and sustained	or	Advanced	Many	Overtly present with progression	Overtly present with or without CV disease events

Modified from reference 26.

*Cardiovascular *(CV)* disease determined by constellation of risk factors, early disease markers, and target organ disease.

(termed *normal*) and 130 and 139/85 and 89 mm Hg (termed *high-normal*) and recommended an initial assessment of CV risk, based on these (and higher) BP thresholds and the number of CV risk factors present in the individual (see later discussion).[25] A different approach was taken by a Writing Group of the American Society of Hypertension (WG-ASH), which proposed that hypertension is a complex CV disorder that includes target organ damage, early disease biomarkers (including BP), and CV risk factors[26] (Table 33.2). This risk-based approach seeks to identify individuals with an increased likelihood of future adverse CV and/or renal events at any BP level, and includes the prehypertension category of JNC 7. In contrast, the recent report of the panel members appointed to JNC 8 focused on BP management and not on classification or risk assessment.[27]

Elevation of Blood Pressure by Arbitrary Cut-Off Points

A second approach defines hypertension by the frequency distribution within a population. This statistical approach arbitrarily designates values

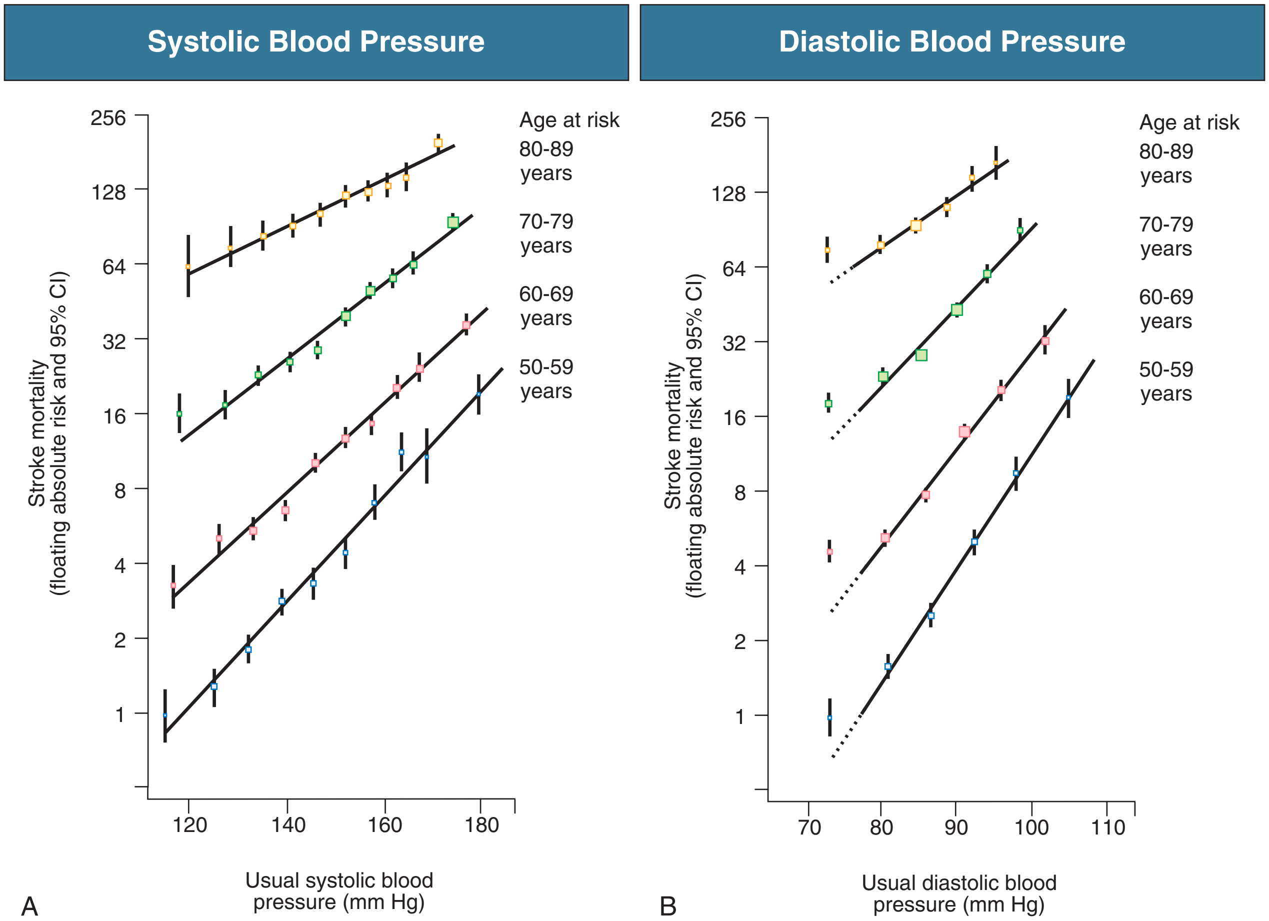

Fig. 33.5 **Stroke mortality rate in each decade of age versus usual blood pressure (BP) at start of that decade.** (A) Systolic BP. (B) Diastolic BP. Floating absolute risk is a relative risk score that adjusts for the absolute death rate within a particular age group. The size of the squares correlates inversely with the variance of the data collected for that data point. *CI,* Confidence interval. (From reference 23.)

above a certain percentile as "hypertensive" and was formerly used in defining hypertension in American children. Age, gender, body size, and race/ethnicity are all significant and strong predictors of BP. Using a frequency distribution method is less helpful for identifying a threshold for initiation of antihypertensive treatment, but is common in epidemiologic studies. The crude prevalence of hypertension in adults (older than 20 years of age) in the United States, traditionally defined as BP of 140/90 mm Hg or greater or taking antihypertensive medication, has increased progressively from 11% in 1939 to 33.5% in 2013 to 2014, but has been relatively stable, after age-adjustment, at 31% ± 2% since the mid-1990s.[28] These prevalence figures are slightly higher than those reported from other high-income countries (28.5%, on average, in 2010), and about the same as those reported from low- and middle-income countries (31.5% in 2010), based on 135 population-based surveys involving 968,419 adults in 90 countries.[28]

Threshold of Therapeutic Benefit

The third concept for defining hypertension is derived from randomized controlled trials (RCTs) that compared two or more BP targets and showed significant reductions in morbidity and mortality. The Hypertension Optimal Treatment (HOT) study showed no significant outcome differences among 18,790 hypertensive subjects randomized to DBP targets of 80, 85, or 90 mm Hg or less, although a significant benefit was seen in diabetic patients with a diastolic target of less than 80 mm Hg.[29] A post hoc analysis of the in-trial BPs determined that maximal prevention of major CV events was seen at a BP of 138.5/82.6 mm Hg. Of the relatively few outcome-based RCTs comparing traditional and lower BP targets, only the recent Systolic blood PRessure INTervention (SPRINT) trial showed significant reductions in both CV events and mortality when treating to a SBP target of less than 120 compared with the traditional less than 140 mm Hg.[30] Some have argued that this benefit came at a huge cost of more medications, more office visits, more adverse effects (including emergency department visits), and greater than 30% worsening of renal function in those without CKD at baseline. Others have cast doubt about SPRINT's generalizability, because less than 17% of adult American hypertensives would have been eligible to participate, because of the large number of exclusion criteria (which, because of prior negative National Institutes of Health [NIH]-sponsored trials, included diabetes mellitus, prior stroke, polycystic kidney disease, or estimated GFR less than 20 ml/min/1.73 m^2, among many others).

Operational Definitions

On 13 November 2017, the American College of Cardiology and American Heart Association, in conjunction with nine other learned societies and volunteer health organizations, issued their "2017 United States hypertension guideline."[32] This guideline "redefined" hypertension as a usual office blood pressure ≥ 130/80 mm Hg, added the new diagnostic category of "elevated blood pressure," re-emphasized the value of out-of-office blood pressure measurements, reinforced lifestyle modifications as appropriate for most people with higher-than-normal blood pressures, and revised some treatment targets for specific patient groups (see Table 33.3 below, and Chapter 36 for more details). About three months earlier, the American Academy of Pediatrics released their "Clinical practice guideline for screening and management of high blood pressure in children and adolescents,"[33] the authors of which were privy to an advance copy of the 2017 adult guidelines, and arranged their recommendations to be consistent with them. These new definitions have increased the overall prevalence of hypertension in US adults to 46%, but decreased the prevalence in children and adolescents to 3.5%. The 2017 ACC/AHA hypertension guideline also recommended an office blood pressure target of < 130/80 mm Hg for individuals with a 10-year cardiovascular risk > 10%, but retained the traditional < 140/90 mm Hg for most lower-risk individuals. These new guidelines are controversial; some learned societies have declined to endorse or adopt them.

The European Society of Hypertension (ESH), recently in conjunction with the European Society of Cardiology (ESC) has traditionally divided "normotension" into three categories (optimum, normal, high-normal) and classified hypertension as mild, moderate, or severe[25] (Table 33.4). The European guidelines also provided threshold values for automated 24-hour BP measurements, divided into daytime and nighttime.

In the United States, JNC 7 defined hypertension for individuals 18 years and older.[24] The Committee classified BPs as normal, prehypertension, and stage 1 and stage 2 hypertension (Table 33.5). For children, JNC 7 agreed with the Fourth Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, so that BP at or above the95th percentile, based on age, gender, and height, is defined as hypertension.

The concept of evaluating a person's "total CV risk" had been prominent in several prior U.S. guidelines on BP, dyslipidemia, and acute coronary syndrome. It was largely abandoned by JNC 7, but still plays a major role in other countries,[25,33] and is now used for determining the BP treatment goal in the 2017 ACC/AHA U.S. hypertension guidelines,[31] because clinicians routinely evaluate hypertensive patients and their progress toward treatment goals on the basis of overall CV risk factors, not by BP alone. Age, gender, and ethnicity are important nonmodifiable risk factors, whereas low-density lipoprotein (LDL) cholesterol, smoking, control of diabetes, obesity, and left ventricular hypertrophy are potentially modifiable[33] (Fig. 33.6). The cluster of risk factors that increase CV risk and are often associated with hypertension is termed the *metabolic syndrome*[34] (Table 33.6). CKD, now diagnosed on the basis of decreased estimated GFR or by increased urinary albumin excretion, is also recognized as an independent risk factor for ESRD, CV events, and death.[35] JNC 7 included recommendations for serial follow-up evaluation of BP and CV risk factors based on initial BP measurement (Table 33.7).

Special Definitions

Prehypertension. Prehypertension was defined in JNC 7 as SBP of 120 to 139 and DBP of 80 to 89 mm Hg[24] and was found in 36.3% of American adults without CV disease or cancer in U.S. national representative surveys from 1999 to 2006.[36] Prehypertension is associated with age, obesity, dyslipidemia, impaired fasting glucose levels, a higher risk for both CV and renal events, and progression to hypertension (which was significantly delayed by drug therapy in two RCTs). Yet all current guidelines

TABLE 33.3 2017 ACC/AHA Hypertension Guideline: Categories of Blood Pressure in Adults

Blood Pressure Category	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	< 120 mm Hg	and	< 80 mm Hg
Elevated	120-129 mm Hg	and	< 80 mm Hg
Hypertension			
Stage 1	130-139 mm Hg	or	80-89 mm Hg
Stage 2	≥ 140 mm Hg	or	≥ 90 mm Hg

Individuals with systolic and diastolic blood pressures in two different categories should be assigned into the higher category. Blood pressures are based on an average of ≥ 2 careful readings obtained on ≥ 2 occasions, usually separated by a week or more.
(From reference 31.)

TABLE 33.5 JNC 7 Classification of Blood Pressure for Adults (2003)

BP Classification	SBP (mm Hg)		DBP (mm Hg)
Normal	<120	and	<80
Prehypertension	120-139	or	80-89
Stage 1 hypertension	140-159	or	90-99
Stage 2 hypertension	≥160	or	≥100

DBP, Diastolic blood pressure; *SBP,* systolic blood pressure.

TABLE 33.4 European Society of Hypertension and European Society of Cardiology Classification Scheme and Diagnostic Thresholds for Hypertension

CLASSIFICATION OF OFFICE BP				THRESHOLD BPS FOR DIAGNOSIS OF HYPERTENSION			
Category	Systolic (mm Hg)		Diastolic (mm Hg)	Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal	<120	and	<80	Office BP	≥140	and/or	≥90
Normal	120-129	and/or	80-84	Ambulatory BP			
High normal	130-139	and/or	85-89	Daytime (or awake)	≥135	and/or	≥85
Grade 1 hypertension	140-159	and/or	90-99	Nighttime (or asleep)	≥120	and/or	≥70
Grade 2 hypertension	160-179	and/or	100-109	24-hour	≥130	and/or	≥80
Grade 3 hypertension	≥180	and/or	≥110	Home BP	≥135	and/or	≥85
Isolated systolic hypertension	≥140	and/or	<90				

Classification scheme proposed by the European Society of Hypertension and European Society of Cardiology 2013 guidelines (see reference 25).

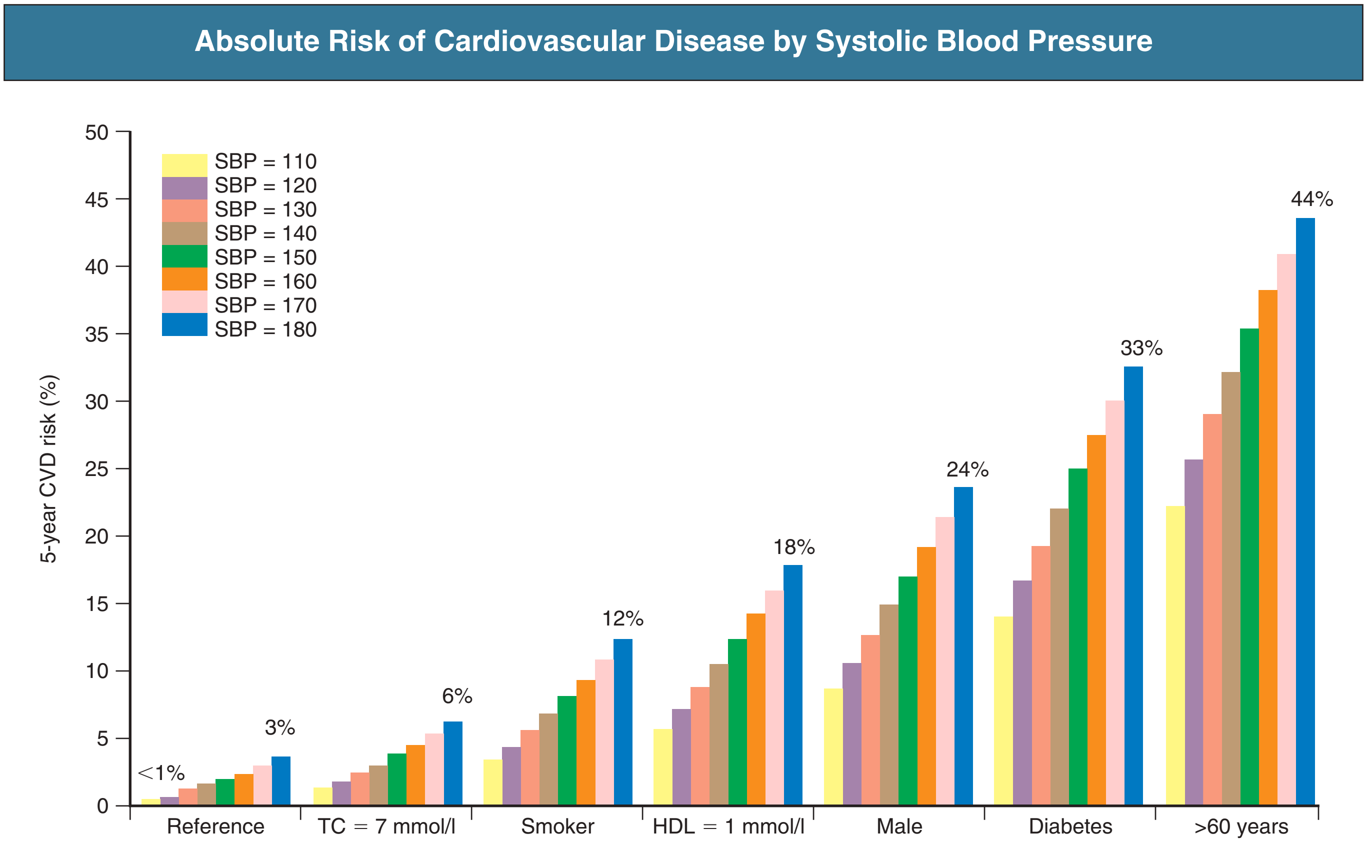

Fig. 33.6 Absolute risk for cardiovascular disease during 5 years in patients by systolic blood pressure at specified levels of other risk factors. Reference category is a nondiabetic, nonsmoking woman age 50 with total cholesterol *(TC)* level of 4 mmol/l (155 mg/dl) and high-density lipoprotein *(HDL)* level of 1.6 mmol/l (62 mg/dl). Risks are given for systolic blood pressure *(SBP)* levels of 110, 120, 130, 140, 150, 160, 170, and 180 mm Hg. In the other categories, additional risk factors are added consecutively; for example, the diabetes category is a diabetic 50-year-old male cigarette smoker with TC level of 7 mmol/l (270 mg/dl) and HDL level of 1 mmol/l (39 mg/dl). *CVD,* Cardiovascular disease. (From reference 33.)

recommend that affected persons receive only lifestyle modifications (see Chapter 35) until their BP exceeds thresholds for hypertension.

White coat hypertension. "White coat" hypertension, defined as normal BP during usual daily activities, yet elevated only in a clinical setting, has a prevalence of 20% to 25% in hypertensive persons and is most accurately diagnosed by ambulatory BP monitoring (with home BP measurements a distant second choice). Unfortunately, ambulatory BP monitoring is not widely available for routine clinical use in many countries (including the United States), despite having become the gold standard for diagnosis in research settings. The "white coat" (or "alerting") phenomenon is less common when a nurse or technician measures the BP (compared with when taken by a physician), and is rare when automated office BPs are taken with the patient alone in the examination room (as was routine in the SPRINT trial[32]). Although the most recent meta-analysis of 14 studies suggests that people with white coat hypertension have an increased long-term risk for CV events,[37] several prior studies (using carefully standardized diagnostic criteria) have concluded that CV risk in untreated persons was not significantly elevated compared with normotensive individuals[38] (Fig. 33.7). Nevertheless, many white coat hypertensive persons have subtle target organ damage and presence of biomarkers that are intermediate between normotensive and sustained hypertensive persons. As many as 50% to 75% of white coat hypertensive persons progress to sustained hypertension over time, which may be less than the more than 90% lifetime prevalence of hypertension for 50-year-old individuals. Most authorities therefore agree on the need for ongoing risk assessment and continued follow-up for persons with white coat hypertension, because many eventually receive antihypertensive medications.

Masked hypertension. Masked hypertension is defined as normal BP in the medical setting but elevated during ambulatory (or, perhaps less strictly, home) BP measurements and has a prevalence of 10% to 15% in the general population. Not surprisingly, such people often have target organ damage (which is often the only clue on initial evaluation) and a CV prognosis that is not much different than individuals with sustained hypertension[38] (see Fig. 33.7).

Sustained hypertension. Sustained (sometimes *persistent*) hypertension is diagnosed when the BP is elevated both inside and outside the medical setting, including at home and during usual daily activities. Patients with sustained hypertension should receive antihypertensive drug therapy, which reduces their risk for CV and renal events, albeit not to the level of normotensives (see Fig. 33.7).

Pseudohypertension. Pseudohypertension is defined as a significantly higher BP measured by cuff compared with that measured by an intra-arterial catheter. Typically this condition occurs in older patients and is attributed to calcium deposition, atheromatosis, and/or medial hypertrophy of the brachial (and likely other) arteries. It is suggested by the presence of a "positive Osler maneuver" in which the nonperfused radial or brachial artery is palpable despite inflating the cuff to greater than 20 mm Hg higher than the palpated SBP. Confirmation requires arterial catheterization documenting a BP 10 to 15 mm Hg lower compared with a cuff-measured BP.

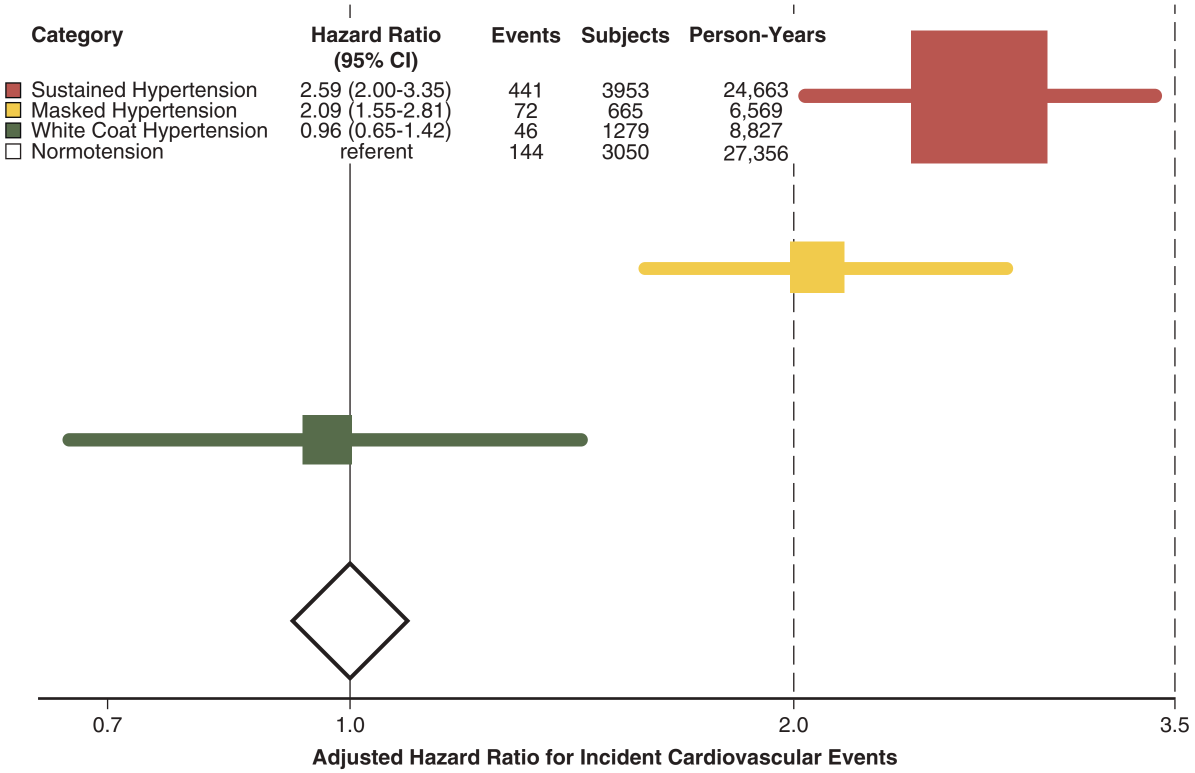

Fig. 33.7 Meta-analysis of prognosis of four types of untreated blood pressure patterns, as classified by ambulatory blood pressure monitoring: Normotension, white coat hypertension, masked hypertension, and sustained hypertension. *Horizontal lines* represent the bounds of the 95% confidence intervals (CI), *squares* are drawn in proportion to the number of events. (Modified from reference 38.)

TABLE 33.6 Common Definitions for the Metabolic Syndrome

Criterion	NCEP ATP III, 2005 Update	International Diabetes Federation, 2005
Criterion	**(≥3 Criteria)**	**(Obesity + 2 Other Criteria)**
Abdominal obesity	Waist circumference	Required for diagnosis
Men	>40 inches (>102 cm)	>94 cm
Women	>35 inches (>88 cm)	>80 cm
Hypertriglyceridemia	>150 mg/dl (≥1.7 mmol/l)	>150 mg/dl (≥1.7 mmol/l), or treatment
Low HDL		
Men	<40 mg/dl (<1.03 mmol/l)	<40 mg/dl (<1.03 mmol/l), or treatment
Women	<50 mg/dl (<1.30 mmol/l)	<50 mg/dl (<1.30 mmol/l), or treatment
Hypertension	≥130/85 mm Hg or taking antihypertensive medication	≥130/85 mm Hg or taking antihypertensive medication
Impaired fasting glucose or diabetes	Glucose ≥100 mg/dl (5.6 mmol/l) or taking insulin or hypoglycemic medication	Glucose ≥100 mg/dl (5.6 mmol/l) or taking insulin or hypoglycemic medication

Modified from reference 34.

HDL, High-density lipoprotein; *LDL,* low-density lipoprotein; *NCEP ATP III,* National Cholesterol Education Program–Adult Treatment Panel III.

TABLE 33.7 Recommendations for Follow-up Based on Initial Blood Pressure Measurements for Adults

INITIAL BLOOD PRESSURE (mm Hg)*		
Systolic	**Diastolic**	**Follow-up Recommendation**
<130	<85	Recheck in 1 year.
130-139	85-89	Recheck in 1 year; provide information about lifestyle modification.
140-159	90-99	Confirm within 2 months.
160-179	100-109	Evaluate or refer to source of care within 1 month.
≥180	≥110	Evaluate or refer to source of care immediately or within 1 week, depending on clinical situation.

*If systolic and diastolic categories are different, follow recommendations for the shorter time for follow-up. The schedule for follow-up should be modified according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease.

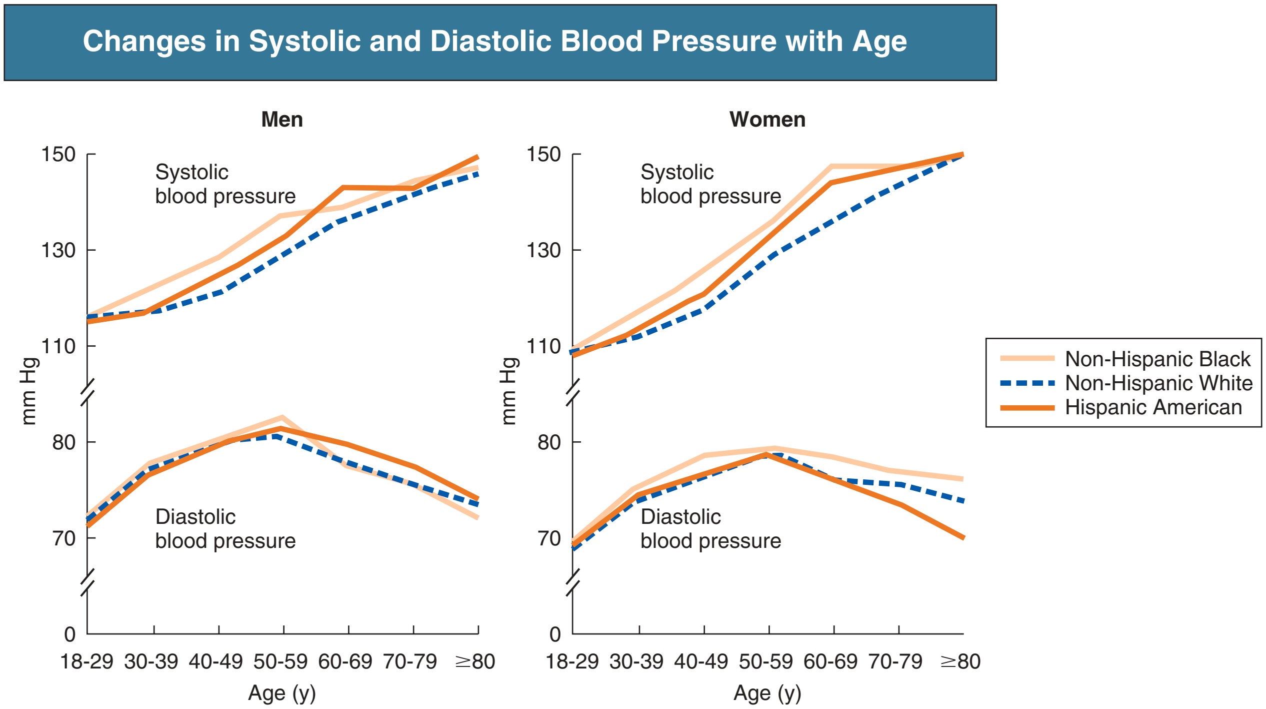

Fig. 33.8 **Changes in systolic and diastolic blood pressures with age.** Systolic blood pressure and diastolic blood pressure by age and race or ethnicity for men and women older than 18 years in the U.S. population (NHANES III, 1988-1991). (From reference 39.)

Isolated systolic hypertension. Isolated systolic hypertension (SBP ≥140 mm Hg, but DBP <90 mm Hg) is recognized by current hypertension guidelines in Europe[25] but not in the United States. Its prevalence increases markedly with age, becoming by far the most common form of hypertension after the age of 60 years. It arises from vascular aging and large artery stiffening, both of which reduce their capacitance, accelerate pulse wave velocity, and widen the pulse pressure. Perhaps as a consequence of these processes, SBP continuously increases throughout life, whereas DBP usually decreases after the age of 50 years (Fig. 33.8).[39] Although there was once great concern that lowering BP in patients with isolated systolic hypertension would push the DBP below the "J-curve inflection point" (and increase the risk for cardiac ischemia), all three RCTs (Systolic Hypertension in the Elderly Program in the United States, Systolic Hypertension in Europe trial, and Systolic Hypertension in China trial) showed a similar, significant decrease in stroke, and *no* increase in cardiac events, with active drug treatment compared with placebo. The significant benefits on stroke and mortality of antihypertensive drug therapy (beginning with a thiazide-like diuretic) have now been extended to relatively healthy octogenarians (most of whom had isolated systolic hypertension) in the Hypertension in the Very Elderly Trial.[40] This RCT established a SBP target of less than 150 mm Hg for octogenarians, which was also recommended by JNC 8 for patients over the age of 60 years,[27] but the dissenting minority of panel members later suggested that the more traditional SBP target of less than 140 mm Hg is reasonable, even if not directly supported by RCT evidence.[41] This position was strengthened by the subgroup analysis of SPRINT subjects over age 75 years of age, who enjoyed a 34% reduction in the primary composite end-point and a 33% reduction in mortality, if randomized to the SBP of less than 120 mm Hg.[42]

Resistant hypertension. Resistant hypertension is defined as BP above treatment goal, despite optimal doses of three antihypertensive drugs, including a diuretic.[43] Some clinical trials suggested that resistant hypertension may occur in 30% of hypertensive patients, but more population-based surveys put the U.S. prevalence at 9% to 12%. Older age and obesity are strong risk factors; in several datasets from Southern European countries, white coat hypertension is found in up to 38% of individuals with resistant hypertension. Although nonadherence to prescribed antihypertensive drug therapy is the most common cause overall, suboptimal medication regimens and secondary hypertension (especially sleep apnea) are more frequently seen in referral centers.

Hypertensive emergencies and urgencies. A hypertensive emergency exists when elevated BP (usually BP >180/120 mm Hg) is associated with severe, ongoing target-organ damage (e.g., aortic dissection, hypertensive encephalopathy, cardiac ischemia, hematuria, etc.), which benefits from BP reduction within minutes to hours, typically using intravenous, short-acting antihypertensive agents in an intensive care unit (see Chapter 37). Examples include acute aortic dissection, acute decompensated heart failure, intracranial hemorrhage, eclampsia, and pheochromocytoma crisis.[44] Hypertensive urgencies, if they really exist, often have similar elevations in BP, but no ongoing severe target organ damage, and can be handled in the outpatient department with oral antihypertensive agents and quick follow-up efforts. Recent data have confirmed observations from nearly 30 years ago that aggressive drug therapy and intensive monitoring in this situation has little benefit.[45]

Hypertension in children and adolescents. As discussed earlier, hypertension in youth was defined in the U.S. (until 2017) on a purely statistical basis: SBP or DBP at or above the 95th percentile for age, gender, and height, measured on at least three occasions.[28] Although this made quality assurance for hypertension simple in large pediatric practices, the 2017 hypertension guidelines for children and adolescents have made this rubric more complex.[31] Children have a higher risk for secondary hypertension than adults; most secondary hypertension in young children has a renal origin. Most adolescents with hypertension have primary hypertension; risk factors include a family history of hypertension and obesity, but renal causes of hypertension are more common in stage 2 hypertension (see Table 33.5).

Hypertension in pregnancy. Hypertension occurs in more than 5% of all pregnancies and in approximately 5% of women taking oral contraceptives.[46] Definitions and implications of hypertension in pregnancy are discussed in Chapters 42 and 43.

Classification by Cause of Hypertension

In 90% to 95% of adults with hypertension, the cause is unknown and therefore the diagnosis is "primary" (or essential) hypertension (see Chapter 34). Table 33.8 lists the more common causes of secondary hypertension, in descending order of prevalence in large series. Renal parenchymal disease is most common (especially in nephrology clinics, particularly in diabetics; see Chapters 31 and 32), followed by endocrine causes (Chapters 38 and 39), renovascular hypertension (Chapter 41), sleep apnea, coarctation of the aorta, drug-induced hypertension, and rare monogenetic causes (see Chapter 47).

EVALUATION OF HYPERTENSION

Blood Pressure Measurement

Arterial BP is traditionally measured in the brachial artery with the cuff-based sphygmomanometer by detecting sounds that are generated (auscultatory method) or by recording vascular pulsations (oscillometric method) after decompression of a compressed artery. Box 33.1 lists guidelines for traditional BP measurement. The most common error is using an inappropriately sized cuff, because cuffs that are too small routinely underestimate the BP. Table 33.9 provides acceptable bladder dimensions for varying arm sizes. Because of the low frequency of Korotkoff sounds, the bell of the stethoscope provides better detection than the diaphragm. Accurately taking BP is a teachable and testable skill, but many routine measurements are made with little effort to ensure their quality. As a result, many health care systems have transitioned to using automated oscillometric office BP measurements, which minimize the white coat effect, and after 5 minutes of quiet rest, provide standardized triplicate measurements in a 5-minute period. Because elemental mercury (used in classic manometers and sphygmomanometers) has been eliminated from workplaces in most countries, because of potential toxicity, and aneroid ("dial") manometers are fragile, oscillometric techniques have become increasing popular. This method directly measures MAP and then uses a proprietary algorithm to estimate SBP and DBPs. Many such semiautomatic (typically for home BP readings) and fully automatic oscillometric devices (more often used for office and ambulatory BP monitoring) have been validated against the traditional mercury column.[47] Unfortunately, semiautomatic and automatic devices may pass certifying protocols with as few as 60% of automated readings within 5 mm Hg of the observed BP. Automated BP devices require regular calibration, validation, and maintenance.

Variability of Blood Pressure

Office Versus Home Blood Pressure and Circadian Variation

BP varies considerably throughout the day, and over time, even in the same individual. This intrinsic variation causes difficulty in identifying hypertensive individuals, because there are many false negatives and even more false positives. Aside from measurement errors (which can be overcome by proper technique), intrinsic biologic variation can be addressed by taking at least three BP readings at a given visit. Recent U.S. guidelines consider the lowest SBP and DBP at any given visit (even if not measured simultaneously) to be *the* BP for that visit.[48] Confirming elevated readings at a second visit takes advantage of "regression to the mean" to better identify the true BP for a given individual. Another widely recommended option is to measure home BPs (see later discussion).

In addition to physical/mental activity, and emotional/environmental stress, BP is affected by circadian variation. About 80% of the population display a "dipping" pattern, with average nocturnal BP that is 10% to 20% lower than the daytime average; this difference diminishes with increasing age. The normal "morning surge" in BP and heart rate that begins about 30 minutes before awakening correlates with an increased risk for death, myocardial infarction, and stroke in the early morning hours. Individuals with a "nondipping" nocturnal BP pattern more commonly have CKD, target-organ damage, secondary hypertension, autonomic dysfunction, and/or an increased risk for CV events.

TABLE 33.8 Secondary Hypertension: Acquired Causes

Condition/ Disorder	Diseases: Comments
Renal disorders	Renal parenchymal disease, including acute and chronic glomerular diseases, chronic tubulointerstitial disease, PKD, diabetic nephropathy, and obstructive uropathy Renovascular disease: Renal artery stenosis caused by atherosclerosis or fibromuscular dysplasia; arteritis; extrinsic compression of renal artery Other renal causes: Renin-producing tumors, renal sodium retention (Liddle syndrome)
Endocrine disorders	Adrenocortical disorders: Primary aldosteronism, congenital adrenal hyperplasia, Cushing syndrome Adrenomedullary tumors: Pheochromocytoma (also extra-adrenal chromaffin tumor) Thyroid disease: Hyperthyroidism, hypothyroidism Hyperparathyroidism with hypercalcemia Acromegaly Carcinoid tumors
Exogenous substances and/or drugs	Oral contraceptives, sympathomimetics, glucocorticoids, mineralocorticoids, NSAIDs, calcineurin inhibitors, tyramine-containing foods and monoamine oxidase inhibitors, EPO, ergot alkaloids, amphetamines, herbal remedies, licorice (mimics primary aldosteronism), ethanol, cocaine and other illicit drugs, abrupt withdrawal of clonidine
Pregnancy	Preeclampsia and eclampsia
Coarctation of the aorta	Usually congenital, diminished pulses below the coarct, positive Hill's sign
Neurologic disorders	Sleep apnea Increased intracranial pressure: Brain tumors Affective disorders Spinal cord injury: Quadriplegia, paraplegia, Guillain-Barré syndrome Baroreflex dysregulation
Psychosocial factors	Hostility, time-urgency/impatience, depression, anxiety, occupational stress
Intravascular volume overload	Pedal or presacral edema, jugular venous distention, pulmonary râles
Systolic hypertension	Loss of elasticity of aorta and great vessels Hyperdynamic cardiac output: Hyperthyroidism, aortic insufficiency, anemia, arteriovenous fistula, beriberi, Paget disease of bone
Obesity	White adipose tissue that has endocrine function: Leptins, adiponectin, cytokines, chemokines, Ang II, other adipokines

Ang II, Angiotensin II; *EPO,* erythropoietin; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PKD,* polycystic kidney disease.

BOX 33.1 Guidelines for Measurement of Blood Pressure: Patient Factors, Equipment, and Technique

Patient Factors

- Caffeine should not be consumed for 1 hour before the BP measurement.
- Cigarettes should not be smoked for at least 15 minutes before the BP reading.
- The standard BP measurement should be made with the patient not talking and seated comfortably, back and arm supported, and legs uncrossed. The cuff must be at the level of the heart, and the arm should be bare.
- The urinary bladder should be empty.
- Initially, BP should also be checked in both arms in the supine position after 5 minutes of rest; thereafter the arm with the higher reading is used for both supine and standing readings (after 2 minutes), especially in patients who are diabetic, older than 65 years, or receiving antihypertensive therapy. If sequential BP readings are taken in the same position, at least 30 seconds should elapse between BP readings. In patients younger than 30 years, check BP in one leg initially.
- To establish a diagnosis of hypertension, obtain BP readings on two different occasions, at least 1 week apart.

Equipment

- The bell of the stethoscope is preferred. The length of the bladder with the cuff should encircle at least 80% of the arm.
- The width of the cuff should be equal to two thirds of the distance from the antecubital space to the axilla and should be 40% of the arm circumference. The best cuff for most adults is the 15-cm-wide cuff with a bladder of 33 to 35 cm in length. The distal edge of the cuff should be 2.5 cm (1 inch) above the antecubital fossa. For leg BP, thigh cuff length should encircle 80% of the thigh, and width should be 40% of the thigh circumference. For leg BP, the patient should be prone and popliteal artery sounds detected by auscultation.
- For infants, ultrasound equipment may need to be used.

Technique

- The initial systolic BP should be checked by palpating the disappearance of the radial or brachial pulse before auscultation and the cuff then deflated.
- The second BP check requires cuff inflation 20 mm Hg above the palpable systolic level.
- Deflate the cuff at a rate of 2 to 4 mm Hg per second, for heart rates of 60 to 120, respectively.
- Record the Korotkoff sound I (appearance of sound) as the systolic BP and record the Korotkoff sound V (silence, 2 mm Hg below the last sound) as the more reproducible diastolic BP. If the sounds do not disappear, record the muffled sound (phase IV) as the diastolic BP.
- The sounds may be augmented by having the patient raise the arm and open and close the hand 10 times before inflating the BP cuff.
- Do not stop between systolic and diastolic BP readings; deflate the cuff, wait at least 30 seconds, and then reinflate. On each occasion, record at least two (and preferably three) BP readings. If the BP readings vary by more than 5 mm Hg, take additional BP readings until two are within 5 mm Hg.
- In children, the same standards apply for cuff size; Korotkoff sound V should be used. If the child is uncooperative, the systolic BP may be determined by palpation.

TABLE 33.9 Acceptable Bladder Dimensions for Various Arm Sizes

Usual Patient	Arm Circumference Range at Midpoint (cm)	Bladder Width (cm)	Bladder Length (cm)
Newborn	6	3	6
Infant*	6-15	5	15
Child*	16-21	8	21
Small adult	22-26	10	24
Adult	27-34	13	30
Large adult	35-44	16	38
Adult thigh	45-52	20	42

From reference 52.

*To approximate a bladder width to arm circumference ratio of 0.4 more closely in children, additional cuffs are available. There is some overlap in the recommended ranges for arm circumference to limit the number of cuffs. It is suggested that the larger cuff be used if it is available.

Home and Ambulatory Blood Pressure Monitoring

Most ambulatory BP monitors use oscillometry and record BPs for 24 hours, making measurements frequently during the daytime (e.g., every 15 minutes) and less so at night (e.g., every 30 minutes). Inaccurate readings can occur with inappropriately sized cuffs, cardiac dysrhythmias, vigorous activity, inability to sleep because of pain resulting from cuff insufflation, and many other conditions. Because ambulatory BP monitoring (1) can diagnose white coat, masked, and nocturnal hypertension; (2) correlates better with both target-organ damage and future CV events than either office or home BPs; and (3) has been found to be cost-saving in many countries, it has been recommended (as at least one of several options) by many policymaking authorities, including the 2011 and 2013 British hypertension guidelines, 2013 European hypertension guidelines,[25] 2016 Canadian Hypertension Education Program, and the U.S. Task Force on Preventive Services,[49] before starting antihypertensive drug therapy. Multiple national and international expert panels have issued guidelines regarding indications, technique, reporting, and implications of the procedure.[50]

Because of the limited availability of, and scarce reimbursement for, ambulatory BP monitoring, home BP monitoring with semiautomated devices (typically duplicate measurements morning and evening for a week) has been recommended.[25] Home BP readings, on average, are slightly higher than ambulatory BP readings (because the latter includes nocturnal BPs) and slightly lower than office BPs. Home BP readings should be obtained with a device that has been calibrated (usually in the practitioner’s office), are subject to reporting bias (which can be minimized by telemonitoring systems), and their interpretation is not often reimbursed. In general, home BP readings correlate better with target-organ damage and CV outcomes than office BP measurements, but less well than ambulatory BP results. The results of an early study with 11 years of follow-up[51] comparing methods of BP measurement (Fig. 33.9) are consistent with this view. For many reasons, therefore, ambulatory BP monitoring is preferred over home BP recording in several settings[48] (Fig. 33.10 and Box 33.2).

Risk Assessment in Hypertension

The medical history, physical examination, and a limited laboratory evaluation (biochemistry panel, including estimated GFR, and fasting

BOX 33.2 Indications for Ambulatory Blood Pressure Measurement

- White coat hypertension
- Evaluation of apparent drug resistance
- Hypotensive symptoms
- Autonomic dysfunction
- Episodic hypertension
- Evaluation of nocturnal decreases in BP as a prognostic factor for target organ damage (e.g., left ventricular hypertrophy, ischemic optic neuropathy)
- Evaluation of BP changes in patients with paroxysmal nocturnal dyspnea and/or nocturnal angina
- Carotid sinus syncope
- Pacemaker syndromes
- Safety of withdrawing antihypertensive medication
- Assessment of 24-hour BP control in patient receiving once-daily medication
- Borderline hypertension with target organ damage (evaluation for masked hypertension)
- Evaluation of antihypertensive drug therapy in clinical trials

glucose and lipid panel, urinalysis and urinary albumin-to-creatinine ratio, complete blood count, electrocardiogram) provide useful information to assess the presence and extent of target-organ damage, and estimate future CV and renal risk (see Chapter 34).[24-26,33] The 2017 ACC/AHA U.S. hypertension guideline added serum thyroid-stimulating hormone to the list of recommended initial tests.[31]

Consideration of Primary Versus Secondary Hypertension

If the history, physical examination, or screening laboratory studies suggest secondary hypertension, additional studies may be warranted (Tables 33.10 and 33.11). If renal parenchymal disease is suspected, ultrasound may be useful to evaluate renal size and echogenicity (to help assess chronicity) and rule out obstructive uropathy; Doppler flow studies also can help stratify risk for renovascular hypertension, although none of four RCTs has shown significant outcome benefits after angioplasty/stenting (see Chapter 38). Because primary aldosteronism can now be controlled either with chronic aldosterone antagonists or (occasionally) after laparoscopic surgery, a ratio of plasma aldosterone to plasma renin activity ratio may be useful (see Chapter 39). Suggested evaluations for other forms of secondary hypertension are listed in Table 33.11.

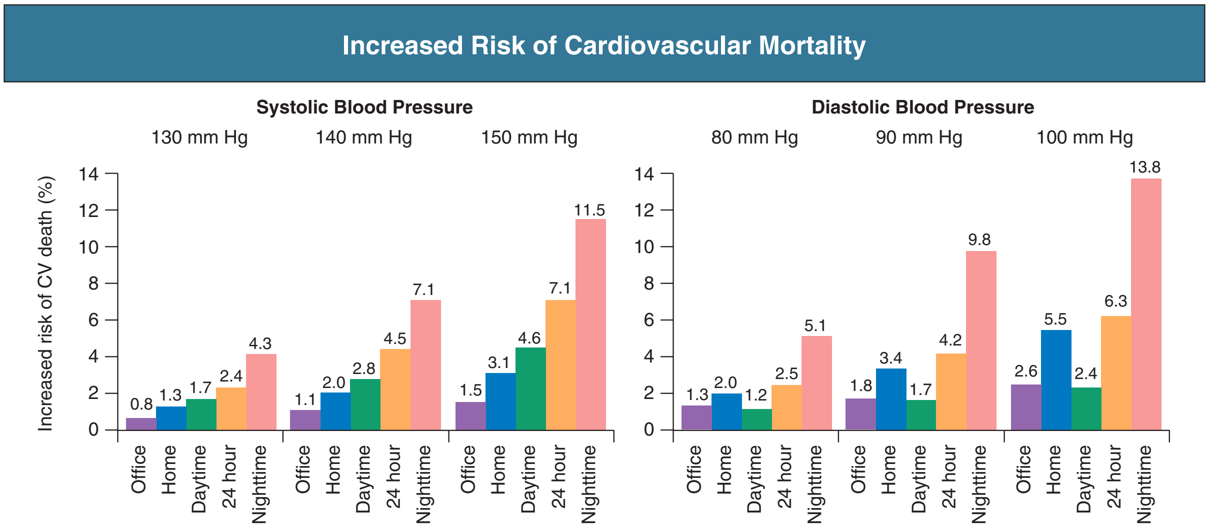

Fig. 33.9 **Risk for cardiovascular mortality in an early population-based Italian study.** Risk for cardiovascular death (%) over 11 years, for a 10 mm Hg increase in office, home, and ambulatory blood pressure (BP) readings at various initial BP values. (From reference 51.)

TABLE 33.10 Evaluation for Primary Versus Secondary Hypertension

Classification	Medical History	Physical Examination	Laboratory Studies
General information and evaluation of target organs	Duration and course of hypertension Prior workup and treatment Diet/lifestyle: Salt intake, tobacco, caffeine	Evaluation of volume status, optic fundi, heart, lungs, peripheral vessels, and nervous system	Complete blood count, fasting glucose, lipid profile (includes HDL, LDL, cholesterol, triglyceride), uric acid Consider echocardiogram
Primary (essential or idiopathic) or secondary?	Family history: Hypertension, cardiovascular and renal diseases Symptoms of target organ disease (related to eyes, central nervous system, cardiorespiratory, and peripheral vasculature)	See Table 33.11 for signs suggestive of secondary hypertension	See Table 33.11 for additional laboratory studies to rule out secondary hypertension

HDL, High-density lipoprotein; *LDL,* low-density lipoprotein.

TABLE 33.11 **History, Physical Examination, and Initial Laboratory Evaluation for Secondary Hypertension**

Target Organ/ System	Medical History	Physical Examination	Laboratory Studies
Kidney			
Renal parenchymal	History of renal disease (including glomerulonephritis, nephrotic syndrome, calculi, urinary tract infection) Symptoms include nocturia, frequency, dysuria, hesitancy, urgency, incomplete emptying, dribbling, hematuria, pyuria, flank pain	Tenderness in costovertebral angles; palpable kidneys, edema	BUN, serum creatinine; urinalysis, urine culture if indicated; first morning urine albumin-to-creatinine ratio
Renovascular hypertension		Epigastric bruit; other vascular bruits	Renal ultrasound with duplex Doppler flow study; consider angiography or magnetic resonance angiography
Endocrine			
Primary aldosteronism	Muscle weakness, cramps		Serum aldosterone/plasma renin activity ratio
Cushing syndrome	Weight gain, muscle weakness, changes in body habitus	Body habitus: Central obesity, dorsocervical fat pad, abdominal striae	Midnight salivary cortisol; consider morning serum cortisol after dexamethasone suppression
Pheochromocytoma	Headaches, vasomotor symptoms, (inappropriate sweating, pallor), cardiac symptoms (awareness, tachycardia, palpitations)	Paroxysmal or intermittent hypertension (50% of patients)	24-hr urine for VMA, metanephrines, and catecholamines or plasma fractionated metanephrines
Carcinoid	Flushing		24-hr urine for 5-hydroxyindoleacetic acid
Hyperthyroidism	Weight loss, tachycardia, palpitations, sweating, heat intolerance	Palpable thyroid	Ultrasensitive serum thyroid-stimulating hormone level
Hypothyroidism	Weight gain, dry skin, cold intolerance, hair loss	Palpable thyroid	Serum ultrasensitive thyroid-stimulating hormone level
Hyperparathyroidism	Nausea, vomiting, bone pain, nephrolithiasis		Serum calcium, intact parathyroid hormone levels
Acromegaly	Change in size of head, hands, or feet (adult)	Appearance	Serum insulin-like growth factor 1level (see Box 40.1)
Medication			
	Review of prescribed and over-the-counter medications (especially oral contraceptives, NSAIDs, sympathomimetic agents [cold and allergy remedies], illicit or recreational drugs, including alcohol, herbal remedies)		
Coarctation of the Aorta			
	Onset or detection of hypertension in childhood or adolescence	Simultaneous palpation of radial and femoral arteries to detect pulse lag in femoral arteries; leg blood pressure	Chest radiograph for heart size, configuration of aorta, rib notching; consider echocardiogram
Neurologic Disorders			
Sleep apnea	Obesity; weight gain; daytime somnolence; snoring, poor sleep habits (frequent awakening, not rested on arising); early-morning headache	Obesity, narrowed airway in hypopharynx, redundant pharyngeal tissue	Berlin questionnaire; consider formal sleep study (polysomnography)
Increased intracranial pressure	Headache, neurologic symptoms	Papilledema	Increased cerebrospinal fluid pressure
Affective disorders*			
Spinal cord injury*			
Psychosocial Factors			
	Family and support structure, occupation, education, stressors		

Continued

TABLE 33.11 History, Physical Examination, and Initial Laboratory Evaluation for Secondary Hypertension—cont'd

Target Organ/ System	Medical History	Physical Examination	Laboratory Studies
Volume Overload	Excess salt and water intake (may be iatrogenic with excess parenteral fluid)	Increased jugular venous distention, pulmonary crackles, presacral and peripheral edema, hepatomegaly	Chest radiograph
Isolated Systolic Hypertension		Pseudohypertension (positive Osler maneuver), cardiac and vascular examination (aortic insufficiency, arteriovenous fistula)	

A more detailed discussion is provided in other relevant chapters. Pregnancy-associated hypertension is discussed in Chapters 42 and 43.
*Medical history, physical examination, and laboratory tests are beyond the scope of this discussion.
BUN, Blood urea nitrogen; *NSAIDs,* nonsteroidal antiinflammatory drugs; *VMA,* vanillylmandelic acid.

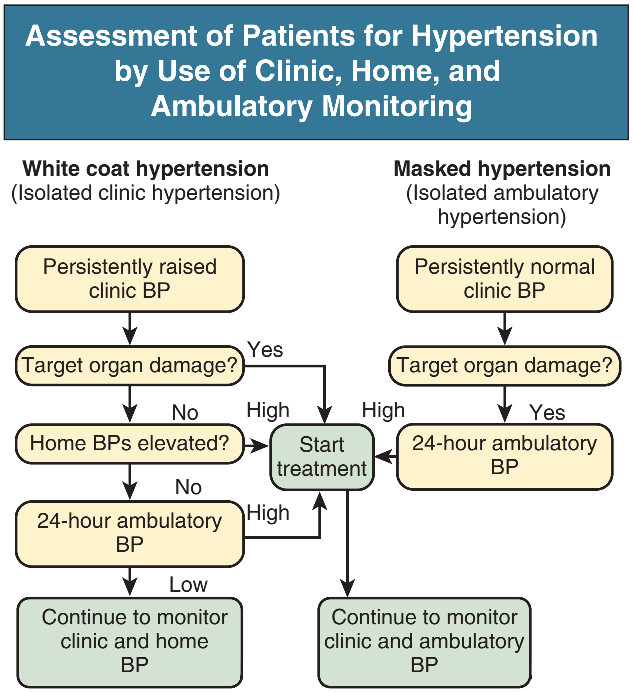
Assessment of Patients for Hypertension by Use of Clinic, Home, and Ambulatory Monitoring
White coat hypertension
(Isolated clinic hypertension)
Masked hypertension
(Isolated ambulatory hypertension)
Persistently raised clinic BP
Persistently normal clinic BP
Target organ damage?
Yes
Target organ damage?
No
High
High
Yes
Home BPs elevated?
Start treatment
24-hour ambulatory BP
No
24-hour ambulatory BP
High
Low
Continue to monitor clinic and home BP
Continue to monitor clinic and ambulatory BP

Fig. 33.10 Algorithm for diagnosis of hypertension using clinic, home, and/or ambulatory monitoring of blood pressure.

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SELF-ASSESSMENT QUESTIONS

1. Short-term (within seconds to minutes) regulation of blood pressure in normal humans is most often attributed to which of the following physiologic systems?
   A. Atrial natriuretic peptides
   B. Endothelin
   C. Kallikrein-kinin system
   D. Renin-angiotensin-aldosterone system
   E. Sympathetic nervous system
2. An asymptomatic, presumably healthy, 67-year-old man visits the physician's office, and has seated blood pressures of 140/96, 138/94, and 142/88 mm Hg, as measured personally and appropriately by the physician. According to guidelines, promulgated by HEDIS 2016 and JNC 7, his blood pressure at this visit was most appropriately classified using which of the following terms?
   A. Normal
   B. Prehypertension
   C. Stage 1 hypertension
   D. Stage 2 hypertension
   E. Isolated systolic hypertension
3. A 62-year old nonblack man visits the nephrologist because his routine tests last week showed that his estimated GFR was 59 ml/min/1.73 m^2 and his first morning voided urine contained 28 mg of albumin per gram of creatinine (normal: <30 mg albumin per gram creatinine or <2.0 (men) and <2.8 (women) mg albumin per millimole creatinine). His past medical history includes prehypertension since 2015, but he takes not medications. Blood pressure is 136/84, 134/86, and 132/82 mm Hg, when measured personally and appropriately by the nephrologist. His 10-year risk of a CV event is estimated at 9.2%. According to the 2017 ACC/AHA U.S. hypertension guidelines, the most appropriate recommendation for this patient is which of the following?
   A. Recheck blood pressure in this office in 1 year.
   B. Recheck blood pressure in this office in 3-6 months and provide guidance about lifestyle modifications.
   C. Repeat blood and urine tests in 3 months, and recheck blood pressure in this office soon thereafter.
   D. Recheck blood pressure within 2 months.
   E. Institute antihypertensive drug therapy with an angiotensin converting-enzyme inhibitor or angiotensin II receptor blocker today.
4. A 32-year-old woman is referred to the nephrologist because her ophthalmologist noted grade II hypertensive retinopathy last month, and her obstetrician/gynecologist noted 2+ proteinuria on dipstick (without blood or nitrite), despite normal office blood pressures last week. Past medical history is remarkable for preeclampsia 4 and 6 years ago, but both of her children were delivered without complications, and her blood pressure has since been normal. Office blood pressures are 128/84, 126/82, and 124/80, measured by a calibrated automated oscillometric device. In addition to the retinopathy, an electrocardiogram shows voltage criteria for left ventricular hypertrophy, and a random urinalysis shows 3+ protein. According to recent surveys, her condition is most commonly seen in what proportion of which population?
   A. Less than 1% of people older than 65 years
   B. 5% to 10% of the hypertensive population
   C. 10% to 15% of the general population
   D. 20% to 25% of the hypertensive population
   E. 29% to 32% of the general population
5. A 56-year-old nonblack man is referred to the nephrologist because his blood pressures in his primary care medical home have never been below 190/120 mm Hg, yet all the rest of his evaluation is normal. A request for prior authorization for ambulatory blood pressure monitoring was denied by his insurance plan. His home blood pressures, measured with a validated semiautomatic oscillometric device, have a mean and standard deviation of 128 ± 4/78 ± 3 (122 measurements over 3 months). He has no family history of hypertension. Office blood pressures, taken with the same machine, were 194/122, 196/120, and 192/118 mm Hg. Physical examination and laboratory studies were unremarkable. The most appropriate recommendation for him is which of the following?
   A. A renal biopsy is indicated to identify the cause of his hypertension.
   B. He should have an iothalamate clearance measured, to ensure that the estimated glomerular filtration rate (GFR) is accurate.
   C. He should undergo renal ultrasound with Doppler flow studies, a 24-hour urine collection for vanillylmandelic acid and metanephrines, and a ratio of plasma aldosterone to renin activity to rule out common causes of secondary hypertension.
   D. He should start an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker today and return to this office in 1 month for repeat blood pressure measurement by his home device.
   E. He should continue to monitor his home blood pressures and call for another appointment when/if they exceed 130/80 mm Hg.

34

Primary Hypertension

Richard J. Johnson, George L. Bakris, Bernardo Rodríguez-Iturbe

DEFINITION

Primary (essential) hypertension is defined as blood pressure (BP) 140/90 mm Hg or greater without an identifiable cause. Several readings at different times, following the American Heart Association and other guidelines, are necessary to document the diagnosis of primary hypertension. Variability in BP results from several factors, but under normal circumstances, a natural circadian rhythm generates the most significant increase in BP in the morning (6 to 10 AM). BP falls during sleep, secondary to a decrease in sympathetic nervous system (SNS) tone and reduced activity of other neuroendocrine systems. There are also minute-to-minute variations in BP (Fig. 34.1). Transient elevations in BP, reaching 150 mm Hg systolic, occur in the majority of normotensive individuals in any given day, especially during exercise.[1] However, BP that is 140/90 mm Hg or greater for an average of two or more seated BP measurements, properly measured with well-maintained equipment, at each of two or more visits to the office or clinic is considered *hypertensive*. Chapter 33 describes the method and interpretation of BP measurements, including the use of ambulatory BP monitoring.

Primary hypertension has recently undergone changes in definition, based on new guidelines from the American College of Cardiology and the American Heart Association Task Force[2]. The definition of stage I hypertension has changed from 140/90 mm Hg to either a systolic BP of >130 and/or a diastolic BP of > 80 mm Hg, and elevated blood pressure has replaced "prehypertension" and is now considered a systolic BP of 120 to 129 mm Hg and diastolic BP < 80 mm Hg (Table 34.1). These changes were made to reduce complacency since increased cardiovascular risk occurs even in the "prehypertensive" group compared to normotensive people.

When only the systolic BP (SBP) is elevated (SBP >140 and diastolic BP [DBP] <90 mm Hg), the term used is *isolated systolic hypertension. White coat hypertension* is an increase of more than 20 mm Hg in SBP noted only in the physician's office above that seen at home or in another setting. In contrast, *masked hypertension* is BP that is normal in the office but elevated by more than 20 mm Hg when measured by ambulatory BP measurement.

Other terms used to describe specific clinical presentations include *hypertensive emergencies,* associated with acute end-organ damage requiring immediate treatment, usually in a critical care setting, and *hypertensive urgencies,* in which BP needs correction in hours or a few days (see Chapter 37). In hypertensive emergencies, the reduction of BP will halt, prevent, or reverse decreasing glomerular filtration rate (GFR). These terms have replaced "malignant hypertension" and "accelerated hypertension." *Resistant hypertension* is defined as hypertension that remains above 140/90 mm Hg despite use of three maximally dosed antihypertensive medications of different classes, including a diuretic.

ETIOLOGY AND PATHOGENESIS

Many studies suggest that the physiologic basis for hypertension is a defect in renal sodium excretion. Whereas in most individuals an increase in sodium intake results in an increase in pressure associated with prompt excretion of the salt load, this "pressure-natriuresis" relationship is abnormal in the hypertensive patient (Fig. 34.2).[3] In some hypertensive patients, especially those under 40 years of age, the response to a salt load is similar to that in normal individuals but is shifted rightward, such that higher pressures are required for a specific salt load, called *salt-resistant hypertension.* In contrast, most hypertensive patients, especially older and African American individuals, have both a rightward shift and a change in the slope, such that BP increases more for the same sodium load, called *salt-sensitive hypertension.* Dietary sodium content also correlates with the prevalence of hypertension in various populations, and intervention studies with salt restriction or loading have shown that the BP response in many hypertensive patients is salt sensitive. The basis for this renal defect in hypertension remains controversial, but three major hypotheses have been proposed.

Genetic (Polygene) Hypothesis

Studies led by Lifton and colleagues[4] have made the compelling case that genetic polymorphisms that favor sodium retention by the kidney, coupled with excessive salt intake (>10 g/day) may have a major role in driving primary hypertension. The observation that numerous monogenic forms of both hypertension and hypotension are mediated by specific mutations involving renal sodium transport, especially involving the epithelial sodium channel (see Chapter 47), supports this hypothesis (Table 34.2). Currently, more than 20 genes have been identified in which mutations or polymorphisms influence BP.[4] Many of these involve sodium transport in the distal tubule or the collecting duct. Some heterozygous mutations, such as the Na-K-2Cl cotransporter *SLC12A1,* the inward rectifier K^+ channel *KCNJ1* (carrier state for Bartter syndrome), and the heterozygous mutation of the Na-Cl cotransporter *SLC12A3* (carrier state for Gitelman syndrome), confer protection from hypertension. Although genetic mechanisms are likely of major importance in the pathogenesis of hypertension, most studies suggest they contribute to only a minority of cases and that other mechanisms are also involved in driving the hypertensive response.

Congenital (Low Nephron Number) Hypothesis

A second major hypothesis is that environmental stress during pregnancy may lead to epigenetic or other changes that affect the fetus and translate into hypertension later in life (fetal programming). In 1989 Barker and associates[5] reported that infants with low birth weight

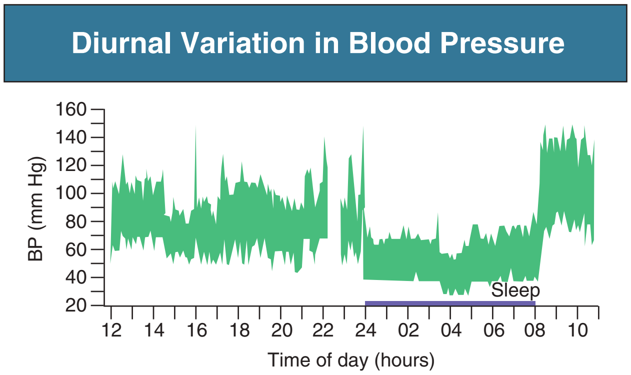

Fig. 34.1 Blood pressure variability in normotensive individual. In most normal individuals, systolic blood pressure (BP) reaches 150 mm Hg at least once daily. (From reference 1.)

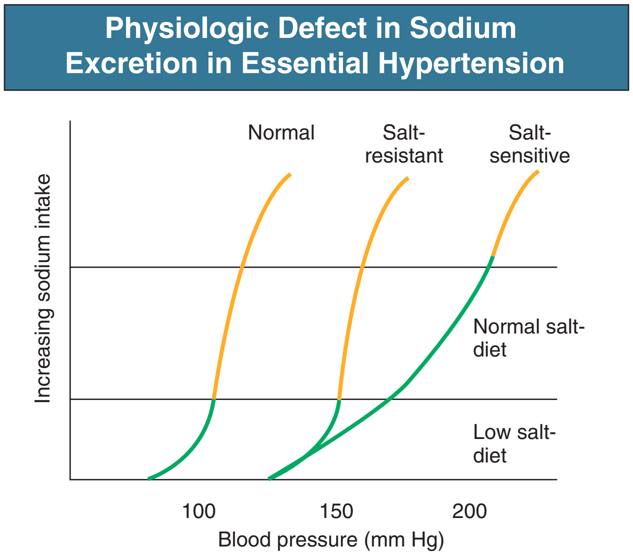

Fig. 34.2 Physiologic defect in sodium excretion in primary hypertension. Evidence suggests that in patients with primary hypertension, a higher blood pressure is required to excrete an individual sodium load. In salt-resistant hypertension, the pressure-natriuresis curve has a rightward but parallel shift; with salt-sensitive hypertension, it is both a shift to the right and a change in slope. (Modified from reference 3.)

TABLE 34.1 **Categories of BP in Adults***

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to higher BP category. BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.

(LBW) are at increased risk for hypertension, and these infants were also shown later to be at risk for diabetes and obesity. Mothers of LBW infants frequently have hypertension, obesity, preeclampsia, or malnutrition, and these maternal factors also carry an increased risk for hypertension in the infant. Brenner and colleagues[6] postulated that LBW might lead to hypertension because of impaired renal development, leading to lower nephron number. Maternal malnutrition in laboratory rats predisposes to small babies, low nephron number, and the future predisposition for hypertension. A study of Whites with primary hypertension found almost 50% fewer nephrons than in age- and gender-matched controls.[7] Other studies, however, could not confirm a relationship between birth weight or low nephron number and hypertension.[8] Another study also reported that LBW infants have a 25% risk for developing hypertension as an adult, but infants with high birth weight also carried a 20% risk.[9] Thus LBW and low nephron number likely reflect risk factors for development of hypertension rather than the underlying mechanism.

The Role of the Immune System and Acquired Renal Injury

The most actively studied mechanism currently involves the role of the immune system, and especially T cells, in mediating hypertension. Low-grade inflammation, consisting of T cells and macrophages, have been demonstrated in the interstitium of 90% or more of renal biopsy samples from patients with primary hypertension.[10] Historically the inflammatory changes, as well as the microvascular injury involving the afferent and interlobular artery, were considered the consequence of hypertensive renal damage.

However, experimental studies have made the compelling case that the immune system may be mediating the hypertensive response by inducing persistent renal vasoconstriction and an impairment in pressure natriuresis. Indeed, in numerous models of hypertension, the administration of mycophenolate mofetil (MMF) could be shown to block the interstitial inflammation and hypertensive response (see Table 34.1).[11] Both T[12] and B[13] lymphocytes are necessary for the development of experimental hypertension. Studies have shown that the effect appears to be mediated by both macrophages and T cells (especially the CD8 cell) and to be counter-regulated by CD4 T regulatory cell populations. More recent studies suggest that the development of hypertension may involve an initial activation of the innate immune system (involving dendritic cells and macrophages via inflammasome-dependent pathways) followed by activation of adaptive immunity in which the T cells become sensitized to neoantigens, leading to an autoimmune mediated hypertension.

Two autoantigens have been identified, including heat shock protein 70 (HSP70) and oxidized (isoketal-containing) proteins.[14,15] The role of HSP70 as a neoantigen that drives an autoimmune response is supported by experimental studies showing that blocking T-cell sensitization to HSP70 can block hypertension and sensitization of T cells to HSP70 in the kidney can induce a rise in BP. Clinical studies also have found evidence for both autoantibodies and T-cell sensitization to HSP70 in humans with primary hypertension. Isoketal accumulation in dendritic cells is associated with production of interleukin-6 (IL-6), IL-1B, and IL-23 and increase in costimulatory CD80 and CD86 proteins. Isoketal-modified proteins have been demonstrated in circulating dendritic cells and monocytes of hypertensive patients, and scavengers of isoketals prevent or ameliorate hypertension in several models of hypertension.[13] Pilot studies also suggest that blocking the immune system, such as by MMF, can lower BP in subjects with primary hypertension.[11]

The mechanism by which T cells reduce sodium excretion is thought to be by mediating intrarenal oxidative stress, inducing a decrease in nitric oxide, and increasing intrarenal angiotensin II (Ang II) levels.[11] Activation of renal afferent sympathetic nerves, likely secondary to the local inflammation, also impairs sodium excretion. The consequence is persistent afferent arteriolar vasoconstriction and a right shift of the pressure-natriuresis curve with a change of the slope, characteristic of salt-sensitive hypertension.

TABLE 34.2 **Monogenic Diseases Associated With Alterations in Blood Pressure**

Condition	Gene	Inheritance	Site	Manifestations
Glucocorticoid-remediable aldosteronism (GRA)	Chimeric ACTH-responsive promoter with aldosterone synthase	AD	Collecting duct	Hypertension, metabolic alkalosis
Mendelian hypertension exacerbated by pregnancy	MR gain of function	AD	Collecting duct	Hypertension, worsened by pregnancy (progesterone)
Liddle syndrome	Gain-of-function of β or γ subunit of ENaC	AD	Collecting duct	Hypertension, metabolic alkalosis
Pseudohypoaldosteronism type 1 (PHA1)	ENaC loss of function MR loss of function	AR AD	Collecting duct	Neonatal hypotension, acidosis, salt wasting
Gitelman syndrome	Na-Cl cotransporter loss of function	AR	DCT	Low BP, salt wasting, metabolic alkalosis
Bartter syndrome	Four gene mutations: Na-K-2Cl, K channel, C1 channel, Barttin	AD or AR	Thick ascending limb	Low BP, salt wasting, metabolic alkalosis
Metabolic syndrome	Mitochondrial transfer RNA	Maternal	?	Hypertension, hypercholesterolemia, hypomagnesemia
Pseudohypoaldosteronism type 2 (PHA2) or Gordon syndrome	WNK1 and WNK4 serine-threonine kinases	AD	DCT and collecting duct	Hypertension, increased K, metabolic acidosis

ACTH, Adrenocorticotropic hormone; *AD,* autosomal dominant; *AR,* autosomal recessive; *BP,* blood pressure; *DCT,* distal convoluted tubule; *ENaC,* epithelial sodium channel; *MR,* mineralocorticoid receptor; *WNK,* "with no lysine" kinase.

WHAT INITIATES THE RENAL INFLAMMATORY RESPONSE?

Several potential mechanisms have been proposed to initiate the renal immune response. Experimentally, one can induce persistent hypertension by inducing vasoconstriction and ischemia to the kidneys that results in local inflammation, such as by transient exposure to Ang II. This could potentially explain why risk factors for hypertension include substances that can induce renal vasoconstriction, such as oxidative stress, endothelial dysfunction, and overactivation of the SNS. Hyperuricemia is also a strong epidemiologic risk factor for hypertension and experimentally induces renal vasoconstriction and ischemia. Similarly, diets high in fructose-containing sugars are also associated with hypertension in humans and can induce hypertension and renal inflammation in vivo. More recently, high-salt diets themselves have been shown to directly induce activation of the immune system through a hyperosmolarity-dependent mechanism.

How Does Sodium Retention Lead to Hypertension?

The two primary hypotheses are that sodium retention may lead to hypertension either as a consequence of volume expansion or as a response to hypertonicity. Most of the recent literature suggests that hypertonicity may play a major role.[16,17]

Salt-induced hypertonicity also can activate the central nervous system (CNS) SNS, induce vasopressin release, and increase BP in mice. A possible explanation is that, in the setting of tubulointerstitial injury and intrarenal ischemia, the salt load triggers an intense renal afferent SNS activity that stimulates CNS sympathetic output. Alternatively there is some evidence that elevated CNS Na concentrations may mediate the effect.[16] Important work by Titze's group[17] suggests that sodium-induced hypertonicity may induce sodium compartmentalization to the interstitium. In particular, the skin can act as a subcutaneous reservoir for sodium in the form of sodium proteoglycans that is mediated by salt-induced hypertonicity with activation of local macrophages to release vascular endothelial growth factor C which stimulates lymphangiogenesis. The increase of lymph capillaries attenuates the hemodynamic effects of sodium retention. In these tissues the macrophages have an antihypertensive effect because depletion of the mononuclear phagocyte system blocks lymphangiogenesis and induces salt-sensitive hypertension (Box 34.1).

BOX 34.1 **Mechanisms That Can Trigger Salt-Sensitive Hypertension in Experimental Animals Through Induction of Microvascular Injury and Interstitial Inflammation**

- Angiotensin II infusion
- Inhibition of nitric oxide synthesis (treatment with L-NAME)
- Catecholamine infusion
- Diet-induced hypokalemia
- Hyperuricemia induced by uricase inhibition
- Reduced nephron number through maternal malnutrition
- Induction of nephrotic syndrome with use of bovine serum albumin
- Page kidney
- Lead-induced hypertension
- Cyclosporine nephropathy
- Genetic models of hypertension (Dahl salt-sensitive rat, spontaneously hypertensive rat)

The role of volume expansion in the increment in BP appears to involve the release of circulating endogenous cardiotonic steroids, which function as Na^+,K^+-ATPase inhibitors. For example, ouabain is a digitalis-like factor that is released from the hypothalamus, hippocampus, and pituitary and stimulates the SNS, and marinobufagenin is a digitalis-like factor released from the adrenal cortex. These factors block Na^+,K^+-ATPase in the kidney, thereby facilitating the excretion of sodium, but at the expense of also blocking Na^+,K^+-ATPase in the vascular smooth muscle, resulting in increased intracellular calcium with vascular smooth muscle contraction and systemic vasoconstriction.[16] Circulating nitric oxide synthase (NOS) inhibitors are also present in some patients with primary hypertension. The increase in systemic vascular resistance also may be amplified by the loss of systemic capillaries (microvascular rarefaction) that occurs in this condition.

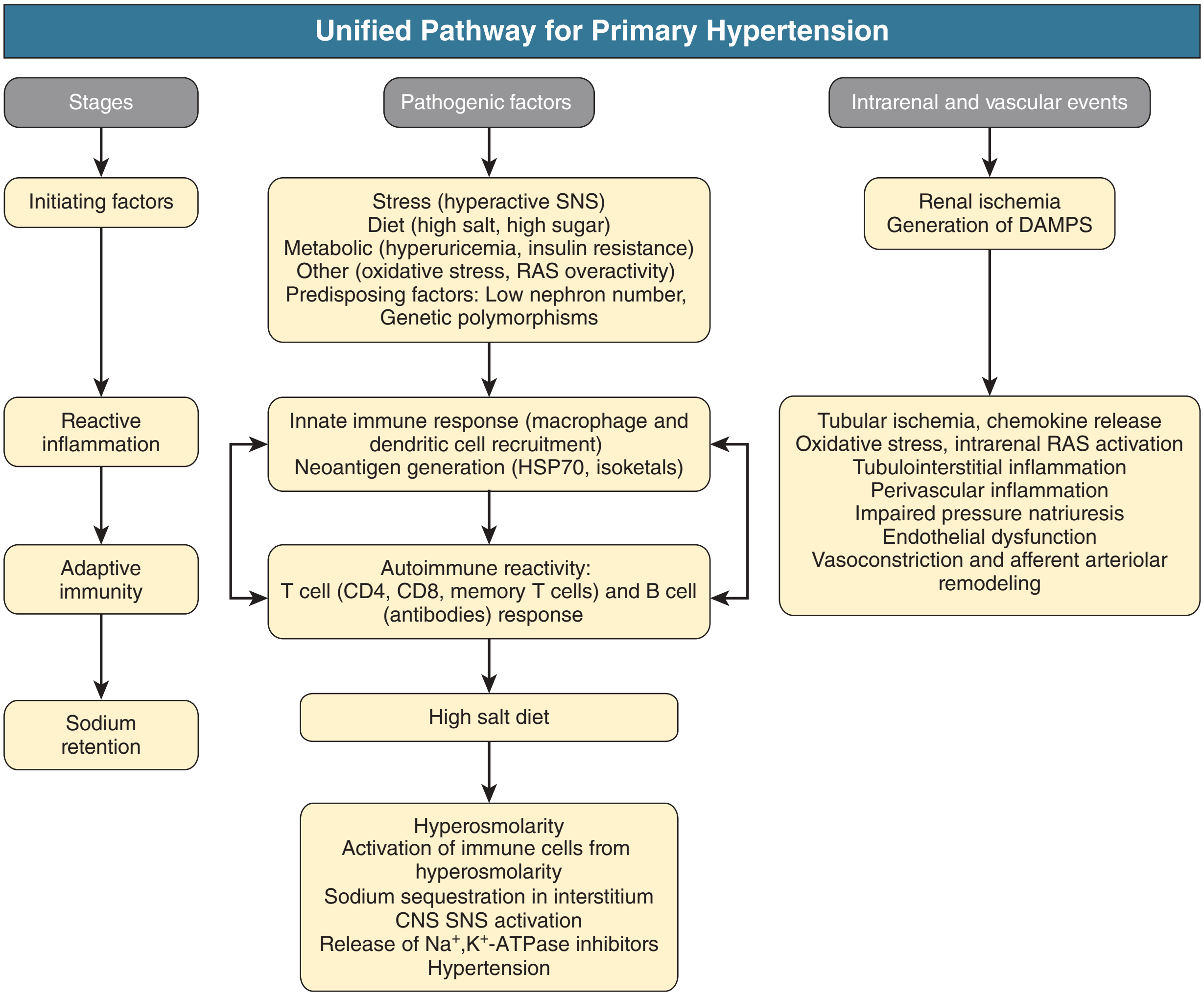
Unified Pathway for Primary Hypertension
Stages
Pathogenic factors
Intrarenal and vascular events
Initiating factors
Stress (hyperactive SNS)
Diet (high salt, high sugar)
Metabolic (hyperuricemia, insulin resistance)
Other (oxidative stress, RAS overactivity)
Predisposing factors: Low nephron number, Genetic polymorphisms
Renal ischemia
Generation of DAMPS
Reactive inflammation
Innate immune response (macrophage and dendritic cell recruitment)
Neoantigen generation (HSP70, isoketals)
Tubular ischemia, chemokine release
Oxidative stress, intrarenal RAS activation
Tubulointerstitial inflammation
Perivascular inflammation
Impaired pressure natriuresis
Endothelial dysfunction
Vasoconstriction and afferent arteriolar remodeling
Adaptive immunity
Autoimmune reactivity:
T cell (CD4, CD8, memory T cells) and B cell (antibodies) response
Sodium retention
High salt diet
Hyperosmolarity
Activation of immune cells from hyperosmolarity
Sodium sequestration in interstitium
CNS SNS activation
Release of Na⁺,K⁺-ATPase inhibitors
Hypertension

Fig. 34.3 Unified pathway for primary hypertension. *CNS,* Central nervous system; *DAMPS,* damage-associated molecular patterns; *HSP70,* heat shock protein 70; *RAS,* renin-angiotensin system; *SNS,* sympathetic nervous system.

Pathogenic Mechanisms Driving the Current Epidemic of Hypertension

As discussed under Epidemiology, there has been a marked rise in the prevalence of hypertension in the last century. The rise in hypertension corresponds with the introduction of Western diet and lifestyle and with the dramatic increase in obesity. Obesity may cause hypertension through multiple mechanisms, including subtle renal injury, effects of hyperleptinemia or hyperinsulinemia, hyperuricemia, coexistence of endothelial dysfunction, and activation of the SNS.[18] Chronically elevated leptin levels, which are common in obese persons, can activate the SNS in the CNS through pro-opiomelanocortin neurons that activate melanocortin-4 receptors.[19]

Another proposed mechanism is an elevated uric acid level, possibly driven by intake of fructose-containing sugars. Experimental studies have reported that elevated uric acid can mediate hypertension in association with the development of subtle renal injury, and small clinical trials have reported a benefit on BP of reducing uric acid in adolescents with either prehypertension or primary hypertension.[20] Some studies also have implicated a hyperactive SNS in early hypertension, particularly in young or borderline hypertensive patients.[21] Postulated mechanisms include a defect in baroreceptor sensitivity and an increase in SNS response to emotional or work-related stress. Activation of either the systemic or the local renin-angiotensin system (RAS) is also common in hypertension. Whereas plasma renin activity is elevated in 20% of patients, renin activity is either normal (50%) or low (30%) in the majority. However, normal renin activity may be inappropriately high in relation to the total body sodium.

In addition, some hypertensive patients have elevated plasma aldosterone, especially if the RAS is inhibited with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), known as *aldosterone breakthrough.*[22] Typically, such patients are obese and have hyperinsulinemia or some degree of endothelial dysfunction. Their aldosteronism is driven by a mechanism other than Ang II or hyperkalemia.

A proposed schema for the pathogenesis of hypertension is shown in Fig. 34.3.

EPIDEMIOLOGY

Primary hypertension is epidemic. In the United States, the prevalence has increased steadily since the early 1900s and has leveled in the last few years[23] (Fig. 34.4). Although some of the increase in hypertension reflects an increasingly aging population, there is also an increase in primary hypertension in the pediatric population. The increase in

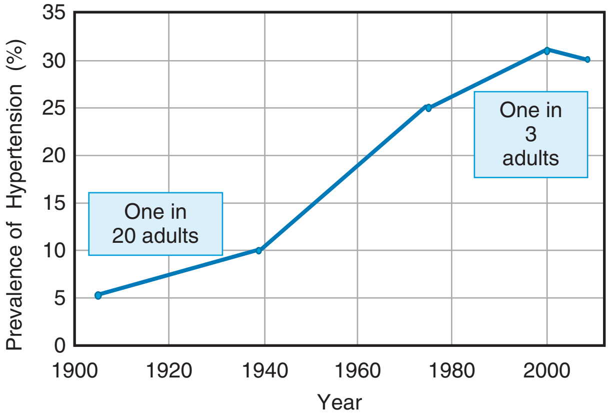

Fig. 34.4 Epidemic of hypertension. The prevalence of primary hypertension (defined as BP >140/90 mm Hg) in the United States increased from 11% in 1939 to 31% in 2008, leveling to 29% of the population in 2012.

TABLE 34.3 Major Risk Factors for Primary Hypertension

Genetic	Family history Polymorphisms (adducin, endothelial nitric oxide synthase, angiotensinogen, β_2-adrenoceptor, human G protein β3 subunit)
Congenital	Low birth weight, low nephron number, maternal hypertension, maternal preeclampsia, maternal malnutrition
Physical	Obesity, older age, African American, African Caribbean, some Bantu-speaking peoples in Africa, increased heart rate (>83 beats/min), increased emotional stress
Diet/toxin	Increased sodium intake, low potassium intake, low dairy products intake, heavy alcohol intake, high intake of added sugars, low level lead or cadmium intoxication
Metabolic*	Elevated serum uric acid, insulin resistance, elevated hematocrit
Other	Low socioeconomic status, urban versus rural

*Laboratory-based parameters.

hypertension correlates with increasing frequency of obesity, type 2 diabetes, and chronic kidney disease (CKD), suggesting a strong interrelationship.

Of risk factors for hypertension, family history is very important (Table 34.3). One major risk factor is age, and by 80 years of age, 90% of individuals are likely to be hypertensive.[24] This age-related increase in prevalence of hypertension has been observed in most Western countries but has not been uniformly observed in all populations. Second, hypertension is more common in men, although the prevalence in women is similar to and slightly exceeds that of men after age 55. Certain racial groups are at increased risk for developing hypertension much earlier in life, particularly African Americans and Filipino Americans in the United States and various minority populations throughout the world (e.g., Australian aborigines and Maoris). Risk factors for hypertension include strong family history, obesity, insulin resistance, hyperuricemia and/or gout, sleep disorders including sleep apnea, and persistent high-stress living environments either at work or home. Certain physical features, such as elevated heart rate or an increased BP response to exercise, are also predictive, as is elevated hematocrit.

Genetic factors also contribute, as discussed earlier. Although the inheritance patterns do not follow Mendelian genetics for a single gene locus, evidence suggests that 20% to 30% of hypertension may have a genetic basis, because of the cumulative effect of multiple susceptibility genes (the polygene hypothesis). A recent genome-wide association screen found 29 polymorphisms that could account for approximately 13% of primary hypertension, with several of the polymorphisms linked with natriuretic peptide and NO signaling.[25] Others have noted polymorphisms involving immune system and oxidative stress mechanisms (HSP-70 variants, xanthine oxidase, and extracellular superoxide dismutase), vasoactive mediators (angiotensinogen, endothelial NOS, prostacyclin synthase, β_2-adrenoceptor, 20-HETE synthase [*CYP4F2* gene], G protein β3), mediators of vascular smooth muscle tone (calcium-dependent potassium channel, *KCNMA*), or mediators controlling renal sodium transport (α-adducin and 11β-hydroxysteroid dehydrogenase type 2, aldosterone synthase, "with no lysine" kinase [WNK] kinases).

Hypertension is more likely to occur if the mother has a history of hypertension, obesity, preeclampsia, or malnutrition. These risk factors are all associated with intrauterine growth restriction and LBW, both of which predispose to future hypertension, as well as diabetes and obesity.

Dietary and other environmental factors may contribute to the risk for hypertension. Obesity, with or without features of insulin resistance and metabolic syndrome, is a major risk factor for hypertension and parallels the rise in hypertension in these countries. Epidemiologic and interventional studies have linked salt intake and low potassium intake with persistent BP elevation, leading to earlier development of hypertension, and although the relationship is best demonstrated in older patients and in African Americans, it is true across the world. Increasing potassium intake lowers BP in both experimental and human studies. More recently, intake of added sugars (e.g., sucrose, high-fructose corn syrup) has been found to predict higher BP. Certain toxins, most notably low-level lead and cadmium intoxication, are also associated with increased frequency of hypertension.

CLINICAL MANIFESTATIONS

Evaluation of a patient with hypertension requires a careful history and physical examination, an evaluation of risk factors for hypertension, a search for potential secondary causes, and an evaluation for end-organ damage.

BP should be measured on at least three occasions to confirm persistent hypertension using the techniques described in Chapter 33. Home BP monitoring or 24-hour ambulatory BP monitoring is recommended to determine if the hypertension occurs only in the physician's office (white coat hypertension) and rarely to identify masked hypertension, in which BP elevations occur only outside the physician's office. White coat and masked hypertension can be associated with end-organ disease, including left ventricular hypertrophy (LVH) and microalbuminuria; diagnosis should be followed by assessment of CV risk factors and frequent reevaluation of BP.

The history should investigate the onset and duration of hypertension and the presence of a family history of hypertension or cardiorenal disease. The history should identify risk factors for hypertension (obesity, diabetes, physical activity, gout, alcohol, smoking, diet, emotional or work-related stress, over-the-counter and prescribed medications) and any hypertension-related morbidity. Hypertension is often asymptomatic, but studies have found that even childhood-associated hypertension can be associated with impaired memory and mental performance, and hypertension remains a major risk factor for vascular dementia. Good BP control improves mental performance and decreases the risk for developing dementia.[26] Hypertension, especially stage 2 (see Table 34.1),

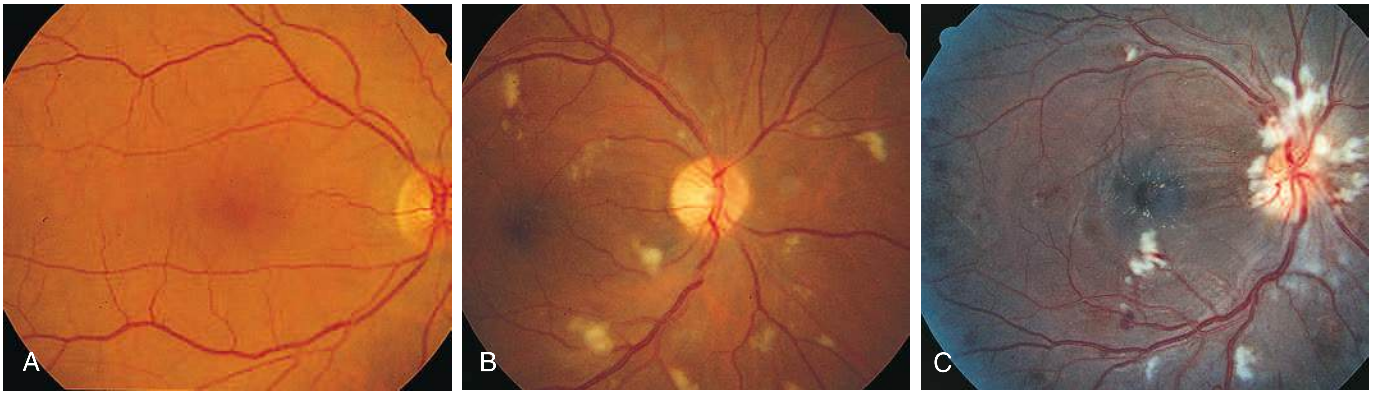

Fig. 34.5 **Different grades of hypertensive retinopathy.** (A) Mild hypertensive retinopathy, with arteriolar narrowing and arteriovenous nicking. (B) Moderate hypertensive retinopathy, with cotton-wool spots (nerve fiber layer infarcts) and arteriovenous nicking. (C) Papilledema, cotton-wool spots, macular yellow exudates (star formation pattern), and retinal hemorrhages in a subject with hypertensive emergency. (Provided by J. Kinyoun, University of Washington.)

also may be associated with headache, classically occipital and pulsatile. In hypertensive emergency, encephalopathy may rarely occur, with an acute decline in mental status and seizures. In addition, rarely, patients may lose vision from papilledema. Stage 2 hypertension also places individuals at acute risk for myocardial infarction (MI), congestive heart failure (CHF) with pulmonary edema, aortic dissection, cerebrovascular accident (stroke), and renal failure.

Physical examination includes BP measurement in both arms and a careful cardiac examination. Attention should be focused on both the large vessels (by both palpation and listening for bruits) and the retina to grade the severity of disease in the microvasculature (Fig. 34.5). Laboratory tests should include hematocrit, electrolytes, creatinine (and estimated GFR), calcium and phosphate (to look for primary hyperparathyroidism), fasting lipid profile (cholesterol and triglycerides), uric acid, and urinalysis. A chest x-ray film and electrocardiogram should be performed to assess cardiac size and look for aortic dilation.

Additional tests include assessment of 24-hour urine sodium and potassium excretion. Urinary Na^+ and K^+ excretion correlates with intake if the patient is in steady state (desirable values are <100 mmol/l Na^+ and >100 mmol/l K^+ in 24 hours). A spot urine albumin-creatinine and an echocardiogram may uncover additional evidence of end-organ damage (Fig. 34.6). Note that a spot urine albumin-creatinine is recommended only for those with diabetes or stage 2 or higher CKD. Echocardiography is not recommended for routine use in patients with hypertension because of its cost, although appropriate for those with cardiac problems.

PATHOLOGY

Primary hypertension is characterized by disease of the preglomerular arterial vessels, primarily the afferent arteriole and interlobular artery. The classic lesion, seen in 90% of patients, is arteriolosclerosis, in which smooth muscle cells of the media in the afferent arteriole are replaced by connective tissue[10] (Fig. 34.7). Often, hyaline material (plasma proteins) accumulates in the subintima (hyalinosis). In addition to the arteriolar disease, there is often evidence of glomerular and tubulointerstitial ischemia with shrinkage of the glomerular tuft, tubular atrophy, and interstitial fibrosis. Occasionally, glomerulosclerosis and severe tubulointerstitial injury are seen. In cases of hypertensive emergency, a proliferative arteriolopathy occurs, occasionally with fibrinoid necrosis. Concentric layers of connective tissue and cells may give an onion-skin appearance to the intima, which may progress to a total obliteration of the lumen.

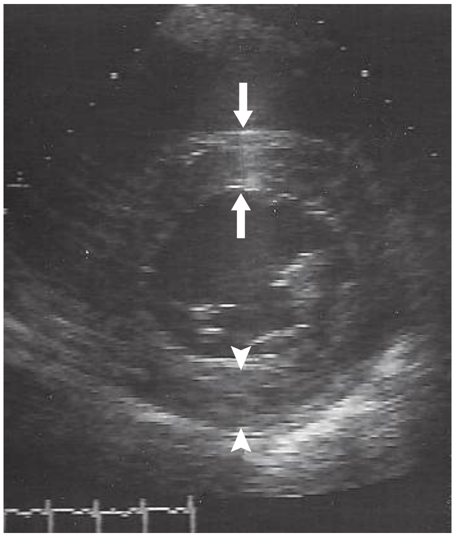

Fig. 34.6 **Echocardiogram showing concentric left ventricular hypertrophy.** Septal thickness *(between large arrows)* and posterior wall thickness *(between arrowheads)* are increased (to 16 mm) in a patient with primary hypertension (normal is 11 mm or less). (Provided by A. Pearlman, University of Washington.)

DIAGNOSIS

The diagnosis of primary hypertension requires the elimination of secondary causes, of which the more common include medications (nonsteroidal antiinflammatory drugs, corticosteroids, sympathomimetics, oral contraceptives), recreational drugs (excessive alcohol intake, cocaine), intrinsic renal parenchymal disease, renovascular disease, and primary aldosteronism from adrenal hyperplasia or tumors. Table 33.10 provides a more complete list along with the recommended evaluation for secondary causes.

NATURAL HISTORY

The major long-term risk of hypertension is cardiovascular disease (CVD), which can be separated into pressure-related (stroke, CHF), atherosclerotic (MI), and renal (CKD) causes. Hypertension is the most common cause of stroke and CHF, and the risk increases linearly with BP[27] (Fig. 34.8).

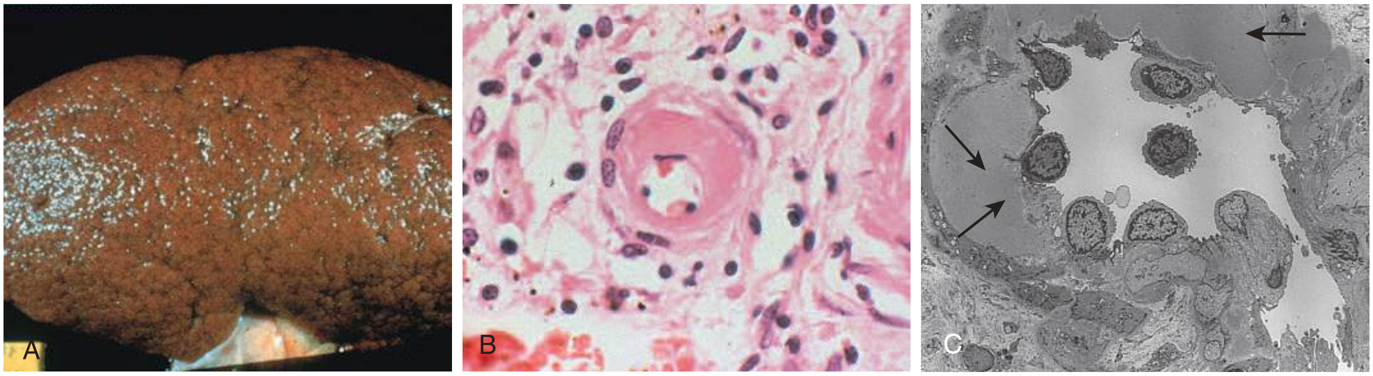

Fig. 34.7 **Renal pathology in primary hypertension.** (A) A granular pitted kidney in a subject with chronic primary hypertension. (B) Arteriolosclerosis with subintimal hyalinosis. (C) Electron micrograph showing hyalinosis with the accumulation of insudative plasma proteins in the subendothelium of an arteriole. (**A,** Gift courtesy Harvard Medical School; **B** and **C,** Courtesy C. E. Alpers, University of Washington.)

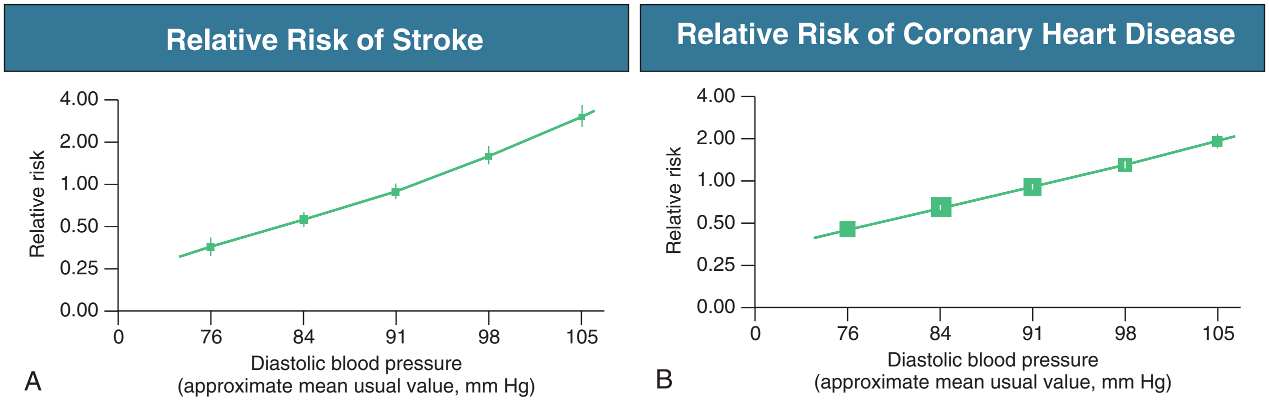

Fig. 34.8 **Relative risk for stroke and coronary heart disease increases with increased diastolic blood pressure.** (A) Cerebrovascular accident (stroke) data are from seven prospective observational studies and 843 events. (B) Coronary heart disease data are from nine studies and 4856 events. Size of *squares* is proportional to the number of events in each category; *vertical lines* indicate 95% confidence intervals. (Modified from reference 27.)

Other rarer pressure-related morbidities include aortic dissection and cerebral and aortic aneurysms. Increased systolic, diastolic, and pulse pressure all confer risk, although the SBP and the pulse pressure (in particular when associated with low DBP) are the more important determinants of risk for the pressure-related morbidities. This increased risk depends on age (increases with age), gender (greater in males), ethnic origin (greater in African Americans), and other conditions (especially diabetes).

Cardiac consequences of poor hypertension control begin with concentric LVH associated with supernormal systolic function. Over time, impaired diastolic dysfunction may occur, as manifested by slow diastolic filling, which reflects decreased diastolic relaxation. This may progress to CHF. Almost 90% of patients with CHF have a history of hypertension.

Hypertension also confers risk for atherosclerotic-associated morbidities, including coronary heart disease,[27] peripheral vascular disease, and carotid atherosclerosis with or without cerebral emboli. In addition to an increased prevalence of hypertension, African Americans also have a 50% greater risk for heart disease.

Kidney Disease

Most patients with newly diagnosed primary hypertension have normal renal function, stage 1 CKD (GFR >90 ml/min/1.73 m^2 with microalbuminuria) or stage 2 CKD (GFR 60 to 90 ml/min/1.73 m^2) with elevated renal vascular resistance.[28] Despite relatively normal renal function, renal biopsy, if done, usually shows arteriolosclerosis and hyalinosis (see Fig. 34.7).

Before use of effective antihypertensive agents, proteinuria developed in up to 40% of hypertensive patients and as many as 18% developed renal impairment over time. Microalbuminuria, which is a marker of vascular disease and CV risk, occurs in 15% to 30% of patients, whereas non-nephrotic proteinuria is uncommon and nephrotic-range proteinuria is rare.[29] Microalbuminuria is associated with salt-sensitive hypertension, the loss of nocturnal dipping in BP, and increased target organ damage, especially LVH. Elevations in serum creatinine develop in 10% to 20% of patients with poorly controlled BP, and the risk is greater in African Americans, elderly persons, patients with hyperuricemia, and those with higher SBP (>160 mm Hg).[30,31] In 2% to 5% of those with poorly controlled SBP (>160), progression to renal failure will occur over the subsequent 10 to 15 years (Figs. 34.9 and 34.10). Despite the relative infrequency for hypertension to progress to end-stage renal disease (ESRD), hypertension is recorded as the second most common cause of ESRD after diabetes in the United States and Europe. Furthermore, almost all patients with diabetes have hypertension when they start dialysis.

The incidence of ESRD in African Americans with hypertension is fourfold to sixfold greater than in Whites.[31,32] Renal biopsies of African

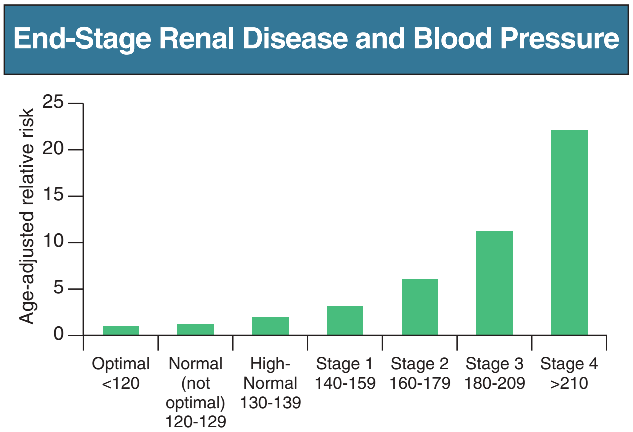

Fig. 34.9 **End-stage renal disease and blood pressure.** Incidence of end-stage renal disease related to baseline blood pressure in the MRFIT study. Blood pressure stages were based on definitions at that time. Mean follow-up was 16 years. (From reference 30.)

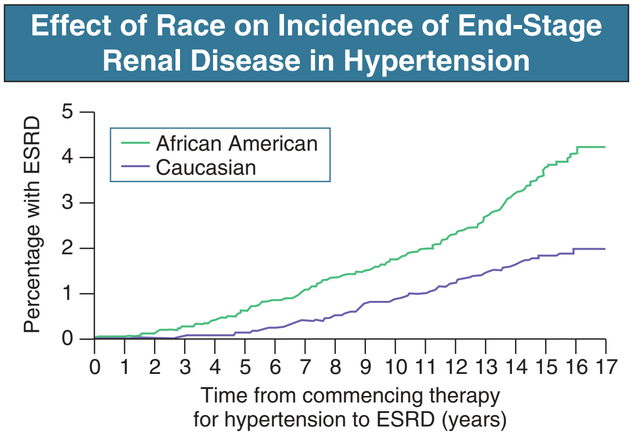

Fig. 34.10 **Effect of race on incidence of end-stage renal disease in hypertensive patients.** The cumulative incidence of end-stage renal disease *(ESRD)* in African American and White hypertensive veterans (Kaplan-Meier estimates). (From reference 31.)

Americans with hypertension show more severe hypertensive injury, with more prominent vascular changes and increased frequency of segmental and global glomerulosclerosis. Although some of these vascular changes may relate to the presence of certain transforming growth factor-β (TGF-β) polymorphisms or the higher uric acid levels that are common in this population, recent studies suggest that the increased frequency of glomerulosclerosis may be caused by a polymorphism in apolipoprotein L1 (APOL1), the product of which is expressed in the podocyte.[33] The mechanism by which *APOL1* polymorphisms increase the risk for progression of renal disease is unclear but may relate to effects on the podocyte or on the microvasculature.

Effect of Antihypertensive Therapy on Natural History of Hypertensive Cardiovascular Disease and Kidney Disease Progression

The specific pharmacologic approach to treatment of hypertension is discussed in Chapter 36, whereas the effect of antihypertensive therapy on CV and renal outcomes is discussed here. As of 2012, only 71% of patients with hypertension in the United States are receiving treatment and only 48% have their BP under adequate (<140/90 mm Hg) control.[34]

TABLE 34.4 Meta-Analysis of Effect of Antihypertensive Agents on Cardiovascular Outcomes in Hypertensive Patients

Outcome	No. of Trials	Effects Model	RR (95% CI)	P Value for Heterogeneity
Coronary heart disease	24	Fixed	0.86 (0.80-0.93)	.55
		Random	0.87 (0.80-0.94)	.55
Stroke	23	Fixed	0.69 (0.64-0.74)	.004
		Random	0.68 (0.61-0.76)	.004
CHF	7	Fixed	0.54 (0.45-0.66)	.66
		Random	0.60 (0.49-0.74)	.80
Major CVD events	28	Fixed	0.78 (0.74-0.81)	<.001
		Random	0.73 (0.62-0.87)	<.001
CVD mortality	23	Fixed	0.84 (0.78-0.90)	.10
		Random	0.84 (0.78-0.90)	.10
Total mortality	25	Fixed	0.90 (0.85-0.95)	.58
		Random	0.90 (0.85-0.95)	.59

From reference 35.
CHF, Congestive heart failure; *CI,* confidence interval; *CVD,* cardiovascular disease; *RR,* relative risk.
Analysis was based on 42 clinical trials that included 192,478 patients randomized to seven major treatment strategies, including placebo.

Although age-adjusted mortality for stroke and coronary artery disease has been significantly reduced since the early 1980s as a result of better BP control (and better treatment of other risk factors such as hyperlipidemia), heart disease and stroke remain the first and third leading causes of death in Western countries. This emphasizes the importance of identifying and treating patients with hypertension.

Antihypertensive therapy reduces stroke, heart failure, and CV complications in patients with hypertension, although historically there were fewer data to support benefit for stage 1 hypertension (see Table 34.4).[35] Recently, the Systolic blood PRessure INTervention (SPRINT) trial documented significant reduction in CV events and mortality in nondiabetic hypertensive subjects in whom SBP was targeted to 120 mm Hg systolic compared with 140 mm Hg in the group with standard treatment.[36] A consequence of the more intensive treatment was a higher risk for complications, including hypotension, syncope, and acute kidney injury. The SPRINT trial is consistent with other studies suggesting the best overall BP control has the best outcome.[37] One exception comes from the recent ACCOMPLISH trial, in which both groups had similar BP control, but the group initially randomized to an ACE inhibitor with a calcium antagonist had a 20% CV risk reduction compared with the ACE inhibitor plus diuretic group.[38] Note that almost all people with some level of kidney disease will require two or more medications.

The effect of antihypertensive therapy on the progression of renal disease secondary to hypertension is more controversial. In subjects with CKD the use of diuretics (e.g., chlorthalidone) is commonly needed and provides greater initial reductions in BP than most antihypertensive agents, although they are not considered agents of first choice for treatment of primary hypertension by any except U.S. guidelines. In the Multiple Risk Factor Intervention Trial (MRFIT), in which diuretics and β-blockers were primarily used to control BP, slowing or stabilization of renal function was not seen in African American men, but was seen in all other racial groups studied.[39] In the African American Study of Kidney Disease, use of an ACE inhibitor (ramipril) was more effective at slowing CKD progression than either the dihydropyridine calcium channel blocker amlodipine (Fig. 34.11) or metoprolol.[40,41] However, both studies, as well

Ramipril Is Superior to Amlodipine in Reducing Renal Events in Hypertensive African Americans with Renal Impairment

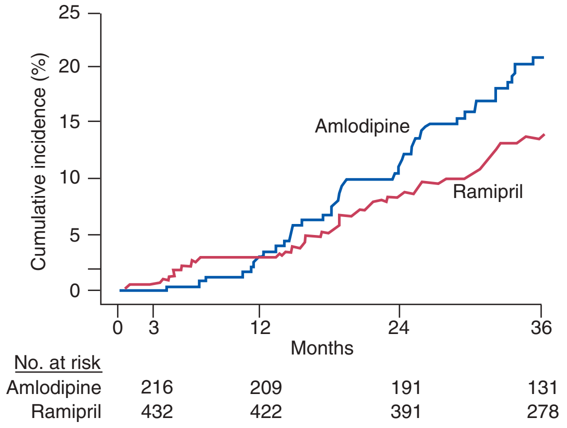

Fig. 34.11 **Ramipril is superior to amlodipine in reducing renal events in hypertensive African Americans with mild to moderate renal impairment.** The angiotensin-converting enzyme (ACE) inhibitor ramipril resulted in fewer renal end-points (proteinuria, decline in renal function, ESRD, death) compared with the dihydropyridine calcium channel blocker amlodipine, in the African American Study of Kidney Disease. (From reference 41.)

as the recent SPRINT study, failed to show superior protection with tight BP control compared with conventional BP targets in patients with renal disease secondary to hypertension.[40,42] Masked hypertension may be a confounder to these results; a subanalysis of ambulatory BP showed inadequate 24-hour BP control in more than 70% of the cohort. Masked hypertension and nondipping (i.e., lack of BP decrease with sleep) were the two most common reasons for poor BP control.[43]

Further studies are being performed regarding the dosing and timing of antihypertensive treatment to evaluate changes in overall BP control. In contrast, post hoc analyses of trials show that patients with diabetic renal disease or proteinuric (>300 mg/day) renal disease, including that caused by hypertension, appear to benefit from lower BP goals in terms of renal protection. Based on current evidence, achieved BP levels should be less than 140 mm Hg systolic for nonproteinuric hypertensive renal disease and less than 130/80 mm Hg in those with diabetes and hypertension.[44] However, because all of the prospective randomized CKD outcome trials have failed to show a benefit, the updated Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a BP goal of less than 140/90 mm Hg in those with CKD, as backed with the highest level of evidence. The previous goal of less than 130/80 mm Hg in the presence of very high albuminuria (>300 mg/day) has a much lower level of evidence and is not endorsed.[45]

Some studies also suggest that thiazide diuretics are associated with worsening of renal function in patients with hypertension. In the European Working Party on High Blood Pressure in the Elderly trial, a significantly higher incidence of impaired renal function was found in those receiving diuretics than with placebo.[46] In the Systolic Hypertension in the Elderly trial, serum creatinine increased significantly in those treated with thiazide diuretics compared with placebo.[47] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the chlorthalidone-treated group showed statistically worse renal function than either the amlodipine or the lisinopril group, at both 2- and 4-year end-points.[48] This could likely be accounted for by volume depletion in many cases, but diuretics have been shown to induce mild renal injury in various animal models, possibly because of hypokalemia, hyperuricemia, and stimulation of the renin-angiotensin-aldosterone system (RAAS) related to decreased renal perfusion pressure.[49]

Can Primary Hypertension Spontaneously Remit?

In those under age 60, as many as 15% to 20% of patients with prehypertension may become normotensive spontaneously. Furthermore, in patients with established hypertension who have good BP control for 5 years under treatment, as many as 20% to 40% can be withdrawn from therapy successfully, especially if they have stage 1 hypertension and adhere to salt restriction and weight reduction. This suggests that the processes that mediate hypertension are at times reversible.

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SELF-ASSESSMENT QUESTIONS

1. Primary hypertension is characterized by all of the following except:
   - **A.** Primary hypertension is more common in older patients.
   - **B.** Salt sensitivity is less common in older patients.
   - **C.** Primary hypertension is associated with a reduction in renal blood flow and usually mild reduction in glomerular filtration rate (GFR).
   - **D.** Primary hypertension is more common in individuals with low birth weight and low nephron number
   - **E.** The presence of the APOL1 polymorphism is associated with more rapid progression of kidney disease in hypertensive African American subjects.
2. The renal pathology in patients with primary hypertension may consist of all of the following except which feature?
   - **A.** Arteriolosclerosis with arteriolar fibrosis or hyalinosis.
   - **B.** Evidence of tubular ischemia change is commonly present.
   - **C.** Glomerulosclerosis may be present, especially in African Americans.
   - **D.** Renal histologic studies can rarely appear normal.
   - **E.** Transmural necrosis of medium-sized vessels can occasionally be observed.
3. Which of the following is not a dietary risk factor for primary hypertension?
   - **A.** Sodium
   - **B.** Potassium
   - **C.** Sugar
   - **D.** Alcohol
   - **E.** Coffee

35

Nonpharmacologic Prevention and Treatment of Hypertension

Brian Rayner, Karen E. Charlton, Wayne Derman

Lifestyle changes, including a combination of increased fat and refined carbohydrate intake and reduced physical activity, have resulted in a worldwide epidemic of obesity, type 2 diabetes mellitus, and hypertension that is most pronounced in underserved and indigenous populations. Adoption of healthy lifestyles is critical preventing and managing high blood pressure (BP). According to the American Society of Hypertension (ASH) and International Society of Hypertension (ISH) Practice Guidelines, lifestyle interventions lower BP, enhance efficacy of antihypertensive medication, and lower overall cardiovascular (CV) risk.[1] The lifestyle changes that are widely agreed to lower BP and CV risk are (1) smoking cessation, (2) weight reduction, (3) moderation of alcohol intake, (4) physical exercise, (5) reduction of salt intake, (6) increase in fruit and vegetable intake, and (7) decrease in saturated and total fat intake. Interventions may have efficacy similar to that of single-drug therapy (Table 35.1). However, lifestyle changes should not delay the initiation of drug therapy in patients at higher CV risk.

PREVENTION

The importance of primary prevention has been underscored by the recognition that hypertension is common, treatment is lifelong, the control of BP in hypertensive individuals does not restore CV risk to normal, and the majority of hypertensive individuals do not reach goal BP readings. The most important individuals to target are those with *prehypertension* (defined by JNC 7 as 120-139/80-89 mm Hg).[2] Those with prehypertension have increased prevalence of early vascular damage, increased risk for incident hypertension, and increased risk for CV events compared with those who have optimal BP levels (<120/80 mm Hg).[3] The World Health Organization (WHO) Global NCD (Non-Communicable Disease) Alliance Action Plan advocates the following voluntary global targets for country member states: 10% reduction in harmful use of alcohol, 10% reduction in insufficient physical activity, 30% reduction in mean population intake of salt, and 30% reduction in current tobacco use. Up to 80% of cardiovascular disease (CVD) can be prevented through lifestyle measures that include maintenance of healthy weight, adequate physical activity, a healthy diet, and avoidance of tobacco.[4] These targets align with *The Lancet's* Commission on Hypertension (2016) that identifies key actions to prevent elevated BP, at both the population and individual level.[5] A life course approach is recommended, which focuses on early lifetime programming. Exposure to CV risk factors in early childhood have been shown to promote adverse vascular damage in early adulthood and increase the trajectory of vascular ageing.[6]

WEIGHT LOSS

Obesity is epidemic throughout the world, and, for example, 65% of the adult population in the United States is either overweight, with a body mass index (BMI) of 25.0 to 29.9 kg/m^2, or obese, with BMI of ≥30 or higher. Obese individuals have a threefold increased prevalence of hypertension. Possible mechanisms for obesity-induced hypertension include overactivity of the sympathetic nervous system (SNS), hyperinsulinemia (which may increase renal sodium reabsorption), increased leptin, hyperuricemia, activation of the renin-angiotensin system, and sleep apnea. Abdominal or visceral obesity is a greater predictor of both hypertension and CV risk than other types of body fat distribution. *Abdominal obesity* is defined as a waist circumference greater than 88 cm (>35 inches) in women and greater than 102 cm (>40 inches) in men. These reference values were developed in White populations and may need to be modified for other ethnic groups.

In obese hypertensive patients or those with high-normal BP, weight loss of as little as 4 to 5 kg (~9 to 11 lb) is often associated with a significant reduction in BP. A meta-analysis has demonstrated that a weight reduction of 5.1 kg reduced systolic BP (SBP) by 4.4 mm Hg and diastolic BP (DBP) by 3.6 mm Hg.[7] A rule of thumb is that for every kilogram lost, there is a reduction of 1 mm Hg in both SBP and DBP. To minimize the risk for relapse and maintain sustainability of the weight loss program, the initial target should be 5% to 10% of current weight, or 1 to 2 BMI units. Marked oscillations in weight should be avoided because this increases the risk for development of hypertension in obese, normotensive persons.[8] A randomized trial of the effectiveness of four popular diets on sustained weight loss and CV disease risk reduction concluded that a variety of diets can similarly reduce weight and BP, but only a minority of individuals can sustain high dietary adherence.[9]

Very-low-carbohydrate weight-loss diets, such as the Atkins Diet and others with a carbohydrate content below 20% of energy, are not recommended because they result in a greater increase in low density lipoprotein cholesterol, despite resulting in a greater weight loss over the short term, as compared with a low-fat diet.[10] The Pan-European Diet and Obesity, and Genes (DiOGenes) study found that BP reduction after weight loss is better maintained when the intake of protein is increased at the expense of carbohydrates, to around 23% to 28% energy from protein, as compared with lower protein intakes of between 10% and 15% energy.[11]

Weight reduction should be accompanied by recommendations to increase physical activity unless it is contraindicated. Bariatric surgery

TABLE 35.1 Lifestyle Modifications for Prevention and Management of Hypertension (JNC 7)

Modification	Recommendation	Average Systolic BP Reduction Range Achieved With Intervention*
Weight reduction	Maintain normal body weight (BMI = 18.5-24.9 kg/m^2)	5-20 mm Hg/10 kg
DASH eating plan	Adopt a diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat	8-14 mm Hg
Dietary sodium restriction	Reduce dietary sodium intake to 100 mmol/day (2.4 g sodium or 6 g sodium chloride)	2-8 mm Hg
Aerobic physical activity	Regular aerobic physical activity (e.g., brisk walking) at least 30 min/day, most days of the week	4-9 mm Hg
Moderation of alcohol consumption	Men: Limit to 2 drinks† per day; women and lighter weight persons: limit to 1 drink per day	2-4 mm Hg

Modified from reference 2.
*Effects are dose and time dependent.
†One drink = ½ oz or 15 ml ethanol (e.g., 12 oz [360 ml] beer, 5 oz [150 ml] wine, 1.5 oz [45 ml] 80-proof whiskey).
BMI, Body mass index; *BP,* blood pressure; *DASH,* Dietary Approaches to Stop Hypertension.

and pharmacologic interventions for weight loss (e.g., orlistat) may be useful to achieve weight loss in some patients, but always as an adjunct rather than a substitute for lifestyle modification.

PHYSICAL ACTIVITY

Physical inactivity may account for 5% to 13% of the risk for developing hypertension.[12] In addition, physical inactivity accounts for 5.5% to 25.1% of the population attributed risk for coronary heart disease.[13] Regular physical activity lowers all-cause morbidity and mortality and provides the basis for public health recommendations to exercise at least 30 minutes per day. A recent review reported that patients with high BP who participated in any level of physical activity had a reduced risk (by 16% to 67%) of CV mortality, whereas a greater than twofold increase in CV mortality risk was observed in nonactive individuals.[14]

Exercise Training Dose Response

In a meta-analysis of studies involving more than 1500 patients, exercise training in normotensive individuals has been shown to reduce SBP and DBP by 3.0 ± 1 and 1.7 ± 1 mm Hg, respectively.[15] However, in hypertensive patients, the effect of exercise training is even more marked. In a meta-analysis involving 27 randomized controlled trials (RCTs) and 1480 patients, aerobic activity was shown to reduce BP on average by 10.8 ± 4.7 mm Hg in hypertensive patients.[16] Studies in hypertensive patients have shown that the benefit of exercise on BP is maximal with 90 minutes of exercise per week, after which there was no further improvement.[17] Furthermore, only a modest amount of exercise was needed to reduce BP in patients with hypertension (>30 min/week). There is no consensus whether high intensity interval is superior to low-intensity continuous aerobic training on BP response.[18,19] Regular exercise prevents the development of left ventricular hypertrophy that is independent of BP in young patients with stage 1 hypertension.[20]

However, there is no benefit to increasing exercise intensity on BP reduction with exercise training, as long as intensity ranges between 40% and 70% of maximal, age-predicted heart rate.[15] Exercise of higher intensity (75% maximum) is associated with a more marked and prolonged reduction in postexercise BP in the postexercise window compared with lower intensity exercise (50% maximum).[21] Despite these promising results, a recent review highlights important limitations in the literature regarding the effects of exercise on BP. These include lower methodologic quality, selective reporting as to BP outcomes, and lack of including participants with hypertension.[22]

Mechanisms

The reduction in BP immediately after exercise has been linked to a sympathetic inhibition and increased release of vasodilator substances. The mechanisms by which exercise lowers BP over the longer term are less well understood, but possibilities include reductions in systemic vascular resistance secondary to neurohumoral and structural adaptations. It has been further suggested that physical inactivity negatively affects brain areas associated with sympathetic outflow. SNS overdrive is thought to account for more than 50% of all cases of hypertension, and a lack of balance between parasympathetic and sympathetic modulation has been observed in hypertensive subjects.[23] Chronic exercise is also associated with a loss of weight and a reduction of serum uric acid levels, both of which could reduce BP.

Antihypertensive Medication and Guidelines for Exercise

Box 35.1 provides exercise guidelines for patients with hypertension.[24] β-Blockers decrease exercise tolerance. β-Blockers and diuretics also may alter thermoregulation in hot environments and provoke hypoglycemia. Patients using these medications should be educated about exercising in the heat, clothing, adequate hydration, and methods to prevent hypoglycemia.[25] However, the use of β-blockers is not the first-line treatment for physically active hypertensive patients. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers may be better suited for patients who exercise frequently or athletes with hypertension.

For patients undergoing supervised exercise training, the monitoring of postexercise BP may be helpful so medications may be adjusted to avoid postexercise hypotension, especially with calcium channel blockers or in patients exercising in a hot environment.

DIET

Salt Intake

Epidemiologic studies demonstrate that the prevalence of hypertension is directly related to dietary salt intake in all societies in which Na intake is above 50 to 100 mmol/day (3 to 6 g salt or NaCl) (Fig. 35.1).[26] In societies in which daily intake is below that range, hypertension is rare. Salt intake also plays an important role in age-related increase in BP (Fig. 35.2).[27] Not all individuals respond similarly to high salt intake. "Salt sensitivity" describes a group of individuals who significantly decrease or increase their BP during periods of salt restriction or loading, respectively. Risk factors for salt sensitivity include Black ethnicity, older age, obesity, elderly people, patients with type 1 or 2 diabetes, treatment with calcineurin inhibitors, and patients with chronic kidney disease (CKD).

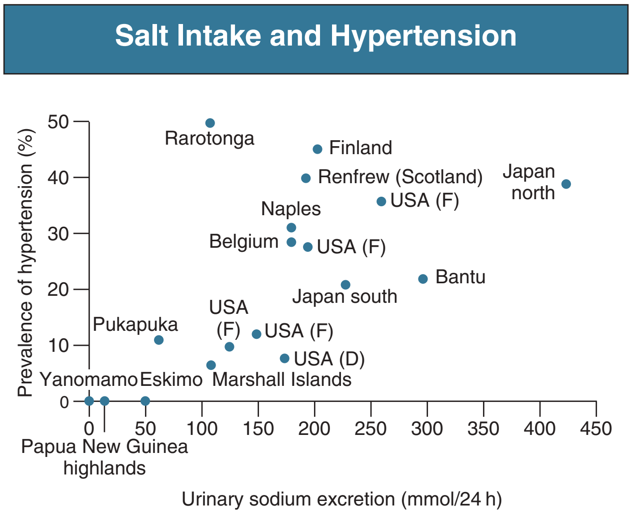

Fig. 35.1 **Relationship of salt intake with prevalence of hypertension in different populations.** *D,* Data from Dahl; *F,* data from Framingham study from different time periods. (Modified from reference 26.)

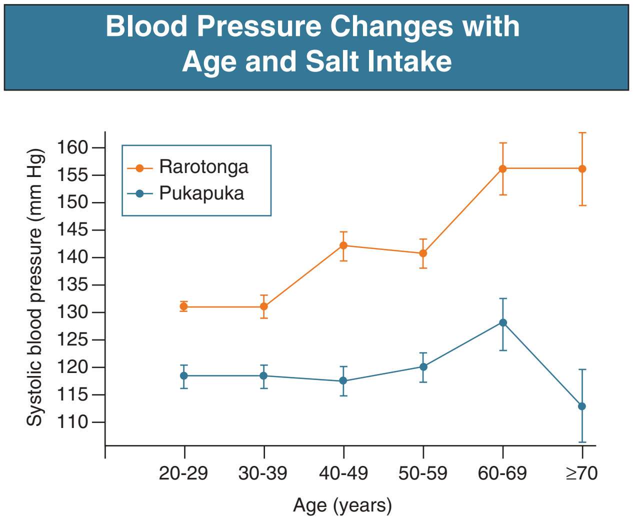

Fig. 35.2 **Blood pressure changes with age and salt intake.** The increase in systolic blood pressure (SBP) with age correlates with a higher salt intake in two Polynesian populations. In men of Rarotonga Island, where the sodium intake averages 130 mmol/day, SBP increases with age. In contrast, it remains constant in men from Pukapuka Island, where the sodium intake averages 50 to 70 mmol/day. (Modified from reference 27.)

BOX 35.1 Practical Guidelines for Exercise in Patients With Hypertension

All apparently healthy individuals should undergo preexercise screening to determine health risk status. The American College of Sports Medicine (ACSM) recognizes that two or more of the following risk factors increase the risk associated with exercise, and individuals should undergo preexercise graded exercise testing. Risk factors include male gender (older than age 45 years) or female gender (older than 55 years), serum cholesterol concentrations greater than 5.2 mmol/l, impaired glucose tolerance or diabetes mellitus, smoking, obesity (body mass index ≥30), inactivity, and family history of cardiovascular disease.

Patients with uncontrolled hypertension should embark on exercise training only after evaluation and initiation of therapy. Furthermore, patients should not participate in an exercise training session if resting systolic blood pressure is above 200 mm Hg or diastolic blood pressure is above 115 mm Hg.

Many patients with hypertension are overweight and should therefore be encouraged to follow a program that combines both exercise training and restricted calorie intake.

Type of exercise: This should be predominantly endurance physical activity, including walking, jogging, cycling, swimming, or dancing. This should be supplemented by resistance exercise that can be prescribed according to the ACSM or American Heart Association guidelines.

Frequency of exercise: Most or preferably every day.

Intensity of exercise: Moderate intensity at 40% to 60% of maximal oxygen consumption ($\dot{V}O_2$ peak).

Duration of exercise: More than 30 minutes of continuous or accumulated moderate physical activity daily.

Modified from references 22 and 23.

Putative mechanisms for salt sensitivity are alterations in circulating levels of (or renal responses to) atrial natriuretic factor, kallikrein, prostaglandins, and nitric oxide (NO); increased levels of norepinephrine; abnormal suppression of both renin and aldosterone; genetic mechanisms; congenital reduction in nephron number; and acquired renal microvascular and tubular injury.

In a Cochrane systematic review of 34 trials the effect of modest salt reduction on BP was studied. The pooled mean change in urinary sodium (Na) was −75 mmol/24 h (equivalent to reduction of 4.4 g of salt) resulting in a mean reduction in SBP of −4.18 mm Hg and DBP of −2.06 mm Hg, respectively. Meta-regression analysis showed that older age, Black ethnicity, hypertensive status, and change in 24-hour urinary Na were associated with a greater fall in BP.[28]

In the Dietary Approaches to Stop Hypertension (DASH)–Sodium Trial, the additional benefits of salt restriction over and above the DASH diet were investigated (Fig. 35.3).[29] Reduction of sodium intake from a high (150 mmol/day, or 9 g salt) to either an intermediate (100 mmol/day, or 6 g salt) or a low (65 mmol/day, or 4 g salt) intake resulted in a stepwise reduction in BP, which was approximately twice as great in participants receiving the control than receiving the DASH diet (see Fig. 35.3). In those following the DASH diet, the addition of salt restriction resulted in a relatively small additional decrease in BP (3.0 and 1.6 mm Hg for SBP and DBP, respectively). Thus the greatest benefits of salt restriction are seen in those with typical Westernized high-fat, low-nutrient diet.

Most hypertension guidelines recommend a reduction of salt intake to about 100 mmol or 6 g of salt. The U.S. Department of Agriculture and U.S. Department of Health and Human Services Joint Dietary Guidelines for Americans calls for stricter reduction in salt intake to no more than 65 mmol/day, or 4 g salt in African Americans, people over age 51, and patients with hypertension, diabetes mellitus, or CKD.[30] WHO recommends less than 5 g salt daily (2 g or 90 mmol/day Na) as a population goal.

A recent meta-analysis has stirred controversy by suggesting potential harm from salt restriction, especially in normotensive individuals, and spurred calls to abandon population-based salt restriction.[31] In this analysis, although increased Na intake was associated with increases in BP, hypertensive subjects in the high Na (>7 g/day) and low Na intake (<3 g/day) had increased risk for CV events and death compared with those with a Na intake of 4 to 5 g/day. In normotensive subjects, high salt intake had no adverse effect and low salt intake was associated with increased risk for CV events. However, this study has been heavily criticized[32] because a single spot urine sample was used to estimate Na intake. Currently only multiple 24-hour urine collections are considered reliable to account for day-to-day variability in Na intake.[33] There was

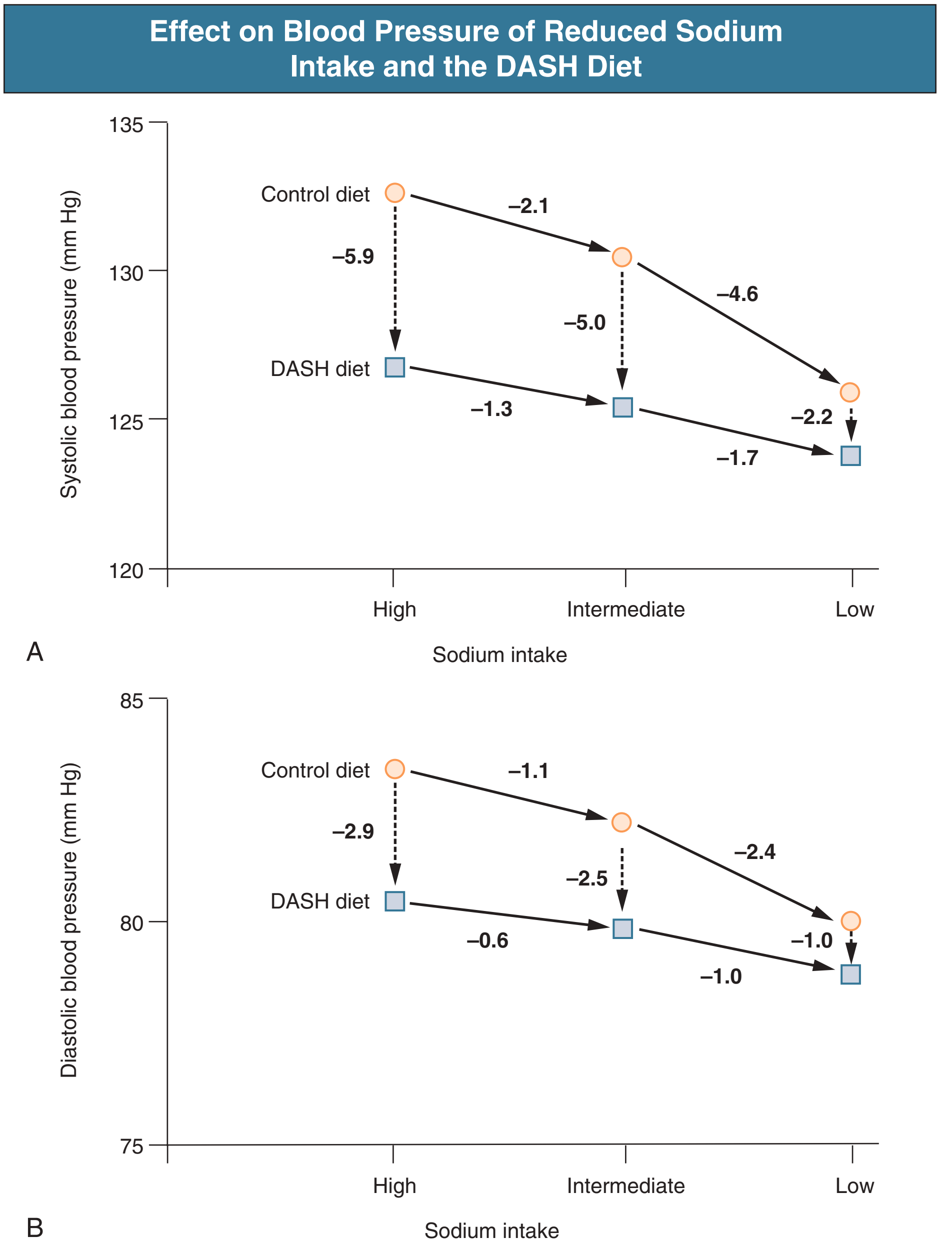

Fig. 35.3 **Reduced sodium intake and DASH diet.** Effect on (A) systolic blood pressure and (B) diastolic blood pressure. (**B,** Modified from reference 29.)

also the question of reverse causality with patients included in the study with significant CV disease in whom there may have been reduced food intake (and hence Na intake) and Na retention by the kidney. In countries where population-based reduction in salt intake has occurred (Finland, United Kingdom, and Japan) there has been an accompanying fall in BP and CV mortality. A recent American Heart Association (AHA) Presidential Advisory review concluded that the evidence supporting the effectiveness of population-level salt reduction to prevent hypertension and reduce the incidence of CV disease and stroke remains robust and persuasive for policy development.[30]

Avoiding added salt and salt-rich processed foods can reduce salt intake from 9 g/day to about 6 g/day. Further reduction in salt requires specialized dietary counseling. Despite these recommendations, long-term studies have reported only small reductions in BP associated with salt restriction (average of only 1.1/0.6 mm Hg).[34] These results undoubtedly reflect limited compliance, but this can be improved by regular contact with the patient, dietetic counseling, and educational sessions.

One of the most cost-effective ways to lower salt intake in the general population is to reduce salt in processed foods. This approach was effective in lowering the BP in patients with drug-treated hypertension in a middle-income community in South Africa through the modification of the salt content of a small number of commonly consumed foods, including bread.[35] In Belgium, the reduction in the salt content of bread between the mid-1960s and the early 1980s was accompanied by marked reductions in 24-hour urinary sodium excretion. In recognition of the need for a concerted global effort to reduce population-wide salt intake, a WHO Forum and Technical meeting in 2006 recommended an integrated approach incorporating a commitment by the food industry to product reformulation, increased consumer awareness, and social marketing around salt and health issues.

The United Kingdom was the first country to set voluntary sodium reduction targets for categories of foods, through its Food Standards Agency (2009), closely followed by Australia, the United States, and Canada. South Africa is the first country to adopt mandatory regulation for maximum sodium levels in food categories that are major contributors to salt intake in that population: bread, margarine and spreads, savory snacks, processed meats, soup powders, and stock cubes. It is estimated that reducing the sodium content of bread by 50%, along with other proposed reductions in margarine, soups, and gravies, would decrease salt intake by 0.85 g/day, resulting in 7000 fewer deaths from CVD and 4000 fewer nonfatal strokes in the country per year, as well as save about $40 million (U.S.) each year in health care costs associated with nonfatal strokes alone. In the United States, as in most developed nations, a major challenge to sodium intake reduction efforts is the widespread use of sodium in the food supply, with more than 75% of total sodium intake from packaged and restaurant foods.[36]

Potassium Intake

One of the confounding factors of the relationship of salt and BP has been the inverse relationship between the intake of salt and that of potassium. Typically, diets with a high salt content are relatively deficient in potassium (and calcium); but in persons who consume little salt, the potassium (and calcium) intake is high.

In normotensive individuals with an average potassium intake above 1.95 g/day (50 mmol/day), potassium supplementation has no significant effect on BP. However, among hypertensive patients who are potassium deficient because of diuretic treatment or low potassium intake, potassium supplementation lowers BP (Fig. 35.4).[37] The DASH diet lowers BP and is high in potassium because of the high fruit and vegetable content and inclusion of low-fat dairy products (Table 35.2). However, the synergistic effect of the various food groups in the DASH diet makes it difficult to ascertain the contribution of the individual nutritional components. The mechanisms by which a low-potassium diet may contribute to hypertension are complex and poorly understood but may relate to stimulation of intrarenal angiotensin II (Ang II), oxidants, and endothelin; inhibition of intrarenal NO and prostaglandins; and induction of renal ischemia.

In the Trials of Hypertension Prevention (TOHP) I and II, a higher sodium-potassium excretion ratio (implying a high-salt and low-potassium intake) was more strongly associated with subsequent CV events than either urinary Na^+ or K^+ excretion alone.[38] Overall, it appears to be beneficial to optimize potassium intake in hypertensive patients to

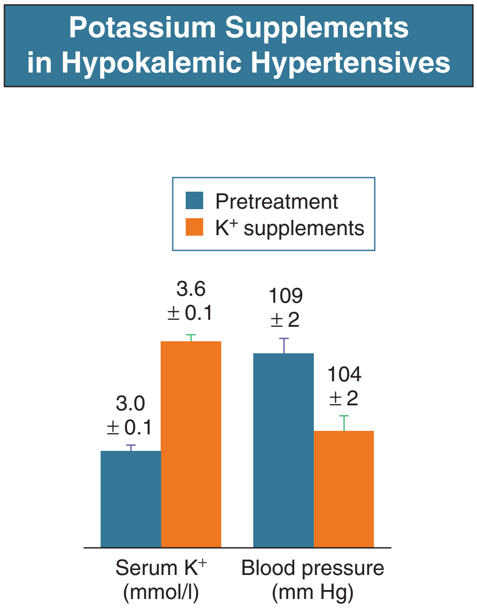

Fig. 35.4 Potassium supplementation lowers blood pressure in hypokalemic hypertensive patients. Treatment with potassium chloride (60 mmol/day potassium for 6 weeks) resulted in an increase in serum potassium concentration and a decrease in mean arterial pressure in hypertensive patients taking thiazide diuretics. (Redrawn from reference 37.)

TABLE 35.2 Dietary Approaches to Stop Hypertension (DASH) Diet*

Food Group	Daily Servings	Serving Sizes	Examples and Notes	Contribution to the DASH Diet Pattern
Grains and grain products	7-8	1 slice bread ½ cup dry cereal ½ cup cooked rice, pasta, or cereal	Whole-wheat bread, muffin, pita bread, bagel, cereals, oatmeal	Major sources of calories and fiber
Vegetables	4-5	1 cup raw, leafy vegetables ½ cup cooked vegetables 6 oz vegetable juice	Tomatoes, potatoes, carrots, peas, squash, broccoli, turnip greens, kale, spinach, artichokes, green beans, sweet potatoes	Rich sources of potassium, magnesium, and fiber
Fruits	4-5	1 medium fruit ¼ cup dried fruit 6 oz fruit juice ½ cup fresh, frozen, or canned fruit	Apricots, bananas, dates, oranges, orange juice, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, prunes, raisins, strawberries, tangerines	Important sources of potassium, magnesium, and fiber
Low-fat or nonfat dairy foods	2-3	8 oz milk 1 cup yogurt 1.5 oz cheese	Skim or low-fat (2%) milk, skim or low-fat buttermilk, nonfat or low-fat yogurt, nonfat or low-fat cheeses	Major sources of calcium and protein
Meats, poultry, and fish	≤2	3 oz cooked meats, poultry, or fish	Select only lean meats; trim away visible fats; broil, roast, or boil instead of frying; remove skin from poultry.	Rich sources of protein and magnesium
Nuts, seeds, and legumes	4-5/wk	1.5 oz or ⅓ cup nuts ½ oz or 2 tbsp seeds ½ cup cooked legumes	Almonds, mixed nuts, peanuts, walnuts, sunflower seeds, kidney beans, lentils, split peas	Rich sources of calories, magnesium, potassium, protein, and fiber

*The DASH eating plan shown is based on 2000 kcal/day. Depending on energy needs, the number of daily servings in a food group may vary from those listed.

minimize hypokalemia, being careful to avoid the risk for hyperkalemia, especially in those with renal impairment. If renal function is normal, optimal potassium intake is 80 to 120 mmol/day. For CVD prevention, the WHO recommends a potassium intake that will keep the urine Na/K ratio close to 1 (i.e., 70 to 80 mmol/day if Na guidelines are met).

Calcium, Vitamin D, and Dairy Food Intake

Cross-sectional population surveys of self-reported nutrient intake suggest an inverse relationship between calcium intake and BP. The relationship is more convincing at low levels of calcium consumption (<300 to 600 mg/day). There may be a threshold of 700 to 800 mg/day, above which any further reduction in BP is attenuated. A meta-analysis of randomized calcium supplementation trials (mostly with 1 or 1.5 g calcium daily) demonstrated reductions in SBP (−0.9 to −1.7 mm Hg) that are of little clinical importance.[39] Although calcium in milk may contribute to BP lowering, dairy products may lower BP by other mechanisms. Biologically active peptides formed during the milk fermentation process, such as the casein-derived tripeptides isoleucine-proline-proline and valine-proline-proline, have ACE-inhibiting properties. Vitamin D, which is often added to milk, also may help reduce BP by reducing renin expression, but in a randomized controlled clinical trial vitamin D had no effect on BP compared with placebo.[40] At present, the AHA does not recognize dairy consumption as a dietary approach to the prevention and management of hypertension. Nevertheless, low-fat dairy products are recommended as an integral part of the DASH diet.

Magnesium Intake, Other Micronutrients, and Bioactive Food Components

A weak inverse relationship has been reported between dietary intake of magnesium and BP, but in a meta-analysis of 34 RCTs, magnesium supplementation with a median dose of 368 mg/day was associated with a 2 mm Hg and 1.78 mm Hg reduction in SBP and DBP, respectively.[41]

In contrast, the inverse association between fruit and vegetable intake and BP and other CV risk factors is well established. Epidemiologic evidence suggests that polyphenol compounds found in fruit may explain in part the cardioprotective properties of fruits. Intervention trials have shown that fruits containing relatively high concentrations of flavonols, anthocyanins, and procyanidins, such as pomegranate, purple grapes, and berries, were effective at reducing CVD risk factors. Regular consumption of flavonol-rich foods, cocoa products, tea, and red wine may reduce BP.

Dietary Sugars and Fats

Added sweeteners, such as table sugar and high-fructose corn syrup, have been linked with the epidemics of obesity, hypertension, metabolic syndrome, diabetes, and CV disease.[42] Experimental studies suggest that the fructose component of sugar may increase the risk for obesity and diabetes because of its unique ability to reduce intracellular adenosine triphosphate levels and generate uric acid.[43] One study has reported that reducing soft drink intake by one drink per day is associated with a decrease of 1.8 mm Hg SBP.[44]

Interestingly, whole fruits appear to be beneficial despite containing fructose, possibly as a result of the high content of protective nutrients such as vitamin C, antioxidants, flavanols, potassium, and fiber. Possibly because of this, a systematic review and meta-analysis of three prospective cohort studies in 37,375 men and 185,855 women reported no association of fructose consumption with the incidence of hypertension.[45] However, although there was no effect of fructose at average levels of consumption over time, a positive association was identified with high intakes of fructose.

Supplementation with omega-3 fatty acids reduces the risk for myocardial infarction (MI) and sudden cardiac death, but their effect on BP is small. In a meta-analysis, omega-3 supplementation significantly reduced DBP by a mean of 1.8 mm Hg but had no effect on SBP, fibrinogen level, or heart rate.[46] About 10 portions of oily fish per week or 9 or 10 fish oil capsules per day are required (equivalent to ~3 g/day long chain n-3 fatty acids), and this is not tolerated by most because of belching and fishy taste. Concerns about the cholesterol content as well as dioxin and polychlorinated biphenyl content (environmental pollutants that have carcinogenic potential and, being fat soluble, can accumulate in the body) of some fish oil supplements also raise questions about the safety of very large doses. As a guideline for overall health, individuals with hypertension should aim to consume about 2 to 3 portions (200 to 400 g) of oily fish (e.g., herring, kippers, mackerel, pilchards, sardines, salmon, trout, fresh tuna, swordfish) per week.

Dietary Approaches to Lower Blood Pressure

Although individual nutrients and components of foods can have an impact on BP, it is necessary to consider these within the context of a total dietary approach because of potential synergistic effects. A meta-analysis of 17 randomized controlled trials showed that a dietary pattern that was rich in fruits, vegetables, whole grains, legumes, nuts, seeds, dairy, and fish and low in processed foods and red meat reduced SBP and DBP by 4.06 mm Hg and 2.30 mm Hg, respectively.[47] These dietary patterns included the DASH diet, the Mediterranean diet, and the Nordic diet, and the key factor is that they all emphasize plant-based foods.

SMOKING

Cigarette smoking is a well-established major risk factor for CV disease, but its role in the development of hypertension is not well elucidated and not routinely included in recommendations for prevention and treatment of hypertension. The relationship with hypertension may be confounded by changes in weight during and after the cessation of smoking. In a large epidemiologic study of middle-aged and older men from the United States, smoking was associated with a modest but important risk for development of hypertension.[48] In addition, smoking increases the risk for CKD progression as well as morbidity and mortality from multiple causes, so all smokers should be advised to stop.

ALCOHOL

There is a linear relationship between alcohol consumption, BP levels, and prevalence of hypertension. In Japan, alcohol intake above 300 g/wk (about three drinks daily) was associated with significantly greater increases of BP during a 7-year period, and baseline BP was higher in drinkers consuming 200 g/wk.[49] Heavy drinking is associated with increased risk for stroke, increase in BP after alcohol withdrawal, and attenuation of antihypertensive efficacy. Paradoxically, alcohol has a J-shaped relationship with coronary heart disease, with moderate consumption (one to two drinks daily) having the lowest risk. In a large epidemiologic study, modest alcohol consumption was protective against first MI.[50] Alcohol may increase BP through activation of the SNS, whereas its protective effects include increasing high density lipoprotein cholesterol, lowering fibrinogen, and inhibiting platelet activation. The JNC 7 guidelines recommend limiting alcohol consumption to no more than two drinks per day (24 oz [720 ml]) beer, 10 oz [300 ml] wine, or 3 oz [90 ml] 80-proof whiskey) in most men and no more than one drink per day in women or lighter weight men (see Table 35.1).[2]

CAFFEINE

Caffeine is the most widely used psychoactive substance worldwide. Caffeine stimulates the CV system through the blockade of vascular adenosine receptors. In a meta-analysis of RCTs of coffee ingestion, there was no effect on BP or risk for hypertension, although the quality of the evidence was low.[51] Caffeine tablets may have a greater effect on BP than coffee. The ASH/ISH guidelines do not address the issue of caffeine, but it seems reasonable to propose that coffee consumption is safe, but that pharmacologic ingestion of caffeine and the use of "smart drinks" supplemented with caffeine should be avoided.

PSYCHOLOGICAL STRESS

Chronic psychological stress is a contributor to the development and maintenance of hypertension. Men exposed to job strain had a 10.7 mm Hg and 15.4 mm Hg higher work and home ambulatory SBP than did controls, respectively.[52] The INTERHEART study showed that psychosocial stress was associated with a twofold increase in the risk for the first MI.[50] Although stress reduction techniques may be beneficial for other reasons, there are few long-term data on efficacy in reducing BP and as a result they are not recommended by ASH/ISH for the management of hypertension.

ADOPTING LIFESTYLE MODIFICATIONS

Maintaining adherence to lifestyle changes has always been challenging. The Prevention of Myocardial Infarction Early Remodeling (PREMIER) trial evaluated the effects of implementing JNC 7 lifestyle recommendations and the DASH diet.[53] Adults with prehypertension or untreated stage 1 hypertension were randomly assigned to one of three groups for 6 months: advice only, JNC recommendations, and JNC recommendations plus DASH diet. At 6 months, the JNC and JNC plus DASH groups had significantly reduced BP compared with the advice-only group, but there was little additional benefit in adding the DASH diet to JNC recommendations. However, participants purchased their own foods in the PREMIER study, instead of being provided with foods as in the DASH and DASH low-salt diet studies. Similarly, in the DASH low-salt diet study, the BP-lowering effect attributable to salt reduction was −6.7/−3.5 mm Hg,[29] whereas in meta-analyses of 34 salt restriction trials in which participants mostly prepared their own low-salt meals, this effect was only −4.18/−2.06 mm Hg.[28] Thus, in the outpatient setting, even highly motivated individuals usually cannot meet DASH dietary goals unless their meals are provided.

The Trials of Hypertension Prevention (TOHP) II study demonstrated the problems of sustainability of dietary intervention and the need for regular counseling.[54] The effect of adding salt restriction to weight loss appeared to offer no further decrease in BP. Assessed by urinary sodium excretion, adherence to lower dietary sodium was poor in the long term. At 36 months of follow-up, mean urinary sodium was 40 mmol/24 h lower than baseline in the sodium-restricted group and only 21% achieved the target of less than 80 mmol/24 h. A higher attendance at counseling sessions was associated with a greater reduction in urinary sodium. At 36 months, a decrease of 84 mmol/day of sodium from baseline levels could be achieved only in those who attended more than 80% of the counseling sessions. In summary, the sustainability of long-term lifestyle interventions remains problematic, but it appears that regular and long-term counseling can improve adherence.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is *not* a lifestyle recommendation of the American Society of Hypertension and International Society of Hypertension (ASH/ISH)?
   A. Reduction in alcohol intake
   B. Reduction in salt intake
   C. Stress reduction
   D. Weight reduction
2. For every kilogram reduction in weight, it is estimated that the systolic blood pressure will be reduced by:
   A. 0.5 mm Hg.
   B. 1 mm Hg.
   C. 2 mm Hg.
   D. 3 mm Hg.
3. Which of the following patients should not be targeted for stricter sodium reduction, according to U.S. Department of Agriculture and Department of Health and Human Services?
   A. African Americans
   B. Patients with chronic kidney disease
   C. Hypertensive individuals
   D. People younger than 40 years
4. Supplementation of vitamin D in hypertensive patients:
   A. Has little or no effect on BP.
   B. Causes a slight reduction in BP.
   C. Causes a slight increase in BP.
   D. Causes a marked reduction in BP.

36

Pharmacologic Treatment of Hypertension

Bryan Williams, Megan Borkum

Successful lifestyle interventions can delay the development of hypertension (see Chapter 35), but the majority of patients with confirmed hypertension require lifelong treatment, usually with more than one drug. This has resulted in a multibillion-dollar industry, in which numerous pharmacologic agents have been introduced (Table 36.1). In turn, this has made it more difficult for clinicians to decide which drugs should be used in specific patient groups. Further, recommended treatment targets are constantly evolving and there are a number of international guidelines, which are discussed in this chapter.

DEFINING WHO SHOULD RECEIVE PHARMACOLOGIC TREATMENT

Blood pressure (BP) follows a normal distribution within populations, and thus "hypertension" is arbitrarily defined by diagnostic thresholds subject to change as new evidence from clinical trials emerges. Hypertension is best defined as *that level of blood pressure at which treatment to lower blood pressure results in significant clinical benefit*. The BP at which treatment results in "significant clinical benefit" for any individual will depend on their absolute cardiovascular (CV) risk.[1-3] This varies because some people will be more vulnerable than others to end-organ damage at a given BP. Differential BP targets and thresholds have emerged, grouping patients into categories defining their threshold BP for therapeutic intervention and optimal BP goals. In some cases, specific drug classes have been given "compelling indications" and "compelling contraindications" for specific groups of patients. This has been useful in tailoring therapy from a wide range of drug classes but must not be misinterpreted as indicating that the specific drug is more important than the achieved BP, which is not the case. The primary objective of therapy is to lower BP as effectively as possible while minimizing side effects from therapy.[4-6]

Blood Pressure Thresholds for Intervention (Office Blood Pressure)

Treating a seated "office" BP above 160/100 mm Hg reduces the risk for stroke, myocardial infarction (MI), heart failure, and mortality.[4-9] There is also evidence that treating pressures above 140/90 mm Hg, especially in high-risk patients, is beneficial. Consequently, most recent guidelines define hypertension as an office BP of 140/90 mm Hg or higher.[7,8] The exception is the recent U.S. American Heart Association/American College of Cardiology (AHA/ACC) hypertension guideline,[9] which recommends a reclassification of hypertension, with stage 1 hypertension defined as a BP of 130/80 mm Hg or greater. Note that the U.S. hypertension guidelines refers to "stages" of hypertension, whereas other guidelines refer to "grades" of hypertension. The U.S. guideline recommends lifestyle advice for such patients and drug treatment to lower BP to less than 130/80 mm Hg if there is coexisting CV disease or an estimated 10-year risk for CV disease greater than 10%.[9] This is a major change, especially the diagnosis of "hypertension" when BP is 130/80 mm Hg or greater, because this will lead to as many as 50% more people being diagnosed as "hypertensive," with the majority recommended for drug treatment. Other international guidelines have adopted a treatment threshold of 140/90 mm Hg for adults and a higher threshold of 150/90 mm Hg in the elderly (variously defined as aged 65 years to 80 years and older), and it is most unlikely that the 140/90 mm Hg definition for hypertension will change outside of the United States.

Table 36.2 provides the contrast between the new U.S. guidance and the various grades of hypertension according to the current European guidelines, which are representative of most international guidelines. All guidelines identify a category of patient with "high normal BP" (often referred to as borderline hypertension or prehypertension), which is designed to highlight people at high risk for progression to hypertension and in whom lifestyle changes can be beneficial by reducing the transition to grade 1 hypertension. Importantly, high normal BP is not benign; data from the Framingham Heart Study show that people with a high normal BP experience a doubling in risk for CV complications (Fig. 36.1).[10] This principle was, in part, the basis for the recent U.S. guidelines to reclassify high-normal BP as stage 1 hypertension, encouraging the wider use of lifestyle interventions and drug therapy in this group of patients.

Clinical Dilemma of End-Organ Damage and "Normal" Blood Pressure

It is not known how best to treat people with high normal BP who already have evidence of end-organ damage, such as left ventricular hypertrophy (LVH), or microalbuminuria. This could be an example of the insensitivity of the defined thresholds for diagnosis of hypertension. Clearly, such a patient has a BP that is causing damage but considered below the usual threshold for intervention. Consequently, clinical understanding of the disease process is critical to enable the optimal use of guidelines for treatment decisions. There remains considerable uncertainty in the evidence base, and clinical judgment cannot be replaced by guidelines. The reclassification of BP in the United States means that many would now be classified as "stage 1 hypertension" and recommended for treatment.

Blood Pressure Thresholds for Intervention (Ambulatory and Home Blood Pressure Monitoring)

Diagnostic thresholds for hypertension vary according to the method of measurement. Ambulatory blood pressure monitoring (ABPM) and home BP monitoring are increasingly advocated and used. When ABPM or home BP are used to classify hypertension, the diagnostic thresholds are lower than office BP because they represent the average of a greater number of measurements under different conditions. The National Institute for Health and Clinical Excellence (NICE) guidelines[8] in the United Kingdom recommends that ABPM be routinely used to confirm the diagnosis of hypertension because of high rates of white coat and masked hypertension (www.guidance.nice.org.uk/CG127). The new U.S. guidance also advises the wider use of "out of office" BP measurement by ABPM or home BP monitoring to confirm the diagnosis of hypertension and monitor the quality of BP control in treated patients. Table 36.3 summarizes the diagnostic thresholds for hypertension according to different methods of measurement (see Chapter 33).

TABLE 36.1 Development of Therapeutic Strategies for Hypertension

Year	Nondrug Therapy
1920s	Strict low-sodium diet
1929	Lumbar sympathectomy
1944	Kempner rice diet
Year	**Drug Therapy**
1930s	Veratrum alkaloids
1940s	Thiocyanates
1948	Reserpine, phenoxybenzamine
1950	Ganglion blockers
1951	Monoamine oxidase inhibitors
1958	Thiazide diuretics (chlorothiazide)
1960s	Central α_2-receptor agonists, nondihydropyridine calcium channel blockers, and β-blockers
1970s	Angiotensin-converting enzyme (ACE) inhibitors, α_1-receptor blockers
1980s	Dihydropyridine calcium channel blockers
1990s	Angiotensin receptor blockers (ARBs)
2000s	Renin inhibitors, angiotensin receptor neprilysin inhibitor (ARNI)

BLOOD PRESSURE TREATMENT GOALS

The ideal BP treatment goal is likely to be patient specific, but guidelines must be generalizable to populations. Guidelines should therefore be conservative and pragmatic, should curb the zeal of specialists to advocate ever lower BP goals, and should only make recommendations supported by solid evidence. Until recently, there was international consensus that two BP goals were appropriate: less than 140/90 mm Hg for those with "uncomplicated hypertension" and a lower goal of less than 130/80 mm Hg for those at higher risk, that is, patients with diabetes, established CV or cerebrovascular disease, or chronic kidney disease (CKD). The SPRINT trial recently challenged this consensus when it showed that more intensive BP lowering (targeting a systolic BP <120 mm Hg), was more effective at reducing major cardiovascular events and mortality than the current less intensive systolic BP goal of less than 140 mm Hg.[11] Importantly, BP was measured in SPRINT using an automated device after 5 minutes of seated rest in a quiet room followed by three oscillometric measurements without an observer in the room. Automated office BP eliminates the white coat effect and, in patients with CKD, automated BP has been shown to be considerably lower than daytime ambulatory BP. Consequently the BP achieved in SPRINT would likely correspond to higher office BP.[12] This trial included a high proportion of patients aged 75 years and older and a high proportion with CKD. The "more intensive" treatment strategy was well tolerated, and there was no evidence of excess falls or reduction in gait speed.[13] However, although there was no difference in the composite end-point of all serious adverse events, the intensive therapy arm was associated with more nonorthostatic hypotension, syncope, electrolyte abnormalities, and acute kidney injury. These findings strongly influenced the recent U.S. guideline recommendation to lower the systolic

High Normal Blood Pressure and the Risk of Cardiovascular Disease

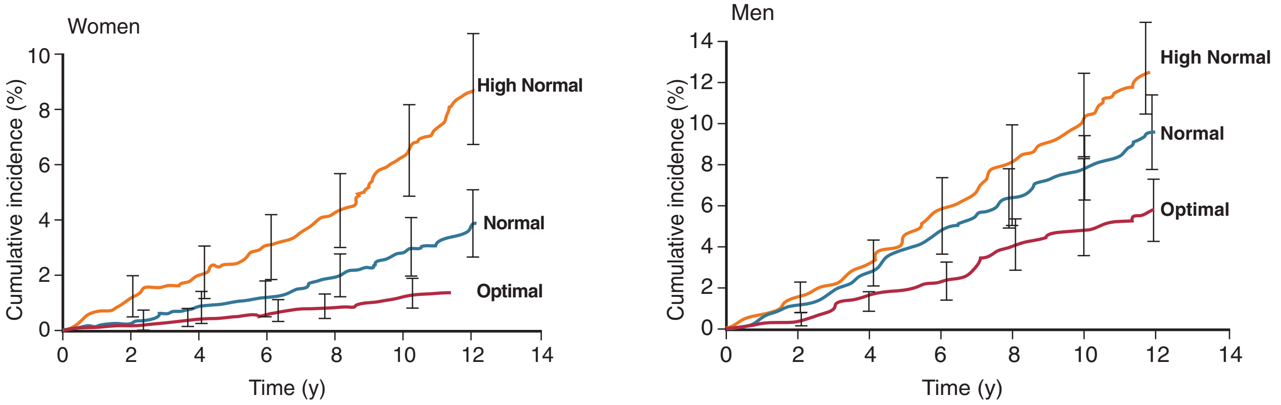

Fig. 36.1 "High Normal" blood pressure (BP) and risk for cardiovascular disease. Cumulative incidence of cardiovascular events in women (left) and men (right) without hypertension, according to BP category at the baseline examination, showing 95% confidence intervals. For this analysis, "optimal" BP was defined as systolic pressure of less than 120 mm Hg and diastolic pressure less than 80 mm Hg; "normal" BP as systolic 120 to 129 or diastolic 80 to 84 mm Hg; and "high normal" BP as systolic 130 to 139 or diastolic 85 to 89 mm Hg. (Modified from reference 10.)

TABLE 36.2 Blood Pressure Treatment Thresholds, Goals, and Initial Therapy Choices According to Most Recent Major International Guidelines

ESH/ESC CLASSIFICATION OF HYPERTENSION (2013)

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High-normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	And	<90

USA CLASSIFICATION OF HYPERTENSION (2017)

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120-129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130-139 mm Hg	or	80-89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

INTERNATIONAL GUIDELINE BP THRESHOLDS AND BP GOALS

Guidelines	BP Threshold (mm Hg)	BP Goal (mm Hg)	Initial Therapy
U.S. 2017	130/80 if existing CV disease or 10-y CVD risk >10% 140/90 in all others	<130/80	ACEi or ARB, or CCB, or thiazide/thiazide-type diuretic, usually as a two-drug combination
ESH/ESC 2013	Age <80 y: 140/90 Age ≥80 y: 160/90	<140/90 <150/90	Thiazide/thiazide-type diuretic, ACEi, ARB, CCB, or β-blocker, usually as monotherapy
NICE U.K. 2011	Age <80 y: 140/90 Age ≥80 y: 160/90	<140/90 <150/90	ACEi or ARB, or CCB, or thiazide/thiazide-type diuretic: Usually as monotherapy

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BB,* β-blocker; *CCB,* calcium channel blocker; *ESH/ESC,* European Society of Hypertension/European Society of Cardiology; *DBP,* diastolic blood pressure; *SBP,* systolic blood pressure.
Hypertension grades or stages replace the older terminology of mild, moderate, and severe.

BP goal to less than 130 mm Hg for almost all patient groups (including the elderly) providing they are independent and well functioning.[9,13] This recommendation also has been supported by recent systematic reviews and meta-analysis but with the caveat that some of these analyses point to an increased risk for harm if the systolic BP goal is below 120 mm Hg.[14,15] The SPRINT trial did not include patients with prior stroke or diabetes, but the systematic reviews show consistent benefit, especially for stroke reduction, in these patients when systolic BP is lowered to less than 130 mm Hg.[3-5] The impact of lower BP goals (i.e., systolic BP <130 mm Hg) on the progression of CKD seems less well established in the same meta-analyses.

It is likely that the decision to lower the systolic BP target to below 130 mm Hg for most patients in the U.S. guideline will be replicated by many future guidelines. It is certainly less controversial than the U.S. guideline decision to reclassify hypertension and begin treating low-moderate risk patients with a systolic BP threshold of 130 mm Hg or more. There still will be concern about over aggressive treatment of older patients aged 65 years and older and especially the very old at 80 years and older. People age at different rates and have different levels of comorbidities, mobility, and independence, so a systolic BP treatment goal of less than 130 mm Hg may be too low for some. That said, the previous systolic BP goal of less than 150 mm Hg was almost certainly too conservative. A reasonable first goal in older patients would be to achieve a systolic BP below 140 mm Hg, with the option of reducing the BP further if treatment is well tolerated. However, there will be benefit from BP lowering even when these goals cannot be achieved. Table 36.4 summarizes the new BP thresholds and treatment goals recommended by the 2017 U.S. hypertension guideline.

There is less evidence available on diastolic BP treatment goals. Concern has been expressed that overaggressive lowering of diastolic BP may compromise coronary artery perfusion in particular and lead to adverse outcomes. Interpretation of the impact of diastolic pressure reduction in trials is complex, especially when conducted post hoc, and is confounded by the fall in diastolic BP with ageing, reflecting arteriosclerosis, and arterial stiffening. Thus a low diastolic BP is often a marker of vascular disease rather than the cause of it. Expert consensus regards a diastolic BP in the range of 70 to 80 mm Hg as optimal. However, some older patients have much lower and sometimes unmeasurably low diastolic BP levels. This should not be a barrier to effective lowering of systolic BP, provided the patient is tolerating the treatment well and is asymptomatic. Some of the most impressive benefits of drug treatment of hypertension have occurred in patients with isolated systolic hypertension (ISH) in whom baseline diastolic pressure has been lower than 70 mm Hg.

GUIDE TO SELECTION OF ANTIHYPERTENSIVE AGENTS

Key Principles From Clinical Trials

BP lowering undoubtedly reduces morbidity and mortality, but there has been much debate about "how low to go." Many large randomized controlled trials (RCTs) have compared different drug classes with placebo and different treatment strategies with each other (see references 4 to 6 for overviews). Table 36.5 and Fig. 36.2 present detailed analyses, reporting the effectiveness of specific drug classes on major CV events and mortality. The differences among the various drug classes on clinical outcomes are primarily driven by differences in BP control. Analysis of trials has provided some important guiding principles with regard to treatment strategies for hypertension, as follows:

1. Effective BP lowering is overwhelmingly important in reducing the risk for major CV events in people with hypertension. Thus the first priority in treatment is to control BP.
2. Early studies focused primarily on diastolic BP as the treatment target, but systolic BP is invariably more difficult to control and more closely linked to CV outcomes and should now be the primary but not the sole focus of treatment.
3. Monotherapy is rarely sufficient to control BP, and the majority of patients will require more than one drug as part of their treatment strategy, especially if lower BP targets, as advocated by the recent U.S. guidelines, are more widely adopted.
4. The response to any class of BP-lowering medication is heterogeneous, with important effects of age and ethnicity.

TABLE 36.3 Diagnostic Thresholds for Hypertension According to Different Methods of Blood Pressure Measurement

	BLOOD PRESSURE (mm Hg)	
Measurement	**Systolic**	**Diastolic**
Office or clinic	140	90
24-hour	125-130	80
Day	130-135	85
Night	120	70
Home	130-135	85

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

ABPM, Ambulatory BP monitoring; *HBPM,* home BP monitoring. 24-Hour, day or night refer to ambulatory blood pressure (BP) averages over these periods. Home refers to an average of at least 4 days of seated readings at home, usually two readings, twice per day, that is, an average of ~16 readings. The top panel shows BP thresholds according to the current ESH/ESH 2013 Guidelines. The bottom panel shows the corresponding values of SBP and DBP for Clinic, HBPM, Daytime, Nighttime and 24 hr ABPM measurements according to the U.S. 2017 Guidelines.

TABLE 36.4 Summary of Blood Pressure Thresholds and Treatment Goals (Office Blood Pressure) Recommended by the U.S. 2017 Hypertension in Adults Treatment

Clincal Condition(s)	BP Threshold (mm Hg)	BP Goal (mm Hg)
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 SBP	<130 SBP
Specific Comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/80	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ASCVD, Atherosclerotic cardiovascular disease; *BP,* blood pressure; *CVD,* cardiovascular disease; *SBP,* systolic BP.

TABLE 36.5 Relative Risk and Benefit of Antihypertensive Drug Classes

Outcome	Thiazide Diuretics (D)	Calcium Channel Blockers (C)	β-Blockers (B)	ACE/ARBs* (A)
Unstable angina	0.89	0.88	0.98	0.97
Myocardial infarction	0.78	0.79	0.85	0.81
Diabetes	0.98	0.80	1.13	0.72
Stroke	0.69	0.65	0.85	0.73
Heart failure	0.53	0.73	0.76	0.64
Death	0.91	0.88	0.93	0.90

Modified from data at www.nice.org.uk/CG034guidance.

*Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were grouped as a single class for the purposes of this analysis.

Effectiveness of drugs: 1.0 = no benefit/harm, <1.0 = benefit, and >1 = potential harmful effect, from a meta-analysis of major blood pressure (BP)-lowering trials conducted for the U.K. National Institute for Health and Clinical Excellence (NICE) Hypertension Guideline Development Group, 2006.

Effects of Reduction in Systolic BP Stratified by Class of Antihypertensive

	Studies	Intervention Events	Intervention Participants	Control Events	Control Participants	RR (95% CI)
Major cardiovascular events						
ACE inhibitor	10	5379	31652	9766	50805	1.03 (1.00–1.06)
ARB	8	3647	27140	3779	29331	0.98 (0.93–1.02)
β blocker	9	2863	25989	2520	27231	1.17 (1.11–1.24)
CCB	21	7857	63693	12808	82904	0.97 (0.94–0.99)
Diuretic	11	5830	38353	6782	42410	0.97 (0.94–1.00)
All-cause mortality						
ACE inhibitor	14	3321	33104	5865	52263	1.01 (0.97–1.05)
ARB	11	2546	29282	2638	31404	0.99 (0.94–1.04)
β blocker	12	2805	40953	2688	42170	1.06 (1.01–1.12)
CCB	26	5602	76672	8428	95932	0.97 (0.94–1.00)
Diuretic	12	3425	41625	3806	45707	1.02 (0.97–1.06)

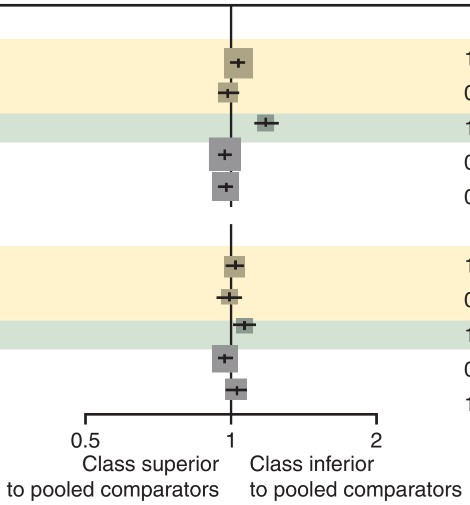

Fig. 36.2 Effects of reductions in systolic blood pressure (BP) stratified by class of BP-lowering drug. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blockers; *CCB,* calcium channel blocker; *CI,* confidence interval; *RR,* relative risk. (From reference 4.)

5. Some trials have indicated that certain comorbidities (e.g., diabetes) and target organ damage (e.g., LVH, CKD) provide compelling indications for inclusion of specific classes of drug therapy in the treatment regimen, but this consideration should not override the importance of BP control and has become less relevant now that most patients are treated with combinations of drugs.
6. There are inadequate clinical outcome data for treatment studies of younger patients. Most studies, especially the more recent, have been conducted in patients older than 55 years and typically with a mean age older than 65 years.
7. On average, lowering of BP by 20/10 mm Hg in hypertensive patients will reduce the risk for major CV events by half.
8. The reduction in stroke risk and heart failure appears to follow the predicted reduction in risk based on the epidemiologic association between these morbidities and BP.
9. The observed benefits of BP lowering on coronary events are lower than expected based on epidemiologic predictions, which is best addressed by attention to concomitant risk factors, especially statin therapy.
10. Another important objective of antihypertensive therapy is reducing the progression of CKD. Some but not all RCTs have shown a protective effect of BP-lowering on progression of CKD toward end-stage renal disease, in both diabetic and nondiabetic nephropathy.[16,17]
11. The risk reduction associated with BP lowering is continuous across a wide range of BP, with the benefit from treatment greatest in those with the highest absolute CVD risk. This provides the rationale for advocating the use of complementary strategies to reduce CVD risk (e.g., statins and antiplatelet therapy in those with established vascular disease, with target organ damage, or at high calculated CVD risk, i.e., ≥20% during 10 years).

Selection of Drug Therapy

The major classes of BP-lowering therapies are summarized here. International guidelines have recommended certain indications and contraindications for the use of specific classes of BP-lowering therapy in specific clinical situations (Box 36.1 and Table 36.6). These lists are

BOX 36.1 Clinical Indications Favoring Use of Specific Antihypertensive Medications

ACE Inhibitors
Heart failure
LV dysfunction
Post-MI
Diabetic nephropathy
Nondiabetic nephropathy
LV hypertrophy
Carotid atherosclerosis
Proteinuria/microalbuminuria
Atrial fibrillation
Metabolic syndrome

Angiotensin Receptor Blockers
Heart failure
Post-MI
Diabetic nephropathy
Proteinuria/microalbuminuria
LV hypertrophy
Atrial fibrillation
Metabolic syndrome
ACE inhibitor–induced cough

β-Blockers
Angina pectoris
Post-MI
Heart failure
Tachyarrhythmias
Glaucoma
Pregnancy

Calcium Antagonists (Verapamil, Diltiazem)
Angina pectoris
Carotid atherosclerosis
Supraventricular tachycardia

Calcium Antagonists (Dihydropyridines)
Isolated systolic hypertension (elderly)
Angina pectoris
LV hypertrophy
Carotid/coronary atherosclerosis
Pregnancy
Hypertension in Blacks

Thiazide Diuretics
Isolated systolic hypertension (elderly)
Heart failure
Hypertension (Blacks)

Diuretics (Antialdosterone)
Heart failure
Post-MI

Loop Diuretics
End-stage renal disease
Heart failure

ACE, Angiotensin-converting enzyme; *LV,* left ventricular; *MI,* myocardial infarction.

TABLE 36.6 Contraindications to Specific Blood Pressure–Lowering Therapies

Pharmacologic Therapy	CONTRAINDICATIONS	
	Compelling	Possible
Thiazide diuretics	Gout	Metabolic syndrome Glucose intolerance Pregnancy
β-Blockers	Asthma A-V block (grade 2 or 3)	Peripheral artery disease Metabolic syndrome Glucose intolerance Athletes, physically active patients COPD Asthma (use cardioselective β-blocker)
Calcium antagonists (dihydropyridines)		Tachyarrhythmias Heart failure
Calcium antagonists (verapamil, diltiazem)	A-V block (grade 2 or 3) Heart failure β-Blocker therapy	
Angiotensin-converting enzyme inhibitors	Pregnancy Angioneurotic edema Hyperkalemia Bilateral renal artery stenosis	
Angiotensin receptor blockers	Pregnancy Hyperkalemia Bilateral renal artery stenosis	
Diuretics (antialdosterone)	CKD stages 4 and 5 Hyperkalemia	
Direct renin inhibitors	Pregnancy Hyperkalemia Bilateral renal artery stenosis	

A-V, Atrioventricular; *CKD, chronic kidney disease; COPD,* chronic obstructive pulmonary disease.

TABLE 36.7 Common Side Effects Associated With Various Classes of Antihypertensive Drugs

Drug Class	Side Effects
ACE inhibitors	Cough, hyperkalemia
ARBs	Much less frequent hyperkalemia compared with ACE inhibitors
CCBs	
DHP CCBs	Pedal edema, headache
Non-DHP CCBs	Constipation (verapamil), headache (diltiazem)
Diuretics	Frequent urination, hyperglycemia, hyperlipidemia, hyperuricemia, sexual dysfunction
Central α-agonists	Sedation, dry mouth, rebound hypertension, sexual dysfunction
α-Blockers	Pedal edema, orthostatic hypotension, dizziness
β-Blockers	Fatigue, bronchospasm, hyperglycemia, sexual dysfunction
Potassium [K^+] channel openers	Hypertrichosis (minoxidil); lupus-like reactions, pedal edema (hydralazine)

ACE, Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *CCBs,* calcium channel blockers; *DHP CCBs,* dihydropyridine calcium channel blockers; *non-DHP CCBs,* nondihydropyridine calcium channel blockers.

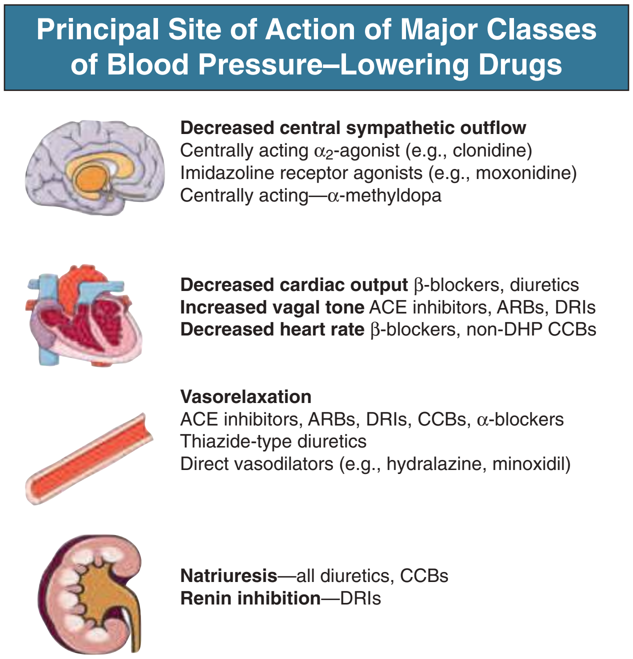
Principal Site of Action of Major Classes of Blood Pressure–Lowering Drugs
Decreased central sympathetic outflow
Centrally acting α_2-agonist (e.g., clonidine)
Imidazoline receptor agonists (e.g., moxonidine)
Centrally acting—α-methyldopa
Decreased cardiac output β-blockers, diuretics
Increased vagal tone ACE inhibitors, ARBs, DRIs
Decreased heart rate β-blockers, non-DHP CCBs
Vasorelaxation
ACE inhibitors, ARBs, DRIs, CCBs, α-blockers
Thiazide-type diuretics
Direct vasodilators (e.g., hydralazine, minoxidil)
Natriuresis—all diuretics, CCBs
Renin inhibition—DRIs

Fig. 36.3 Principal site of action of major classes of blood pressure–lowering drugs. *ACE,* Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *CCBs,* calcium channel blockers; *DRIs,* direct renin inhibitors; *non-DHP CCBs,* nondihydropyridine calcium channel blockers.

not comprehensive and are subject to change as new evidence emerges. Moreover, the compelling indications have become less important now that few patients are treated with monotherapy and most patients will receive renin-angiotensin-system (RAS) inhibitors with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), along with a calcium channel blocker (CCB) or thiazide or thiazide-type diuretic as part of their treatment strategy. Table 36.7 outlines the more common adverse effects associated with the major classes of BP-lowering drug therapies. Fig. 36.3 shows their sites of action.

Thiazide and Thiazide-Like Diuretics

The class of diuretics includes the traditional thiazide diuretics such as hydrochlorothiazide and bendroflumethiazide, as well as thiazide-like diuretics such as chlorthalidone and indapamide. The latter are termed *thiazide-like* because, like the thiazides, they act primarily by inhibiting the Na$^+$-Cl$^-$ cotransporter in the distal tubule, promoting sodium excretion, which is integral to their antihypertensive effect. However, the thiazide-like diuretics have different structure than the thiazides and differing actions on other aspects of renal tubular function, such as carbonic anhydrase inhibition in the proximal tubule. Thiazide and thiazide-like diuretics remain an important therapeutic option for the treatment of hypertension. The early changes in salt and water balance they induce are usually accompanied by counteractivation of several vasoconstrictor mechanisms, including the RAS, which may transiently raise peripheral vascular resistance (PVR) and attenuate BP lowering. Subsequently, a gradual reduction in PVR and a new steady state of reduced total body sodium and BP are established, usually after about 2 months of treatment.

The sustained actions of these diuretics on the kidney make them preferable to loop diuretics for the control of BP. Although loop diuretics are more potent promoters of acute sodium and water loss, their shorter duration of action can result in compensatory sodium retention during the latter part of the dosing interval, thereby reducing their BP-lowering efficacy. Loop diuretics have no place in the routine management of primary hypertension in patients with well-preserved glomerular filtration rate (GFR). However, thiazide and thiazide-like diuretics lose efficacy in patients with GFR below 30 ml/min. In such patients, loop diuretics are often required for effective BP lowering, especially when there is clinical evidence of sodium and water retention.

The main adverse effects of thiazide and thiazide-like diuretics are metabolic: hypokalemia, hyponatremia (less frequently), impaired glucose tolerance, and small increments in blood levels of low-density lipoprotein (LDL) cholesterol and triglycerides. These diuretics also elevate serum uric acid levels and should be avoided in patients predisposed to gout, as well as in those receiving lithium because of a high risk for lithium toxicity. Lithium reabsorption is similar to sodium in the proximal tubule, and thus distal sodium loss caused by thiazide and thiazide-like diuretics can promote proximal reabsorption of sodium and lithium; because lithium has a narrow therapeutic window, this can lead to lithium toxicity. An incidental advantage of thiazide and thiazide-like diuretics may be reduction in osteoporosis, especially in women, as a result of calcium retention.

There has been a trend during recent years to reduce the recommended dose of these diuretics to minimize their adverse metabolic effects. The dose-response for BP to thiazide and thiazide-like diuretics is flat (unlike the adverse effect profile); however, some patients respond well to higher doses, which they tolerate. Moreover, when thiazide or thiazide-like diuretics are combined with drugs that block the RAS, such as ACE inhibitors or ARBs, the dose-response curve is steeper and higher doses (e.g., hydrochlorothiazide 25 to 50 mg or chlorthalidone 25 mg) may be especially effective in patients with more resistant hypertension. The most recent NICE hypertension guidelines recommend the preferential use of thiazide-like diuretics such as chlorthalidone and indapamide, rather than traditional thiazides such as hydrochlorothiazide because there are limited outcome data with the latter when used at low dose.[8]

Potassium-Retaining Diuretics

This class of agents includes spironolactone, eplerone, and amiloride. Spironolactone is an aldosterone receptor antagonist that acts in the distal tubule and collecting ducts, decreasing the reabsorption of sodium and water and decreasing the excretion of potassium. The main action of spironolactone is to decrease tubular expression of epithelial sodium channels (ENaC) and renal outer medullary potassium (ROMK) channels, and thus it has a relatively slow onset and offset of action. Because its main site of action is on sodium and water handling in distal tubule and collecting ducts, spironolactone is a relatively weak diuretic. Nevertheless, it is effective as a BP-lowering agent although rarely used as initial therapy for hypertension. Spironolactone has the advantage over thiazide-like diuretics that it does not cause hypokalemia or hyperuricemia and it does not impair glucose tolerance. However, spironolactone has antiandrogen activity by binding to the androgen receptor and preventing it from interacting with dihydrotestosterone. Consequently, it can cause nipple tenderness and gynecomastia in some male patients (~6%) that is dose dependent and can limit its use. Another concern with potassium-sparing diuretics in general is the risk for hyperkalemia in people with substantially reduced GFR (see later discussion).

Eplerenone is more selective for the aldosterone receptor than spironolactone and consequently avoids its antiandrogen effects. There is very limited experience with use of eplerenone for the routine management of hypertension. Empirically, milligram per milligram, eplerenone is less potent than spironolactone and less effective at lowering BP.

Amiloride is an antagonist of ENaC in the distal convoluted tubules and collecting ducts, decreasing sodium and water reabsorption and promoting potassium excretion. Previously, amiloride was a popular treatment of primary hypertension, when, like spironolactone, it was often used in combination with thiazide-like diuretics. Amiloride is less used now even though it shares the advantage of spironolactone over thiazide-like diuretics of not causing hypokalemia, hyperuricemia, or impaired glucose tolerance.[18] Amiloride is the treatment of choice in patients with Liddle syndrome who have hypertension caused by a gain-of-function mutation of ENaC.

The reason for the decline in popularity of potassium-sparing diuretics for the initial treatment of primary hypertension is not clear; it may reflect the increasing use of ACE inhibitors and ARBs for the routine management of hypertension and the increased risk for hyperkalemia when these are combined with spironolactone or amiloride, especially in patients with renal impairment. Spironolactone and amiloride are, however, increasingly used as additional diuretic therapy in multidrug strategies for the treatment of resistant hypertension, when these drugs can be very effective.[19,20]

β-Adrenoceptor Blockers

β-Blockers reduce BP and CV events in patients with hypertension. Most β-blockers, with the exception of those with strong intrinsic sympathomimetic activity, reduce cardiac output by their negative chronotropic and inotropic effects. As with diuretics, short-term hemodynamic responses can be offset by counteractivation of vasoconstrictor mechanisms, which may limit initial BP lowering. Longer term reduction in arterial pressure occurs because PVR is restored to pretreatment levels. Partial blockade of renin release from the kidney may contribute to the later hemodynamic response.

β-Blockers differ in their duration of action, selectivity for β_1 receptors, lipophilicity, and partial agonist activity. Side effects include lethargy, aches in the limbs on exercise, impaired concentration and memory, aggravation of depression and psoriasis, erectile dysfunction, vivid dreams, and exacerbation of symptoms of peripheral vascular disease and Raynaud syndrome. Nonselective β-blockers are contraindicated in asthma patients and can cause adverse metabolic effects, including impaired glucose tolerance and worsening of dyslipidemia, notably reduced high-density lipoprotein (HDL) cholesterol and raised triglyceride levels. There is accumulating evidence that β-blockers increase the likelihood of new-onset diabetes, particularly in combination with thiazide-type diuretics.[21,22] Moreover, recent meta-analyses suggest that there is a shortfall in CV protection with β-blocker–based treatment of hypertension (especially in stroke reduction) compared with treatment with other major drug classes[4,23,24] (see Table 36.5 and Fig. 36.2). As a consequence, the U.K. guidelines and recent U.S. guidelines both state that β-blockers are not preferred as initial therapy for routine hypertension and should be used only when there is a compelling indication other than BP control (e.g., in patients with angina or chronic heart failure as well as hypertension).[8,9]

Another exception is in younger women in whom β-blockers are often effective at lowering BP and are safer than ACE inhibitors or ARBs in women anticipating pregnancy. The good BP-lowering efficacy in younger people most likely reflects higher renin levels, and the BP-lowering action of β-blockers, at least in part, relates to suppression of renin release. Newer β-blockers have associated α-blocking activity, such as carvedilol and nebivolol. However, there are no clinical outcome trial data for the treatment of hypertension with these agents. The European Society of Hypertension/European Society of Cardiology (ESH/ESC) guideline did not come out quite so strongly against β-blockers but did not specifically endorse these agents as a preferred initial treatment or as an ideal drug in combination with other treatments.[7]

Calcium Channel Blockers

CCBs effectively reduce BP and have extensive evidence supporting their use for the treatment of hypertension[4,6]; they are also effective antianginal agents. They are metabolically neutral with regard to glucose tolerance and lipid parameters. More recent data have highlighted that CCBs are especially effective at smoothing BP variability, which is an independent risk factor for stroke. This may explain why systematic reviews have shown CCBs (particularly amlodipine) to be the most cost-effective treatment option for hypertension, mainly because they are the most effective agent at preventing stroke.[4,25] BP response to CCBs is largely determined by the magnitude of BP elevation, more so than with other drugs. Thus patients with higher baseline BP experience greater BP lowering with CCBs than those with only modest elevations of BP. This property also may explain the smoothing effect of CCBs on BP variability.

There are two main groups of CCBs, the dihydropyridines (e.g., amlodipine, nifedipine) and the nondihydropyridines (e.g., diltiazem, verapamil). The dihydropyridine (DHP) CCBs act mainly by inducing relaxation of arterial smooth muscle by blocking L-type calcium channels, thereby inducing a fall in PVR and arterial pressure. Nondihydropyridine (non-DHP) CCBs block calcium channels in cardiac muscle and reduce cardiac output. Verapamil has an additional antiarrhythmic action through its effects on the atrioventricular node. DHP and non-DHP CCBs have occasionally been combined, but no robust data are available on the BP-lowering efficacy or clinical outcomes of this approach and it is not a recommended combination therapy in international guidelines.

Earlier formulations of some DHP CCBs, such as capsular nifedipine, had a rapid onset and a short duration of action, with unpredictable effects on BP. These responses were often accompanied by reflex sympathetic stimulation and tachycardia. These shorter acting oral preparations of CCBs have no place in the routine management of hypertension. Longer acting formulations of DHP CCBs produce more sustained and predictable responses.

Side effects of DHP CCBs include dose-dependent peripheral edema, which is not caused by fluid retention but by transudation of fluid from the vascular compartments into the dependent tissues as a result of preapillary arteriolar dilation. This edema does not respond to diuretic therapy but is alleviated by limb elevation. There is emerging evidence that this edema may be reduced by coadministration of an ACE inhibitor or ARB because of their effects on venous capacitance. Gum hypertrophy can occur with DHP CCBs but is rarely seen with non-DHP CCBs. Non-DHP CCBs cause less peripheral edema but are negatively inotropic and negatively chronotropic and should therefore be avoided in patients with compromised left ventricular function and in combination with β-blockers. Verapamil use is commonly accompanied by constipation.

Blockade of Renin-Angiotensin System

Inhibition of RAS is predictably effective at lowering BP by inhibiting the various central and peripheral pressor effects of angiotensin II (Ang II). Blockade of RAS also may lower BP by other mechanisms involving improvements in endothelial function, vagal tone, and baroreceptor function and through inhibition of the renal tubular reabsorption of sodium. In addition, RAS inhibition has been popularized by clinical trial evidence that treatment with RAS inhibition reduced morbidity and mortality in patients with heart failure, delayed progression of renal disease, and reduced CV events in those at high CV risk.[6] Three classes of drugs are now available that directly target the RAS (Fig. 36.4): ACE inhibitors, ARBs, and the direct renin inhibitors (DRIs).[26] However, the DRIs are not recommended for routine treatment of hypertension in international guidelines because of a lack of evidence on their impact on CV outcomes.

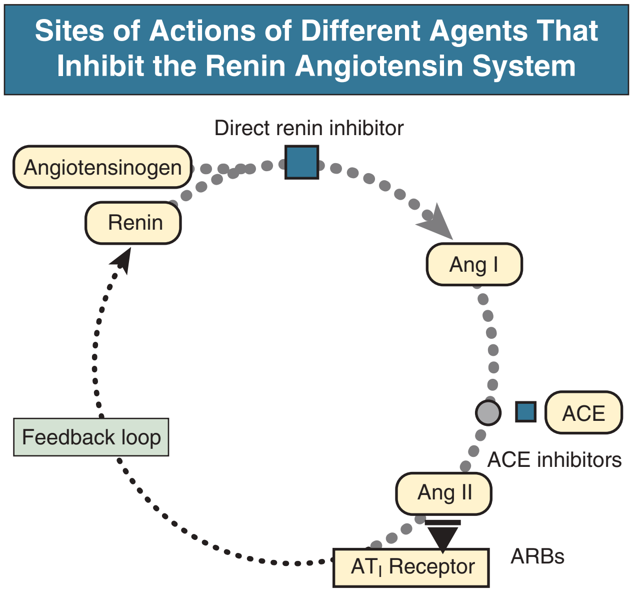

Fig. 36.4 Sites of actions of different agents that inhibit the renin-angiotensin system. The resulting neurohumoral profile is also shown. *ACE,* Angiotensin-converting enzyme; *Ang,* angiotensin; *ARB,* angiotensin receptor blocker; *DRI,* direct renin inhibitor.

Angiotensin-converting enzyme inhibitors. ACE inhibitors block the conversion of Ang I to Ang II by inhibiting ACE. The resulting reduction in levels of Ang II leads to vasodilation and a fall in BP. Ang II has many additional actions that are potentially harmful to the CV system and has been implicated in the pathogenesis of structural changes in the heart, blood vessels, and kidneys in hypertension. Sharp falls in BP after the introduction of ACE inhibitors may occur when the RAS is activated, for example, in patients who are dehydrated, in heart failure, or with accelerated hypertension. This is rarely a problem when therapy is initiated in uncomplicated hypertensive patients.

Side effects of ACE inhibitors include the development of a persistent dry cough in about 20% of users. This is more common in women and in people from East Asia and the Pacific Rim. The cough disappears only after discontinuation of the drug. Another rare but important complication is angioedema, which occurs in about 1% and is much more common in the Black population (~4%). ACE inhibitors should be avoided in women of childbearing potential because of the danger of fetal malformation, especially from exposure in the first trimester, when women may be unaware they are pregnant. ACE inhibitors should not be used in patients with significant bilateral renal artery disease because they may precipitate deterioration in renal function and renal failure. Careful monitoring of renal function and serum potassium concentration is also required in patients with more advanced renal impairment of any cause, because of the risk for hyperkalemia.

Angiotensin receptor blockers. ARBs are highly selective inhibitors of the Ang II type 1 receptor (AT_1). In common with ACE inhibitors, ARBs inhibit the actions of Ang II on the CV system and kidney. ARBs reduce BP as effectively as ACE inhibitors and generally have a longer duration of action. ACE inhibitors and ARBs appear to be equally effective in reducing albuminuria and preserving GFR,[27] and have similar efficacy for preventing major CV events in patients with established CVD.[4,28] Because of their selectivity and specificity for the AT_1 receptor, the ARBs are well tolerated, with a placebo-like adverse effect profile. Cough and angioedema are much less likely to occur with ARBs than with ACE inhibitors, and most guidelines recommend switching patients to an ARB when an ACE-induced cough occurs. Cautions and contraindications are similar to those outlined for ACE inhibitors.

Direct renin inhibitor. The first nonpeptide, orally active DRI, is aliskiren.[26] which has high specificity for renin and is a potent inhibitor of plasma renin activity with a long half-life (~24 hours). Aliskiren inhibits the rate-limiting step in angiotensin production, the renin-dependent conversion of angiotensinogen to Ang I. DRIs have BP-lowering efficacy similar to that of ACE inhibitors and ARBs but with fewer side effects than ACE inhibitors.[26] The contraindications to use are similar to those for ACE inhibitors and ARBs. The main differentiating factor is that ACE inhibitors or ARBs activate plasma renin activity, whereas the DRI inhibits plasma renin activity. Aliskiren also has a much longer duration of action than the other forms of RAS blockade. The ALTITUDE trial tested the efficacy of aliskiren at reducing CV and renal events when added to preexisting RAS blockade in patients with type 2 diabetes and high CVD risk.[29] The study was discontinued for futility, and there was a signal for increased risk for harm when aliskiren was combined with another RAS blocker in this group of high-risk patients. The use of DRIs for the treatment of hypertension continues to decrease because of the absence of evidence for benefit of DRIs on outcomes in hypertensive patients and the lack of any guideline endorsement of their use.

α-Adrenergic Blockers

The original members of the α-adrenergic blocking class (e.g., prazosin) were short-acting drugs that blocked the activation of α_1-adrenoceptors in the vasculature, leading to vasodilation. Initially, the recommended dosage was too high, and postural hypotension and syncope were frequent. The use of lower doses and the development of longer acting agents (e.g., doxazosin) have largely overcome this problem. Blockade of sphincteric receptors improves symptoms in patients with benign prostatic hypertrophy. On occasion, these same sphincteric effects can worsen symptoms of stress incontinence in women. Uniquely among antihypertensive drugs, the α_1-antagonists produce modest favorable changes in plasma lipids, with a reduction in total and LDL cholesterol and triglyceride levels and an increase in HDL cholesterol. Despite the beneficial effects of α_1-antagonists in specific circumstances (e.g., prostatic outflow obstruction), they do not form part of the routine treatment strategy for hypertension in modern guidelines and are largely reserved for their specific indications (e.g., prostatic outflow obstruction), or as "add-on" treatment for resistant hypertension when alternative treatments are not tolerated.

Combined α-Adrenergic and β-Adrenergic Blocker

The use of β-blockers with vasodilatory properties has increased in recent years. Drugs in this class include carvedilol, nebivolol, and labetalol. Carvedilol and nebivolol have been shown to improve outcomes in RCTs in heart failure.[30] Labetalol has a rapid onset of action, making it a useful intravenous medication for the treatment of hypertensive emergencies. Labetalol is also safe in pregnancy and in patients with coronary disease because it does not increase heart rate. Labetalol should not be used without prior adequate α-blockade in patients with hyperadrenergic states, such as pheochromocytoma, because unopposed, inadequately blocked α-adrenergic activity can increase BP if β-blockade is not complete.

Centrally Acting Sympatholytic Drugs

Some of the earliest drugs developed to treat hypertension targeted the activation of the sympathetic nervous system (SNS) at various levels, including the CV regulatory nuclei in the brainstem, the peripheral autonomic ganglia, and the postganglionic sympathetic neuron. Few of these agents have any residual role to play in the modern treatment of hypertension because side effects are common.

Methyldopa reduces sympathetic outflow from the brainstem and frequently causes sedation, impaired psychomotor performance, dry mouth, and erectile dysfunction. Its unfavorable impact on quality of life resulted in methyldopa being gradually replaced by more effective drugs, although it is still extensively used in the management of hypertension of pregnancy, which is now its main indication.

Clonidine is now rarely used because of its short duration of action and risk for withdrawal syndrome, which occurs when sudden discontinuation results in a rebound rise in catecholamines with features that may resemble those of pheochromocytoma, such as severe hypertension, tachycardia, and sweating. This is exacerbated when patients are also receiving nonselective β-blockers such as propranolol. The syndrome is treated by readministration of the drug and then gradual discontinuation or the intravenous infusion of labetalol in an emergency. Clonidine is still used occasionally and can be effective in some patients with resistant hypertension. Longer-acting preparations of clonidine are being developed.

A newer centrally acting agent, *moxonidine* is an imidazoline receptor agonist that reduces sympathetic outflow and BP. It has a lower incidence of side effects and is better tolerated than other centrally acting agents. Moxonidine has no clinical trial evidence to support its use as a preferred first-line agent but is used empirically in some patients with resistant hypertension.

Direct Vasodilators

Hydralazine is no longer recommended as a first-line agent for hypertension management. The main disadvantages of hydralazine are sympathetic activation and the development of a lupus-like syndrome, particularly in patients with the slow acetylator genotype. Also, multiple daily dosing was required. It is still occasionally used in severe hypertension and hypertension associated with pregnancy.

Minoxidil is a potent vasodilator, and its use is largely confined to specialist centers for the treatment of severe and resistant hypertension. Its side effect profile includes stimulation of body hair growth; tachycardia and severe fluid retention reflect its potent vasodilator action and concomitant reflex SNS activation. For this reason, minoxidil is usually combined with a potent loop diuretic and a β-blocker as part of a triple-therapy approach to severe hypertension. Long-term use can be associated with insidious development of peritoneal and pericardial effusions (especially in patients with impaired renal function), which usually respond to treatment withdrawal.

Treatment Strategies

Given the multiple drug classes for the treatment of hypertension, there is a need for a treatment strategy that identifies the preferred drugs for initial therapy and preferred combinations for patients requiring more than monotherapy to control their BP. The use of drug therapy to lower BP should usually follow a period of observation and repeated measures of BP to ensure there is a sustained elevation of BP that merits treatment. The duration of the observation period is inversely related to the severity of hypertension. This ranges from immediate treatment to repeated measurement over days or months.

Lifestyle interventions should be initiated during this period of observation and continued even if treatment with drug therapy is initiated

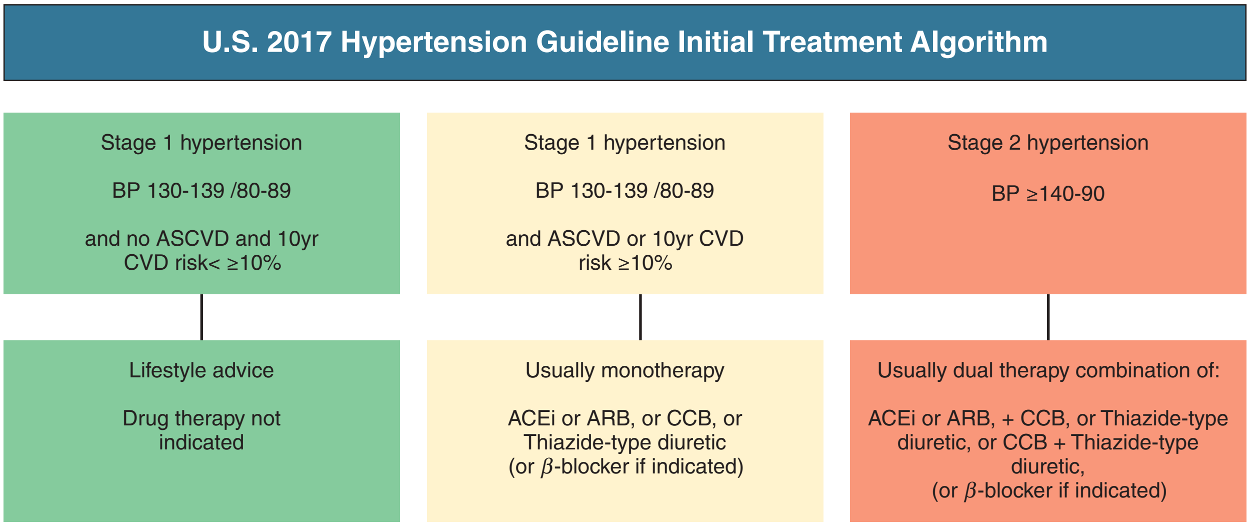
U.S. 2017 Hypertension Guideline Initial Treatment Algorithm
Stage 1 hypertension
BP 130-139 /80-89
and no ASCVD and 10yr CVD risk< ≥10%
Stage 1 hypertension
BP 130-139 /80-89
and ASCVD or 10yr CVD risk ≥10%
Stage 2 hypertension
BP ≥140-90
Lifestyle advice
Drug therapy not indicated
Usually monotherapy
ACEi or ARB, or CCB, or Thiazide-type diuretic (or β-blocker if indicated)
Usually dual therapy combination of:
ACEi or ARB, + CCB, or Thiazide-type diuretic, or CCB + Thiazide-type diuretic,
(or β-blocker if indicated)

Fig. 36.5 U.S. Hypertension Guideline Initial Treatment Algorithm. All patients in these categories of blood pressure *(BP)* should receive lifestyle advice to aid reduction of their BP and CV risk. Patients with stage 1 hypertension and established atherosclerotic cardiovascular disease *(ASCVD)* or calculated to be at least 10% 10-year risk for a cardiovascular disease event *(CVD),* also should receive drug therapy, usually as a monotherapy. Patients with stage 2 hypertension also should receive drug therapy, usually as a dual therapy combination as initial therapy. *ACEi,* Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *CCB,* calcium channel blocker.

(see Chapter 35). This is important because the actions of drug therapy often can be potentiated by concomitant lifestyle changes, especially body weight reduction and reduction in dietary sodium intake.[31] Furthermore, lifestyle changes are also important to improve the overall health and CV risk profile of the patient, beyond the impact on BP. Another key aspect of the initial assessment of patients is to identify concomitant risk factors, comorbidities, and target organ damage, all of which might influence the selection of drug therapies to improve BP control.

Initial Drug Therapy

The most important change in emphasis in the treatment of hypertension has been a shift toward recommending initiating therapy with a two-drug combination of treatment. This is because monotherapy is rarely sufficient to control BP, and this will be especially true if BP targets are universally lowered to less than 130/80 mm Hg. This was exemplified by the recent U.S. guideline that recommends initial dual therapy for most patients with hypertension, except those with stage 1 (i.e., systolic BP 130 to 139 mm Hg) (Fig. 36.5). Other guidelines recommend initiation with monotherapy and a stepped care approach for most patients, except those with grade 2 hypertension (i.e., BP ≥160/100 mm Hg) or those with grade 1 hypertension and high or very high CV risk, in whom initial dual therapy should be considered.

Choice of initial therapy. There is variation in international guidelines with regard to the preferred initial therapy for primary hypertension. In 2001 the U.S. JNC VII report recommended low-dose thiazide diuretics as initial therapy for all, unless contraindicated. The 2017 U.S. guidelines recommend an ACE-inhibitor or ARB as initial therapy, with the addition of a CCB or thiazide-type diuretic for patients with stage 2 hypertension. For stage 1 hypertension, any of these drugs are recommended as monotherapy. β-Blockers are reserved for specific indications, such as angina, after MI, and heart failure.

The current European guideline (2013) recommend that ACE-inhibitors, ARBs, low-dose thiazide-like diuretics, CCBs, or β-blockers were all suitable as initial therapy, usually as monotherapy, guided by the specific indications shown in Fig. 36.6.[7] The U.K. NICE guidelines (2011) adopted a different approach and suggested that both age and ethnicity are important determinants of the BP response to initial therapy (Fig. 36.7).[8] The rationale for this approach is that the RAS is usually more active in younger people and Black people at any age. The U.K. NICE guidelines recommend initial therapy with an ACE

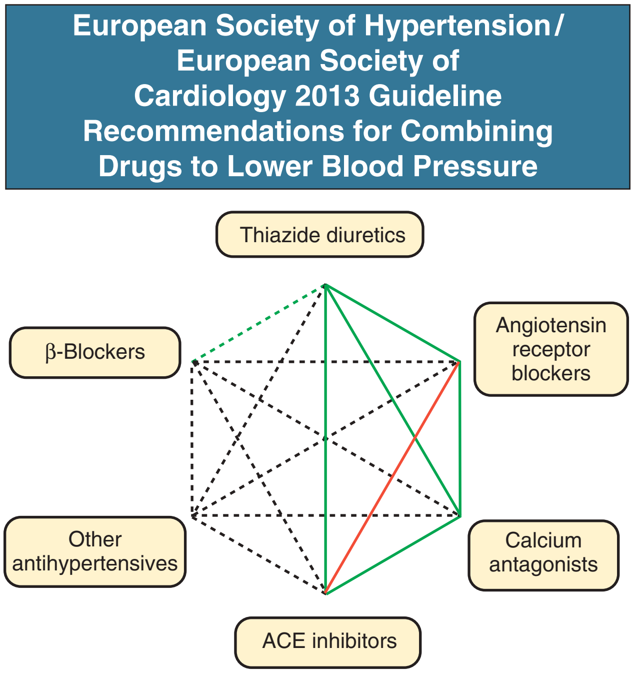
European Society of Hypertension/ European Society of Cardiology 2013 Guideline Recommendations for Combining Drugs to Lower Blood Pressure
Thiazide diuretics
β-Blockers
Angiotensin receptor blockers
Other antihypertensives
Calcium antagonists
ACE inhibitors

Fig. 36.6 ESH/ESC recommendations for combining drugs to lower blood pressure. *Green continuous lines* are the preferred combinations, *green dashed line* is considered a useful combination but with some limitations, *black dashed line* is possible but less well-tested combinations; and the *red line* is not recommended as a combination treatment for hypertension. *ACE,* Angiotensin-converting enzyme. (From reference 7.)

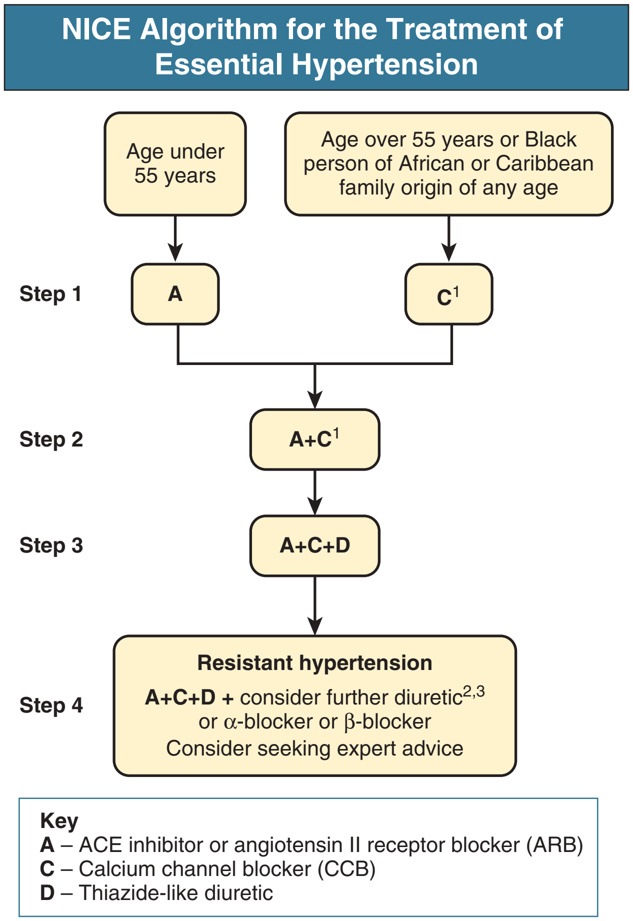
NICE Algorithm for the Treatment of Essential Hypertension
Age under 55 years
Age over 55 years or Black person of African or Caribbean family origin of any age
Step 1
A
C1
Step 2
A+C1
Step 3
A+C+D
Step 4
Resistant hypertension
A+C+D + consider further diuretic2,3 or α-blocker or β-blocker
Consider seeking expert advice
Key
A – ACE inhibitor or angiotensin II receptor blocker (ARB)
C – Calcium channel blocker (CCB)
D – Thiazide-like diuretic

Fig. 36.7 **Algorithm for treatment of essential hypertension.** U.K. National Institute for Health and Clinical Excellence (NICE) guidelines: [1]CCB is preferred, but consider a thiazide-like diuretic (chlorthalidone or indapamide) if a CCB is not tolerated or the patient has edema or heart failure or is at high risk for developing heart failure; [2]consider low-dose spironolactone; [3]higher doses of the thiazide-like diuretic. (Modified from reference 8.)

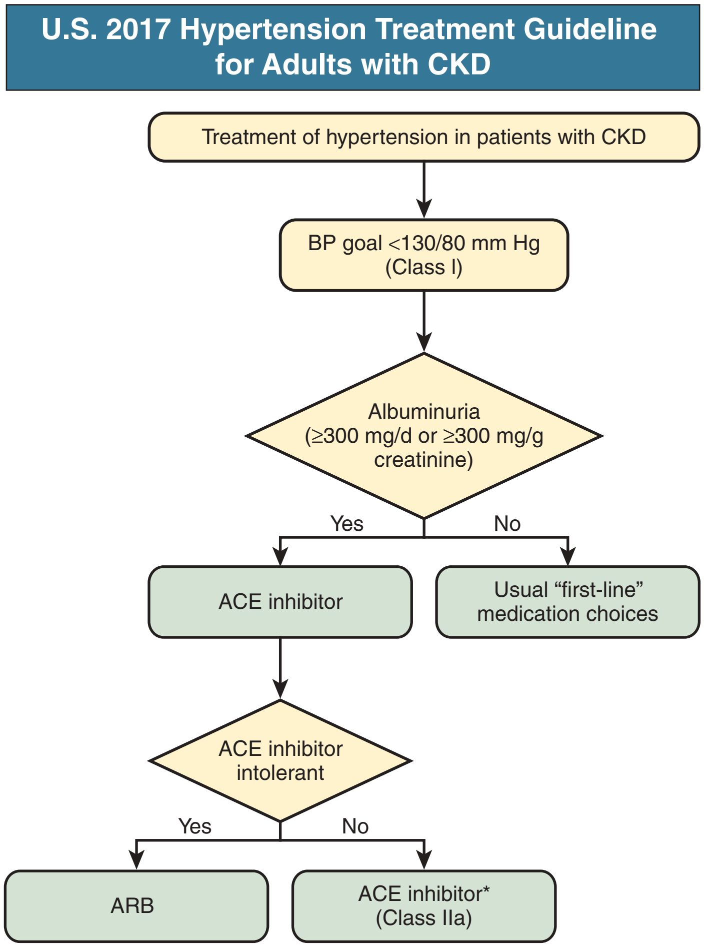
U.S. 2017 Hypertension Treatment Guideline for Adults with CKD
Treatment of hypertension in patients with CKD
BP goal <130/80 mm Hg (Class I)
Albuminuria (≥300 mg/d or ≥300 mg/g creatinine)
Yes
No
ACE inhibitor
Usual "first-line" medication choices
ACE inhibitor intolerant
Yes
No
ARB
ACE inhibitor* (Class IIa)

Fig. 36.8 **U.S. 2017 hypertension treatment guideline for adults with chronic kidney disease** ***(CKD).*** *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure.

inhibitor or ARB in non-Black patients younger than 55 years and a CCB as the preferred initial therapy for most patients aged 55 and older. For Black patients of any age, the U.K. NICE guideline recommends a CCB as the preferred initial therapy. The caveats to these recommendations are (1) that a thiazide-type diuretic may be preferred to a CCB where a CCB is not tolerated or in those with signs of heart failure or at high risk for heart failure (e.g., the very elderly) and (2) that an ACE inhibitor or ARB should not be used in women of childbearing potential, when instead a β-blocker may be preferred. Thus the U.S. 2017 guideline has moved much closer to U.K. NICE guidance with regard to choice of drug therapy for routine treatment of hypertension (Fig. 36.5). The reason for the nonroutine use of β-blockers in the U.K. and recent U.S. guidance is that they (1) appear less effective than alternative drugs at reducing the risk for stroke; (2) were no more effective than other drugs at preventing incident coronary events; (3) were more likely to increase the risk for developing type 2 diabetes, especially when combined with diuretic therapy; and (4) were, as a consequence, the least cost-effective option for the initial treatment of primary hypertension.[8,24]

The U.S. 2017 guideline made specific recommendations for drug treatment in patients with CKD, recommending a BP goal of less than 130/80 mm Hg and a drug treatment strategy that included an ACE-inhibitor (or an ARB if ACE inhibitor intolerant), specifically when there was albuminuria greater than 300 mg/day (Fig. 36.8).

Combination Therapy

There is an emerging consensus in guidelines that the usual combination of drug treatment for hypertension should comprise an ACE inhibitor or ARB with CCB and/or thiazide or thiazide-type diuretic, for the preferred dual or triple therapy combinations. The U.K. NICE guidelines were the first to give explicit guidance for the use of ACE inhibitor or ARB with a CCB (A+C) as the preferred two-drug combination for most people, while accepting that an ACE inhibitor or ARB with a low-dose thiazide or thiazide-like diuretic is a suitable alternative (Fig. 36.7). The recommendation for the preferred use of A+C is supported by the ACCOMPLISH trial, which compared two different single-pill combinations (an ACE inhibitor with a CCB vs. the same ACE inhibitor combined with a low-thiazide diuretic) in a high-risk group of patients.[32] There was a significant (~20%) reduction in the primary end-point of CV morbidity and mortality in favor of the ACE inhibitor and CCB combination, with no difference in BP control between the two treatment groups. These data from ACCOMPLISH, along with the wealth of data from ACE inhibitor or ARBs in combination with low-dose thiazide diuretic therapy, provide evidence-based options to combine with either an ACE inhibitor or ARB as a two-drug combination therapy (i.e., A+C or A+D), with the use of A+C+D when a three-drug combination is required. The preferred combinations are now similar in European, U.S., and U.K. guidance (i.e., A+C or A+D, and A+C+D when required) (Fig. 36.8). The only difference is that the European guidelines also endorse the combination of CCB plus a thiazide-type diuretic, which has been effective in some trials but is rarely used because it excludes RAS blockade, which many would consider complementary to either a CCB or thiazide-type diuretic, lowering BP and preventing reflex activation of the RAS system, which would otherwise occur with a C+D combination. What is clear is that all guidelines have converged and are closer than they have ever been with regard to preferred combination therapies.

Initial therapy with a two-drug combination. "Low-dose" two-drug combination therapy is recommended in the European and American hypertension guidelines when BP is more than 20/10 mm Hg above goal and therefore unlikely to be controlled with monotherapy. The recommendation of a two-drug combination is in part driven by concern that the upward titration of treatment in people at high risk may be too slow and leave them at risk for too long. A two-drug combination is also logical because the response to a single drug is often limited by counteractivation of pressor systems. This also explains why many BP-lowering drugs in monotherapy have a relatively flat dose-response curve. For example, sodium and water loss caused by diuretics or vasodilation with CCBs will activate RAAS, which limits the BP lowering. Thus a two-drug combination therapy is likely to (1) produce much greater BP lowering, (2) reduce heterogeneity in the BP-lowering response, and (3) have a more effective dose-response to upward titration of either component. The main concern has been adverse events related to potentially large initial BP falls in treatment-naïve patients. If the lower BP targets recommended in the recent U.S. hypertension guideline (i.e., <130/80 mm Hg) are replicated by other guidelines, it seems inevitable that low-dose combinations will become necessary for the majority of patients as initial therapy, with the preferred combinations likely to be RAS blockade plus diuretic and RAS blockade plus CCB.

Combining Renin-Angiotensin System Blockade

The view that RAS blockade may help prevent or regress hypertension-mediated structural and functional damage led to the use of dual RAS blockers. However, data from the ONTARGET and ALTITUDE trials demonstrated that dual RAS blockade in high-risk patients with an ACE inhibitor plus ARB combination in ONTARGET,[28] or an ACE inhibitor or ARB plus a DRI in ALTITUDE,[29] was no more effective than RAS blocker monotherapy at preventing major CV events in a high-risk population, including those with diabetes. Moreover, in both studies, the risk for adverse events, especially renal impairment, was greater with dual RAAS blockade. These findings have prompted all international guidelines to state that dual RAAS blockade should not be used for the management of hypertension.

Resistant Hypertension

Resistant hypertension has been defined as BP that remains above target despite the concurrent use of three antihypertensive agents of different classes. The U.S., European, and U.K. guidance all suggest that one of the three agents should be a thiazide-type diuretic and that all agents should be prescribed at optimal doses.[7,9,22] The NICE guidelines state that the three agents should usually comprise A+C+D in best tolerated doses.[8] White coat hypertension should be excluded by 24-hour ABPM. Most of these people will be older, often obese, and invariably with evidence of target organ damage. Other causes of resistant hypertension also should be considered (Table 36.8).[17,33,34]

Most patients with drug-resistant hypertension are likely to be retaining sodium and will respond to further diuretic therapy. A recent study (PATHWAY-2) demonstrated that low-dose spironolactone 25 to 50 mg/day, when added to A+C+D, was more effective at lowering BP than placebo, a β-blocker (bisoprolol), or an α-blocker (modified-release doxazosin).[19] Thus spironolactone has the best evidence for the treatment of resistant hypertension. However, the PATHWAY-2 study was conducted in patients with normal renal function, and careful monitoring for hyperkalemia is required, especially in patients with reduced GFR. Moreover, approximately 6% of men will develop gynecomastia with longer term use of spironolactone, necessitating its withdrawal. Alternatives to spironolactone include eplerenone, higher doses of thiazide-type diuretics, or high-dose amiloride 10 to 20 mg/day. For patients with reduced GFR (<45 ml/min/1.73 m^2), replacing the thiazide-type diuretic with a loop diuretic is usually necessary. For some patients, it may be necessary to use a combination of minoxidil, loop diuretic, and β-blocker to improve BP control.

TABLE 36.8 Considerations in the Patient With Resistant Hypertension

Patient Factors	Secondary Causes of Resistant Hypertension	Concomitant Medications That May Raise BP	Causes of "Pseudoresistant Hypertension"
Demographics	**Common Causes**	**Prescription**	**Poor Patient Adherence to Medications**
Older age, especially over 75 Obesity Women > men More common in Blacks Excess dietary sodium High baseline BP and chronicity of uncontrolled hypertension	Primary hyperaldosteronism (Conn adenoma) Atherosclerotic renovascular disease Sleep apnea CKD	Oral contraceptives NSAIDs Sympathomimetics (e.g., decongestants in cold remedies) Cyclosporine Erythropoietin Corticosteroids (e.g., prednisone, hydrocortisone)	Check BP response to directly observed medication
Concomitant Disease	**Uncommon Causes**	**Nonprescription**	**Errors in BP Measurement**
Target organ damage: LVH or CKD Diabetes Atherosclerotic vascular disease Aortic stiffening	Pheochromocytoma Aortic coarctation Cushing disease Hyperparathyroidism	Drug abuse (e.g., cocaine, amphetamines) Excess licorice ingestion Herbal remedies (e.g., ephedra, also known as ma huang)	Including BP cuff too small for arm circumference
			White Coat Hypertension
			Check BP with ABPM or home BP measurements.

Modified from reference 20.

ABPM, Ambulatory blood pressure monitoring; *BP,* blood pressure; *CKD,* chronic kidney disease; *LVH,* left ventricular hypertrophy; *NSAIDs,* nonsteroidal antiinflammatory drugs.

Medication to Reduce Cardiovascular Risk

Treating hypertension should be considered part of a more comprehensive strategy to reduce CVD risk. Patients at high risk are those with established CVD, target organ damage, or diabetes and those with a high calculated CVD risk; they should be considered for additional interventions to reduce risk. Various tools to assess CVD risk, usually over a 10-year time frame are available. The proposed level of CVD risk considered sufficient to warrant additional interventions has varied; it was typically 20% CVD risk over 10 years but is being progressively reduced toward 10% CVD risk over 10 years. Patients at increased risk, because of established atherosclerotic cardiovascular disease (ASCVD), diabetes, target organ damage, or an elevated 10-year CVD risk score, should receive reinforcement of lifestyle advice, especially smoking cessation, and treatment with statin therapy to further reduce the risk for stroke and coronary heart disease. Routine use of statins to reduce total cholesterol values by 40 mg/dl (~1 mmol/l) has been associated with a reduction in the risk for coronary events by about one third and for stroke by about one fifth, over and above the benefit already accrued from BP lowering.[35,36] Moreover, the relative risk reduction associated with statin therapy in higher risk hypertensive patients is not dependent on a high baseline cholesterol value. Higher risk hypertensive patients should be considered for treatment with antiplatelet drugs once BP has been controlled.

Follow-Up

In the early stages of treatment, the frequency of monitoring will be determined by the patient's response to therapy, the comorbidities, and the complexity of the treatment regimen required to control the BP. After initiating therapy, patients should be reviewed frequently to adjust treatment, monitor for adverse effects, and establish BP control. Once BP is controlled, patients should be reevaluated at least annually for a formal review, and most will be reevaluated every 6 months. Patients are increasingly monitoring their own BP in the intervening periods, and this trend is likely to increase.

Withdrawal of Therapy

Most patients with hypertension require lifelong therapy. Some with grade 1 hypertension who make major adjustments to their lifestyle may obtain sufficient fall in their BP to warrant safe withdrawal of monotherapy. However, patients with target organ damage or those at high CVD risk usually should not have their therapy withdrawn unless there is a compelling clinical reason to do so.[7-9] In patients with previously severe hypertension that has subsequently been well controlled, treatment withdrawal may not always result in an immediate increase in BP, which can sometimes take many months to rise progressively back to dangerously high pretreatment values. Any patient who discontinues therapy must remain under review with regular BP monitoring. All but a very few will require treatment again.

Indications for Specialist Referral

Referral to a specialist center is sometimes indicated for the patient in management of hypertension. Indications include uncertainty about the decision to treat, investigations to exclude secondary hypertension, severe and complicated hypertension, and resistant hypertension (see Table 36.8).

Hypertension in People of Black African Origin

Hypertension is more prevalent in Black patients, is associated with more target organ damage, and carries a worse prognosis, with a particularly high risk for stroke.[37] Black patients tend to respond better to diuretics, CCBs, and dietary salt restriction than White patients. ACE inhibitors, ARBs, and β-blockers are generally less effective as initial therapy in Black patients but become more effective in combination with diuretics or CCBs. When a RAS blocker is used as part of the treatment strategy, an ARB may be preferred because of the increased risk for angioedema with ACE inhibitors in Black patients.

Hypertension in Older People

If a BP of 140/90 mm Hg or higher is used to define hypertension, more than 70% of people older than 60 years will be hypertensive, the majority of these patients having ISH.[38] The lower BP threshold in the new U.S. guidelines means that almost all older patients, and especially those older than 70 years, will be classified as hypertensive. Surveys suggest that physicians consistently underestimate the risks and undertreat hypertension in older people. However, important considerations in treating older people include the following:

1. The arterial wall stiffening that gives rise to systolic hypertension and increased pulse pressure (ISH) is also associated with impaired baroreflex sensitivity with increased risk for orthostatic hypotension. Thus it is important to record lying and standing BP readings in elderly patients.
2. Estimated GFR declines with age, with impaired renal conservation of sodium and fluid in the face of depletion. Elderly patients are therefore more subject to volume depletion as a result of diuretic therapy.
3. Clearance of drugs and their active metabolites is decreased as a result of declining hepatic and renal function.
4. Cardiac function and reserve are often reduced, and patients are therefore much more likely to develop cardiac failure. Trials in elderly patients have consistently shown that treatment of hypertension reduces morbidity and mortality from cardiac failure.
5. Multiple comorbidity is much more common in elderly patients.
6. Communication and adherence with therapy may be more difficult with decline in cognitive function. Some evidence from clinical trials suggests that this decline may be slowed by antihypertensive treatment.

Despite these considerations, elderly patients generally tolerate BP-lowering medications well, and BP reduction leads to substantial benefits in the risk for stroke, coronary events, and heart failure. As a general rule, drug regimens should be as simple as possible and dosages increased more gradually. The greatest danger results from lowering of BP too rapidly. The benefits of treating hypertension in people older than 80 years was illustrated by the Hypertension in the Very Elderly Trial (HYVET), which confirmed that treatment was well tolerated and associated with impressive reductions in the risk for stroke, heart failure, and mortality.[39] Furthermore, approximately one third of patients in the SPRINT study were older than 75 years and there was no evidence that these older patients experienced more harm or received less benefit from more intensive BP lowering.[13] Thus there is no reason to manage very elderly patients any differently from those who are not as old. The recent U.S. guideline has recommended that ambulant, independent, and noninstitutionalized elderly patients should be treated with medication when their systolic BP is 130 mm Hg or higher and treated to a systolic BP of less than 130 mm Hg. This is a very dramatic reduction in both BP thresholds and targets, a recommendation that has been strongly influenced by the outcome of the SPRINT study.[13] This magnitude of BP reduction may be too aggressive for many elderly patients, especially those with a high baseline BP. Moreover, elderly participants in clinical trials such as SPRINT tend to be fitter and more independent than the many millions of elderly patients to whom this guideline will be applied. It seems likely that this recommendation will not be endorsed by other international guidelines that are more likely to consider initiating treatment when systolic BP is 140 mm Hg or greater and target systolic BP to less than 140 mm Hg but not less than 130 mm Hg. Finally, there remains a dilemma, compounded by a paucity of data, with regard to treatment strategies for the more frail and dependent elderly patients, often with limited life expectancy, which in many cases is unlikely to be influenced by treatment of hypertension. Treatment decisions for such patients have to be individualized, in consultation with the patient, family, and carers.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is true of calcium channel blockers (CCBs) for the treatment of hypertension?
   - **A.** Nondihydropyridine CCBs have the strongest evidence base and are the most widely used for treatment of hypertension.
   - **B.** CCBs are not a cost-effective treatment for hypertension.
   - **C.** The peripheral edema associated with CCBs is often improved when combined with renin-angiotensin–blocking drugs.
   - **D.** CCBs are less effective at reducing the risk for stroke compared with other antihypertensives.
   - **E** CCBs are less effective at reducing blood pressure (BP) variability.
2. Which of the following statements is true of recommended BP targets for treated hypertensive patients?
   - **A.** 2017 U.S. hypertension guidelines have recommended a BP target similar to those of other international guidelines, that is, the BP target for most people should be less than 140/90 mm Hg.
   - **B.** Similar targets have been recommended in all guidelines (<140/90 mm Hg) for people 80 years and older.
   - **C.** The evidence for optimal BP targets is stronger for systolic versus diastolic BP.
   - **D.** All guidelines recommend the routine use of ambulatory or home BP monitoring for checking BP control.
   - **E.** The BP targets are similar for office, home, and ambulatory BP measurements.
3. Which of the following statements is true of combination therapies for high BP?
   - **A.** Guidelines acknowledge that combination of two or more drugs are rarely required to control BP in most patients.
   - **B.** Combinations of two or more renin-angiotensin system (RAS)–blocking drugs are no longer recommended for the treatment of hypertension.
   - **C.** RAS-blocking drugs are suitable treatment for women of childbearing potential, either alone or as part of combination treatment, as long as they are discontinued by the third trimester in pregnant women.
   - **D.** β-Blockers are especially effective as part of combination therapy in reducing the risk for stroke in older patients
   - **E.** There is good clinical trial evidence that starting treatment with a combination of two drugs is more effective than a standard "stepped care" approach in reducing CV events.
4. Which of the following statements are true for resistant hypertension?
   - **A.** Resistant hypertension is common, affecting approximately 30% of treated patients.
   - **B.** When patients are thoroughly investigated, resistant hypertension is usually found to be due to a secondary cause of hypertension.
   - **C.** Resistant hypertension is more common in younger patients.
   - **D.** It is only rarely possible to control BP in resistant hypertension with additional drug therapy.
   - **E.** Resistant hypertension is most effectively treated with further diuretic therapy.
5. The 2017 U.S. guidelines recommend which of the following for treatment of patients with chronic kidney disease (CKD)?
   - **A.** Recommend a similar treatment strategy for hypertension irrespective of the presence of proteinuria
   - **B.** Recommend an optimal BP treatment target of less than 140/90 mm Hg
   - **C.** Recommend the use of ACE-inhibitors in preference to angiotensin receptor blockers in patients with proteinuria
   - **D.** Recommend the use of ARBs in preference to ACE inhibitors in patients with proteinuria

37

Evaluation and Treatment of Hypertensive Emergencies and Urgencies

Pantelis A. Sarafidis, George L. Bakris

The term *malignant hypertension* first appeared in 1928 and described patients with extremely high blood pressure (BP) values, to emphasize that because of rapid target organ damage, their average prognosis was similar to that of most cancer patients.[1] Subsequently, malignant (or accelerated) hypertension was used to describe patients with greatly elevated BP and vascular damage that could manifest as retinal hemorrhage/exudate and papilledema, usually associated with encephalopathy, acute kidney injury, and microangiopathic hemolytic anemia.[2,3] However, dramatic advances in both in-hospital and outpatient treatment of hypertensive emergencies have led to an improved prognosis: a decrease in 1-year mortality from 80% in 1928 to 50% in 1955 and to less than 10% after 1990.[4,5] Thus terms such as *malignant* and *accelerated hypertension* have been progressively replaced by the terms *hypertensive emergency* and *hypertensive urgency*.

Marked elevations in systolic BP (SBP) and diastolic BP (DBP) (usually above 180/120 mm Hg) can be classified as either emergencies or urgencies.[6,7] A *hypertensive emergency* is defined as a marked elevation in BP complicated by evidence of acute target organ damage, such as coronary ischemia, dissecting aortic aneurysm, pulmonary edema, hypertensive encephalopathy, cerebral hemorrhage, and eclampsia. In most hypertensive emergencies, BP should be reduced usually by 20 to 40 mm Hg (or no more than 25%) within minutes to an hour using parenteral drug therapy in an intensive care unit (ICU) to limit end-organ damage.[6] *Hypertensive urgency* is a clinical setting of significant BP elevation without acute target organ dysfunction. The approach to hypertensive urgency is a gradual BP reduction within hours, usually with oral medications.[4,6-9] Recently, the American College of Emergency Physicians proposed the term *asymptomatic markedly elevated BP* to be used instead for the term *hypertensive urgency* for patients presenting in the emergency department (ED) with BP above 160/100 mm Hg.[10]

ETIOLOGY AND PATHOGENESIS

Hypertensive emergencies and urgencies can develop de novo in normotensive individuals or can complicate underlying primary or secondary hypertension[4,9,11]; Box 37.1 shows the most common causes. In some hypertensive emergencies, an underlying condition is the clear cause of acute BP elevation. In acute glomerulonephritis, renal crisis in patients with systemic sclerosis, or renal artery stenosis, severe BP elevations are evoked through increased activity of the renin-angiotensin system (RAS). In pheochromocytoma, cocaine intoxication, or spinal cord injury, acutely elevated BP is the result of excess catecholamine release. In other patients, acute sustained elevations in BP itself are the etiologic factor, resulting in conditions such as hypertensive encephalopathy or severe hypertension with acute left ventricular failure and pulmonary edema. In some cases, however, it may be difficult to differentiate whether BP elevation is the cause or the result of a hypertensive emergency. For example, in a patient with intracerebral hemorrhage an acute marked BP increase may be the primary cause; alternatively a hemorrhage of other etiology (i.e., coagulation deficit) may have occurred, followed by BP elevation to preserve cerebral tissue blood supply. Thus a careful diagnostic evaluation of hypertensive emergencies and urgencies is essential to guide proper treatment.

A hypertensive emergency can occur in various clinical settings, but the most common is chronic hypertension (often untreated or poorly controlled) in a patient whose usual BP is above 180/120 mm Hg.[11] In many of these patients, chronically elevated BP does not affect target organ perfusion because of autoregulation. *Autoregulation* is the ability of blood vessels to dilate or constrict in response to changes in perfusion pressure and thereby maintain normal organ perfusion. This mechanism is present in the brain and kidneys and involves L-type calcium channels.[7] Arteries from normotensive individuals can maintain flow over a wide range of mean arterial pressures, 70 to 150 mm Hg, associated with SBP of around 90 to 180 mm Hg. Chronic BP elevations cause compensatory functional and structural changes in the arteriolar circulation and shift the autoregulatory curve to the right, which allows hypertensive patients to maintain normal perfusion and avoid excessive blood flow at higher BP levels.[3,12] Over time, the structural and functional changes in cerebral and renal arterioles may lead to a progressive inability of the arterioles to autoregulate properly (Fig. 37.1).[9,13]

The factors that lead to the severe and rapid BP elevation causing a hypertensive emergency are poorly understood. The rapidity of the onset suggests a triggering factor (i.e., release of a humoral vasoactive factor) superimposed on preexisting hypertension; however, the hypertensive emergency is likely a nonspecific consequence of chronically elevated BP.[3,7] In any case, target organ damage associated with hypertensive emergency results from the inability of autoregulatory mechanisms to maintain normal perfusion pressures in certain vascular beds (especially of brain and kidney) when BP rises above the autoregulatory range.[12] The resultant endothelial injury causes a loss of endothelial antithrombotic properties, with activation of platelets and the coagulation cascade, increased vascular wall permeability, and vascular smooth muscle cell proliferation culminating in an increase of tissue ischemia and ultimately fibrinoid necrosis. This is coupled with activation of hormonal systems and release of vasoactive substances (RAS, catecholamines, endothelin, vasopressin) that maintain a vicious cycle of elevated BP and vascular injury.[3,9] According to recent studies of patients with hypertensive emergency, the typical structural kidney changes are onion-skin appearances of small arteries and arterioles and glomerular collapse (Fig. 37.2) with electron-lucent widening of the subendothelial zone and wrinkling of the glomerular capillary walls, with fibrinoid necrosis of small arteries being less common.[14] Other findings include injury of the affected organs (e.g., cerebral edema).[3,12] Hypertensive emergency may rarely present as a thrombotic microangiopathy, for example, in patients with scleroderma renal crisis (see Chapter 28). Although direct observations on acute kidney dysfunction in hypertensive crises are rare, a recent study reported that patients presenting with hypertensive emergency had lower glomerular filtration rate and increased biomarkers of early kidney injury, such as urine neutrophil gelatinase-associated lipocalin (NGAL), compared with patients with hypertensive urgency or controls.[15]

In normotensive or minimally hypertensive individuals, such as children or pregnant women, the symptoms and signs of a hypertensive emergency occur at lower BP levels than in hypertensive patients because adaptive chronic vascular changes are absent. However, most hypertensive emergencies occur in patients with chronic hypertension. This may relate to other mechanisms contributing to impaired autoregulation, such as progressive arteriolar disease (in both cerebral and renal circulation) and pharmacologically impaired autoregulation (e.g., use of dihydropyridine calcium channel blockers [CCBs], or furosemide).

BOX 37.1 Common Hypertensive Emergencies and Urgencies

Acceleration of Chronic Hypertension
- With papilledema ± encephalopathy ± renal failure
- With features of thrombotic microangiopathy (thrombocytopenia, hemolytic anemia, renal failure, ± papilledema, ± encephalopathy)

Cardiovascular Conditions
- Acute myocardial ischemia/infarction caused by coronary artery disease
- Acute left ventricular failure/pulmonary edema
- Acute aortic dissection
- Severe hypertension after coronary bypass or other vascular surgery
- Epistaxis unresponsive to anterior/posterior packing

Renal Conditions
- Acute or rapidly progressive glomerulonephritis
- Renovascular hypertension
- Renal crises from scleroderma or collagen vascular disease
- Severe hypertension after kidney transplantation

Neurologic Conditions
- Hypertensive encephalopathy
- Intracerebral hemorrhage
- Subarachnoid hemorrhage
- Cerebral embolism or atherothrombotic cerebral infarction
- Severe hypertension after thrombolysis for atherothrombotic stroke
- Acute head trauma
- Guillain-Barré syndrome

Excess Circulating Catecholamine Conditions
- Pheochromocytoma crisis
- Interactions of tyramine-containing foods with monoamine oxidase inhibitors
- Rebound hypertension after sudden withdrawal of centrally acting α_2-agonists (clonidine, methyldopa, or other)
- Use of sympathomimetic drugs (phencyclidine, phenylpropanolamine, cocaine, or other)
- Automatic hyperreflexia after spinal cord injury

Pregnancy-Related Condition
- Eclampsia

Surgical Conditions
- Severe hypertension in patients requiring immediate surgery
- Perioperative hypertension
- Postoperative bleeding from vascular suture lines
- Hypertension after organ transplantation

Hypertension Associated With Severe Burns

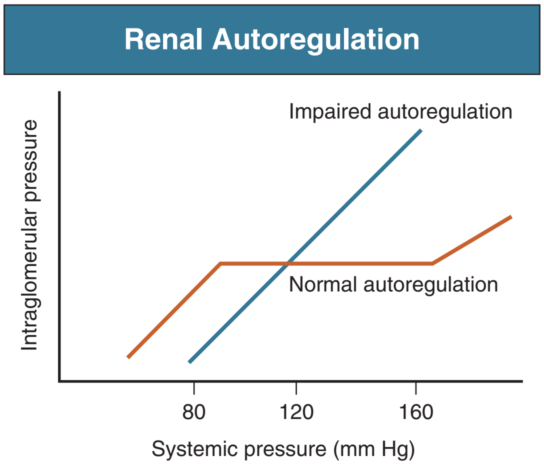

Fig. 37.1 Renal autoregulation. Relationship of systemic to glomerular pressure in the setting of normal or abnormal renal autoregulation.

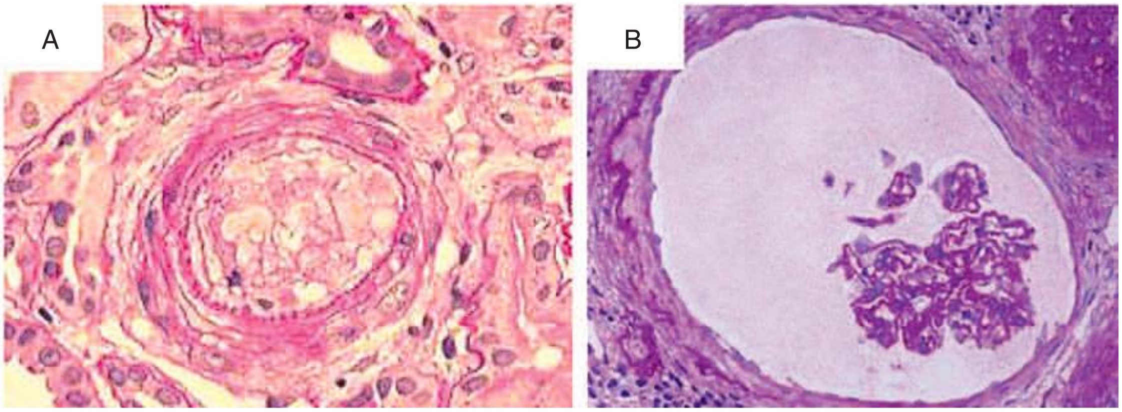

Fig. 37.2 Common kidney biopsy findings in patients with hypertensive emergency–related renal dysfunction. (A) Concentric subendothelial edematous thickening (onion-skin appearance) of an arteriole. (B) Collapsed glomerulus. (Periodic acid–Schiff staining). (Reprinted with permission from reference 14.)

EPIDEMIOLOGY

The exact incidence of hypertensive emergencies and urgencies or the demographic distribution is not known, but an estimated 1% to 2% of individuals with hypertension develop a hypertensive emergency.[16] One study reporting on more than 14,000 ED visits showed that hypertensive urgencies accounted for 76% and emergencies for 24% of hypertension-related visits, which in turn represented 3% of total visits.[17] In this study, the most common manifestations of hypertensive emergency were associated with cerebral infarction (24.5%), acute pulmonary edema (22%), hypertensive encephalopathy (16%), and acute heart failure (14%), followed by myocardial infarction (12%), cerebral hemorrhage (5%), eclampsia (5%), and aortic dissection (2%). In a different series of 435 ED visits for hypertension, 40% were hypertensive urgencies, almost all with some degree of preexisting kidney disease, and 60% were emergencies.[18] Hospitalization for hypertensive emergency occurs at a rate of 1 or 2 cases per 1 million population per year in the United States.[12]

In developed countries, widespread use of antihypertensive agents has reduced the incidence of hypertensive emergencies, as supported by previous indirect observations.[12] Use of any antihypertensive drug reduces the risk for hypertensive emergency because poor treatment compliance and outpatient BP control are predictors of subsequent hypertensive urgency and or emergency.[19] A recent retrospective study on the incidence, cause, and prognosis of hypertensive emergencies in an academic medical center covering a 20-year period documented that 80.3% of patients had been previously diagnosed with hypertension and were undertreated, and the incidence of hypertensive emergency was reduced from 12.7 per 100,000 admissions during 1991 to 1995 to 6.2 per 100,000 admissions during 2006 to 2010, and 1-year mortality decreased from 16.7% to 3.6% over the same periods.[20] With regard to long-term renal prognosis, another study in 120 patients with malignant hypertension showed that during a median follow-up of 67 months, 24% of patients developed end-stage renal disease and started dialysis and another 7% had a greater than 40% decline in estimated glomerular filtration rate.[21] Hospitalization for hypertensive emergency is more common in developing countries, ethnic minorities of developed countries,[5] and individuals of low socioeconomic status, that is, in patients who often have poor BP control.

DIAGNOSTIC EVALUATION

The primary goal of the diagnostic process is to differentiate a true hypertensive emergency from a hypertensive urgency, because of the different therapeutic approaches. The second goal is rapid assessment of the type and severity of ongoing target organ damage. In some hypertensive emergencies, the history (e.g., acute head trauma, preeclampsia, scleroderma) or overt symptoms and signs (e.g., chest/back pain, dyspnea, throbbing abdominal mass) may guide the diagnosis; whereas in other cases (e.g., severe hypertension with altered mental status), the evaluation must be more comprehensive.

The diagnostic approach begins with the patient's history, with attention to duration, severity, and treatment of preexisting hypertension and associated conditions[8,9,11] (Box 37.2). BP measurements should be performed in both arms (if possible, in both sitting and standing positions) and a leg[2] (see Chapter 33). A careful examination and assessment of cardiac, pulmonary, peripheral vascular, and neurologic systems with assessment of mental status should follow, along with a thorough funduscopic (ophthalmoscopic) examination for hemorrhages, exudates, and papilledema.

Signs of secondary hypertension should not be missed in this initial examination. For example, an abdominal bruit may indicate renovascular hypertension; a palpable abdominal mass suggests abdominal aneurysm or polycystic kidneys; a radial-femoral pulse delay suggests aortic coarctation; abdominal striae and central obesity are observed with Cushing syndrome; and exophthalmos may indicate hyperthyroidism.

BOX 37.2 Diagnostic Evaluation for Hypertensive Emergencies and Urgencies

History
- Previous diagnosis and treatment of hypertension
- Symptoms, previous diagnoses, and treatment of cardiac, cerebral, renal, and visual damage
- Intake of pressor agents: Sympathomimetics, illicit substances

Repeated Blood Pressure Measurements (First Measurement in Both Arms)

Physical Examination
- Cardiac
- Vascular
- Pulmonary
- Neurologic
- Optic fundi

Laboratory Studies
- Complete blood count urinalysis, creatinine, urea, electrolytes
- Plasma renin activity, aldosterone, and catecholamines if secondary hypertension is suspected

Electrocardiography

Chest Radiograph

Further Investigations (According to Clinical Presentation)
- Renal ultrasound
- Brain CT scan or MRI
- Echocardiography (transthoracic, transesophageal)
- Thoracoabdominal CT scan or MRI

CT, Computed tomography; *MRI,* magnetic resonance imaging.

The initial laboratory studies in a hypertensive emergency include a complete blood count with peripheral smear, urinalysis, creatinine and urea concentrations, and electrolyte values.[8,9,11] Comparison of kidney function with a patient's recent measurement is important. Severe hypertension accompanied by acute deterioration in kidney function, microscopic hematuria with red blood cell casts, or nephritic urine sediment suggests acute glomerulonephritis. Patients with features of hemolytic anemia and thrombocytopenia should be evaluated for causes of thrombotic microangiopathy. If a secondary form of hypertension is suspected, samples for plasma renin activity, aldosterone concentration, and plasma free catecholamines and metanephrines also should be drawn *before* initiation of treatment. Testing should be performed with the patient supine, and ideally the patient should not be receiving β-blockers, especially labetalol, because of false-positive metanephrine and total catecholamine values. Electrocardiography to rule out myocardial ischemia and left ventricular strain or hypertrophy, as well as chest radiography, should be performed in every patient.[8] Renal ultrasound, if available, is also useful to rule out abnormalities such as differences in size or perfusion, especially in patients with altered renal function or with abnormalities on urinalysis.

Neurologic syndromes associated with hypertension, including subarachnoid hemorrhage, intracerebral hemorrhage, thrombotic stroke, and hypertensive encephalopathy, are difficult to distinguish from one another. Computed tomography (CT) or magnetic resonance imaging (MRI) provides a definite diagnosis of a hemorrhagic or thrombotic stroke. Echocardiography, thoracoabdominal CT or MRI, or abdominal ultrasound may be needed in patients with suspected aortic dissection or pheochromocytoma.[8]

TREATMENT

General Principles for Managing Hypertensive Emergencies

Although therapy with parenteral antihypertensive agents may be initiated in the ED, patients with a hypertensive emergency should be admitted to an ICU for continuous BP monitoring, clinical surveillance, and continued parenteral administration of an appropriate agent (Tables 37.1 and 37.2). Specific BP levels do not determine the severity and the emergency of the situation because the autoregulatory structural and functional changes may vary among individuals, such that some may develop target organ damage at lower BP.

Understanding of autoregulation as well as cardiovascular (CV) comorbidities such as age and extent of vascular disease are crucial for therapeutic decisions; sudden lowering of BP into a normal range could lead to inadequate tissue perfusion.[12] Clinical data document that lowering BP in hypertensive emergencies is beneficial: papilledema and exudates regress, hypertensive encephalopathy vanishes, pulmonary edema resolves, and renal function improves. However, there is also evidence that abrupt lowering of BP can be harmful. For example, the use of sublingual nifedipine with potent but unpredictable BP lowering may shunt blood away from the penumbra of the brain (ischemic penumbra), resulting in a vascular infarct.[22] Thus the goal of antihypertensive therapy is not to normalize BP rapidly, but rather to prevent target organ damage by gradually reducing BP while minimizing the risk for hypoperfusion.

For most patients with hypertensive emergency, the mean BP should be reduced by no more than 20% to 25% within the first hour.[6,8] A DBP target between 100 and 110 mm Hg or a reduction of 25% compared with the initial baseline, whichever is higher, is an appropriate goal within the next 2 to 6 hours. Reduction of DBP to less than 90 mm Hg or by 35% of the initial mean BP has been associated with major organ dysfunction, coma, and death. Similarly SBP should be reduced to levels around 160 mm Hg within the first hour and slowly over the next 24 hours reduced to levels around 140 mm Hg. If the degree of BP reduction is well tolerated and the patient is clinically stable, further gradual reductions toward levels below 140/90 mm Hg should be implemented within the next 24 to 48 hours.

An important consideration before initiation of intravenous therapy is assessment of the patient's volume status. With the exception of patients presenting with volume overload and pulmonary edema, some patients with a hypertensive emergency may be volume depleted because of pressure natriuresis, and diuretics should not be used; rather, fluid administration may help restore organ perfusion and prevent a precipitous fall in BP.[9] Diuretics especially should be avoided in hypertensive emergencies because of catecholamine excess states (pheochromocytoma, monoamine oxidase inhibitor crisis, cocaine intoxication), because these patients are usually volume depleted.

Major exceptions to these treatment recommendations include patients with acute stroke; in ischemic stroke there is no clear evidence to support immediate BP lowering, and a more cautious approach is needed (see Chapter 40), but the recent INTERACT2 trial in patients who presented with a *hemorrhagic* stroke showed that lowering SBP to less than 140 mm Hg within an hour is safe and may improve functional outcome.[23] This observation has led to changes in relevant guidelines.[24] In patients with aortic dissection, SBP should be lowered to less than 100 mm Hg if tolerated; another group of patients who would benefit from BP being lowered to levels between 100 and 110 systolic are those who require thrombolytic agents.[8,16]

After BP has been controlled for a suitable period, typically 12 to 24 hours, allowing autoregulation to reestablish, the intravenous medication is gradually reduced and replaced by oral agents. Typically, a CCB, α- and β-blocker, or RAS blocker can be used, depending on the suspected cause and possible ongoing investigations for secondary hypertension.[12]

Specific Aspects of Antihypertensive Drug Use for Hypertensive Emergencies

The need for gradual and tightly controlled BP reduction requires the use of short-acting intravenous drugs (see Table 37.1), the effects of which can be promptly reversed if the response is excessive. Previous systematic reviews and meta-analyses showed minor differences in the degree of BP lowering and no differences in morbidity or mortality among these agents, because of the relative paucity of large, randomized controlled trials (RCTs) with appropriate follow-up.[25,26] Thus treatment practices were mainly empiric. Recent evidence, however, suggests benefits of novel agents, a result expected to change clinical practice.

For several years, *sodium nitroprusside* was considered the first-choice drug for almost all hypertensive emergencies. It is easily titrated, is inexpensive, and has a long record of effectiveness.[8,12,27] It also has several drawbacks, including accumulation of toxic metabolites (thiocyanate and cyanide) when used for more than 48 hours, especially in patients with renal or hepatic dysfunction, and the need for invasive BP monitoring and an administration system that protects it from light. High-dose nitroprusside increases intracranial pressure. It also obliterates cerebral autoregulation and reduces regional coronary blood flow. These attributes of nitroprusside limit its usefulness in patients with neurologic complications or acute coronary syndromes.[9,16]

Clevidipine butyrate is a new, ultra-short-acting (within 1 to 2 minutes) third-generation CCB that acts through inhibition of extracellular calcium influx via the L-type channel and reduces peripheral vascular resistance without affecting venous vascular tone or cardiac filling pressure. Clevidipine is rapidly hydrolyzed by blood esterases, and thus its metabolism is not affected by renal or hepatic function.[9,16,28] In clinical studies, clevidipine was shown to be effective and safe in the control of perioperative hypertension and hypertensive emergencies.[28,29] The Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) report included three randomized trials with more than 1500 patients with perioperative acute hypertension and compared clevidipine, nitroglycerin, sodium nitroprusside, and nicardipine.[30] In this study, no difference was observed among clevidipine, nitroglycerin, or nicardipine in the primary end point of death, myocardial infarction, stroke, or renal dysfunction at 30 days, but clevidipine was more effective in maintaining BP within the prespecified target range and, most important, was associated with lower mortality than nitroprusside.[30] In view of these data, nitroprusside should be used in hypertensive emergencies only when no other intravenous antihypertensive drug is available.[7,16]

Nicardipine is a dihydropyridine CCB with intermediate onset and duration of effect, prolonged half-life, and strong cerebral and coronary vasodilatory activity. It is useful for most hypertensive emergencies, especially in patients with coronary artery disease. Nicardipine potentiates curare effects and interacts with inhalant anesthetics.[12,27] In an RCT of 226 patients with acute SBP of 180 mm Hg or higher, those receiving nicardipine reached physician-specified target range slightly more often (92% vs. 83%, $P = .039$) than those receiving labetalol.[31] In a subsequent post hoc multivariate analysis, treatment with labetalol (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.1-6.7), history of stroke (OR 5.4, 95% CI 1.6-18.5), and being male (OR 3.3, 95% CI 1.4-8.1) were associated with failure to achieve target BP in this study.[32]

TABLE 37.1 Pharmacologic Agents for Treatment of Hypertensive Emergencies

Drug	Mechanism of Action	Dose	Onset of Action	Duration of Action	Adverse Effects*	Special Indications
Vasodilators						
Nicardipine hydrochloride	Calcium channel blocker	5-15 mg IV every hour	5-15 min	15-30 min, may exceed 4 hr	Tachycardia, headache, flushing, nausea, vomiting, local phlebitis	Most hypertensive emergencies except acute heart failure
Fenoldopam mesylate	Dopamine-1 receptor agonist	0.1-0.3 mcg/kg/min IV infusion	>5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Clevidipine butyrate	Calcium channel blocker	1-2 mg/hr IV infusion; increase every 5-10 min up to 16 mg/h	2-4 min	5-15 min	Tachycardia, headache, flushing, heart failure deterioration	Most hypertensive emergencies; caution with severe aortic stenosis
Sodium nitroprusside	↑ Cyclic GMP, blocks intracellular Ca^{2+} increase	0.25-10 mcg/kg/min IV infusion[†]	Immediate	1-2 min	Nausea, vomiting, muscle twitching, thiocyanate and cyanide intoxication, impaired cerebral autoregulation, coronary steal syndrome	Caution in situations associated with CNS manifestations, hepatic or renal failure; probably should be avoided if given other agents, especially fenoldopam
Nitroglycerin	↑ Nitrate receptors	5-100 mcg/min IV infusion	2-5 min	5-10 min	Headache, vomiting, methemoglobinemia, tachyphylaxis, tolerance with prolonged use	Coronary ischemia, pulmonary edema
Enalaprilat	ACE inhibitor	1.25-5 mg every 6 hr IV	15-30 min	6-12 hr	Precipitous fall in BP in high-renin states, variable response, acute renal failure	Acute left ventricular failure; avoid in acute myocardial infarction
Isradipine	Calcium channel blocker	0.15 mcg/kg/min IV, increase by 0.0025 mcg/kg/min every 15 min. Maintenance infusion 0.15 mcg/kg/min	1-10 min	1-2 hr	Headache, flushing, peripheral edema, dizziness, tachycardia	Perioperative, pregnancy
Hydralazine hydrochloride	Opens K^+ channels	10-20 mg IV	10-20 min	1-4 hr	Tachycardia, flushing, headache, vomiting, aggravation of angina	Must be given with concomitant IV β-blockers to avoid precipitation of angina but *not* a preferred initial choice or treatment
Adrenergic Inhibitors						
Labetalol hydrochloride	α_1-, β-Blocker	20-80 mg IV bolus every 10 min *or* 0.5-2 mg/min IV infusion	5-10 min	3-6 hr	Nausea, vomiting, scalp tingling, bronchoconstriction, dizziness, heart block, heart failure	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	β_1-Blocker	0.5-2 mg/min IV infusion *or* 250-500 mcg/kg/min IV bolus, then 50-100 mcg/kg/min by infusion; may repeat bolus after 5 min or increase infusion to 300 mcg/min	1-2 min	10-30 min	Nausea, asthma, first-degree heart block, heart failure, thrombophlebitis, COPD	Aortic dissection, perioperative, increased heart output or heart rate
Urapidil	α_1-Blocker, serotonin (5-HT_{1A}) receptor agonist	12.5-25 mg IV bolus followed by 5-40 mg/hr IV infusion	3-5 min	4-6 hr	Headache, dizziness	Perioperative
Phentolamine	α-Blocker	5-15 mg IV bolus	1-2 min	10-30 min	Tachycardia, flushing, headache	Catecholamine excess

*Hypotension may occur with all agents.

[†] Requires light-resistant delivery system.

ACE, Angiotensin-converting enzyme; *BP,* blood pressure; *CNS,* central nervous system; *COPD;* chronic obstructive pulmonary disease; *GMP,* guanosine monophosphate; *IV,* intravenous(ly).

TABLE 37.2 Management of Specific Types of Hypertensive Emergencies

Type of Emergency	First-Choice Drug(s)	Second-Choice or Additional Drug(s)	Drugs to Avoid	Aim of BP Reduction
Cardiac				
Coronary ischemia/ infarction	Nitroglycerin, nicardipine, clevidipine, labetalol	Sodium nitroprusside, esmolol if heart failure absent	Diazoxide, hydralazine	Improvement in cardiac perfusion
Heart failure, pulmonary edema	Nitroglycerin, fenoldopam, clevidipine	Sodium nitroprusside, enalaprilat; loop diuretics	Diazoxide, hydralazine; β-blockers	Decrease in afterload
Aortic dissection	Labetalol or combination of esmolol with sodium nitroprusside or fenoldopam or nicardipine		Diazoxide, hydralazine	Decrease of aortic wall stress with systolic BP reduction <100-120 mm Hg in 20 min (if possible)
Renal				
Acute glomerulonephritis, collagen vascular renal disease, or renal artery stenosis	Fenoldopam	Nicardipine, labetalol, clevidipine; diuretics for volume overload	Sodium nitroprusside; ACE inhibitors and ARBs	Reduction in vascular resistance and volume overload without compromise of renal blood flow or glomerular filtration rate
Scleroderma crisis	Enalaprilat or other ACE inhibitor	Angiotensin receptor blocker, fenoldopam	Corticosteroids,* diuretics	Decrease in BP to <140/90 mm Hg with long-term goal of <130/85
Neurologic				
Hypertensive encephalopathy	Nicardipine, fenoldopam, labetalol, clevidipine	Nitroprusside, esmolol, urapidil		20%-25% reduction in mean BP over 1-2 hr
Ischemic stroke	Nicardipine, labetalol, clevidipine	Nitroprusside, nimodipine, esmolol, urapidil		Reduction of BP if above 220/120 mm Hg (mean BP >130) by no more than 10%-15% within first 24 hr to avoid impairing cerebral blood flow in penumbra
Intracerebral hemorrhage	Nicardipine, labetalol, clevidipine	Fenoldopam, nitroprusside, esmolol, urapidil, nimodipine for subarachnoid hemorrhage		For patients presenting with SBP 150-220 mm Hg and without contraindication to acute BP treatment, decrease SBP to 140 mm Hg, as it is safe and can improve functional outcome. For patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring. For subarachnoid hemorrhage in normotensive patients, reduction to systolic BP of 130-160 mm Hg
Catecholamine Excess States				
Pheochromocytoma	Phentolamine or labetalol	β-Blocker in the presence of phentolamine, sodium nitroprusside	Diuretics, β-blockers alone	Control of BP paroxysms from sympathetic stimulation
Ingestion of cocaine or other sympathomimetic	Phentolamine or labetalol	β-Blocker in the presence of phentolamine, sodium nitroprusside	Diuretics	Control of BP paroxysms from sympathetic stimulation
Perioperative/Postoperative Hypertension				
Coronary artery surgery	Nitroglycerin, nicardipine, clevidipine	Esmolol, labetalol, fenoldopam, isradipine, urapidil		Protection against target organ damage and surgical complications (keep BP <140/90 or mean BP <105 mm Hg)
Non-cardiac surgery	Esmolol, labetalol, fenoldopam, nicardipine, clevidipine, urapidil, nitroglycerin			Protection against target organ damage and surgical complications

Continued

TABLE 37.2 Management of Specific Types of Hypertensive Emergencies—cont'd

Type of Emergency	First-Choice Drug(s)	Second-Choice or Additional Drug(s)	Drugs to Avoid	Aim of BP Reduction
Pregnancy Related				
Eclampsia	Labetalol, urapidil	Nifedipine isradipine, nicardipine, $MgSO_4$, methyldopa, hydralazine	Nitroprusside, ACE inhibitors, ARBs	Control BP (typically <90 mm Hg diastolic but often lower) and protect placental blood flow

*Corticosteroids may worsen hypertension in scleroderma renal crisis.

ACE, Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *BP,* Blood pressure; *SBP,* systolic blood pressure.

Fenoldopam mesylate is a selective agonist of dopaminergic 1 receptors located mainly in the renal and splanchnic arteries, with lesser density in the coronary and cerebral arteries.[9,12,27] Intravenous fenoldopam does not cross the blood-brain barrier and has no central nervous system activity because it is a poorly lipid-soluble molecule. In clinical studies, compared with sodium nitroprusside, fenoldopam demonstrated similar BP-lowering efficacy and beneficial renal effects (increased diuresis, natriuresis, creatinine clearance).[33] Thus fenoldopam is mostly useful for BP reduction in patients with renal impairment, those with heart failure, and those undergoing vascular surgery. Fenoldopam must be administered with caution, if at all, to patients with glaucoma because it increases intraocular pressures.[12,27]

Labetalol is a nonselective α_1- and β-blocker (in 1:7 ratio) given intravenously that can be used in many hypertensive emergencies because it has rapid onset of action, potent and sustained effect, and low toxicity. Labetalol reduces peripheral vascular resistance without a reflex increase in systolic volume, while cerebral, renal, and coronary blood flow is maintained. Its main indications are aortic dissection, acute coronary syndromes, hypertensive encephalopathy, and adrenergic crisis. Labetalol can be used in pregnancy-induced hypertensive crisis because little placental transfer occurs as a result of its negligible lipid solubility.[8,9,16] *Esmolol* is a β_1-blocker with an immediate onset and a short duration of action, whose metabolism is not dependent on renal or hepatic function. Esmolol is used particularly in patients with severe postoperative hypertension, and it can be useful in those with increased cardiac output and heart rate.[9,27] Labetalol may be used in chronic obstructive pulmonary disease if the patient has no history of an asthmatic component.[34]

Table 37.1 provides pharmacologic characteristics and adverse effects of other agents that have been used in the treatment of hypertensive emergencies. Table 37.2 includes a general guide for use of these drugs according to the type of hypertensive emergency.[7,11]

Treatment of Hypertensive Urgencies

Although hypertensive urgencies are particularly common, quality studies on the value of extensive diagnostic testing for target-organ damage, the need of hospitalization, the type of treatment and the optimal follow-up in asymptomatic patients with BP elevation are clearly missing.[10] A recent retrospective cohort study with propensity matching that included all patients presenting with hypertensive urgency (BP >180/110) to an office in a large health care system in the United States showed that patients sent home compared with those sent to the ED had an equally low risk for major CV events (0.9%) and equal chance to have uncontrolled hypertension (65% vs. 67%) at 6 months.[35]

Because there is no proven benefit from rapid BP reduction in asymptomatic patients without evidence of acute target organ damage, most agree that BP lowering should occur over a longer time than for a hypertensive emergency. BP reduction to levels below 160/100 mm Hg may be accomplished within 2 to 4 hours in the ED with the oral drugs described later. This may be particularly important for patients without ongoing target-organ damage, who are judged to be at high risk for CV events over the next days because of severe hypertension (e.g., those with known history of aortic aneurysm, repeated pulmonary edema, etc.). However, there are many different types of patients who may present as a hypertensive urgency, the most common of which is the hypertensive patient with low compliance and chronically elevated BP levels. Thus less aggressive lowering of BP (over several hours to days) is also proposed by some, using strategies such as resumption of antihypertensive therapy (in nonadherent patients), initiation of antihypertensive therapy with long-acting agents (if patients are treatment naive), and treatment modification or addition of another antihypertensive drug (in patients who are currently treated). In short, the most important aspect of treatment of hypertensive urgency is not achieving a BP goal but rather ensuring adequate follow-up, generally within 1 week, to an appropriate site of care for chronic hypertension to optimize care and improve BP control of uncontrolled hypertensive patients.[8,9,12] There are data, however, suggesting that most of these patients do not receive medications or instructions in the ED as traditionally described in the literature and providers overestimate how often they refer patients for follow-up, resulting in questionable improvement in long-term outpatient BP control.[10]

Patients with hypertensive urgency should be provided a quiet room in which to rest because this maneuver was associated with BP fall of 20/10 mm Hg or greater in one third of such patients.[36]

Another major factor to consider before prescribing medication is assessment of pain. Patients with severe pain not secondary to cardiac or cerebral origin should be given analgesics first to improve pain. If such patients present with hypertensive urgency and are given acute-acting medications such as clonidine or labetalol, they could become hypotensive once pain is alleviated with nonsteroidal agents, opioids, or steroids.

The choice of drugs for treatment of hypertensive urgencies is much broader than for emergencies, because almost all antihypertensives lower BP effectively given sufficient time. Captopril, clonidine, labetalol, and other short-acting drugs have been used most often (Table 37.3).[8,9] A careful history to assess chronic antihypertensive treatment and patient adherence to medication is critical for drug and dose selection, and clinical surveillance is always advisable during the first few hours after drug administration. In an acute situation, if uncertain whether the patient may have a pheochromocytoma, it is advisable to avoid β-blockers because they can increase BP. This includes labetalol because its α-blocking effect is very small. An α-blocker such as doxazosin or prazosin should always be a first-line drug in these patients.

Oral captopril is typically given in a 12.5- to 25-mg dose; angiotensin-converting enzyme (ACE) inhibitors must be used with caution because they can cause or exacerbate renal impairment in the occasional patient

TABLE 37.3 **Pharmacologic Agents for Treatment of Hypertensive Urgencies**

Drug	Mechanism of Action	Dose	Onset of Action	Duration of Action	Adverse Effects
Captopril	ACE inhibitor	12.5-25 mg PO every 1-2 hr	15-30 min	4-6 hr	Angioedema, cough, acute renal failure
Clonidine	Central α_2-agonist	0.1-0.2 mg PO every 1-2 hr	30-60 min	6-8 hr	Sedation, dry mouth, bradycardia, rebound hypertension after withdrawal
Labetalol	α_1-, β-Blocker	200-400 mg PO every 2-3 hr	30-120 min	6-8 hr	Bronchoconstriction, heart block, congestive heart failure
Furosemide	Loop diuretic	20-40 mg PO every 2-3 hr	30-60 min	8-12 hr	Volume depletion, hyponatremia, hypokalemia
Isradipine	Calcium channel blocker	5-10 mg PO every 4-6 hr	30-90 min	8-16 hr	Headache, tachycardia, flushing, peripheral edema

PO, Taken orally.
Shown are short-acting agents commonly used in the emergency room setting. However, as noted in the text, sometimes longer-acting drugs can be used.

with critical renal artery stenosis.[3,8] A recent study suggested that sublingual captopril had a more pronounced BP lowering effect than oral captopril at 10 and 30 minutes, but similar at 60 minutes after dosing.[37] Oral clonidine, 0.1 to 0.2 mg, is one of the most common agents used in this setting. However, patients should not be discharged on clonidine if they have a history of nonadherence to drug regimens, because of the risk for rebound hypertension if clonidine is abruptly stopped. Furosemide also can effectively lower BP if elevated pressure is related to volume overload, especially if renal dysfunction is present. However, a common physiologic response of the kidney to elevated BP is natriuresis, so many patients, especially those with normal renal function, are volume depleted rather than volume expanded.[8,9] Further, furosemide is not considered a drug choice for primary hypertension because of its short duration of action.

Sublingual short-acting nifedipine, although once frequently used, is now contraindicated secondary to a higher incidence of stroke, myocardial infarction, and death related to precipitous hypotensive episodes after ED release.[22] However, intermediate-acting dihydropyridine CCBs, such as intravenous nicardipine, may be used. A possible exception to this rule is pregnant patients with acute BP elevations, in whom oral nifedipine was shown in randomized studies to reduce BP faster than intravenous labetalol and without safety concerns.[38] Longer acting CCBs, such as once-daily nifedipine or nifedipine XL, amlodipine, and sustained-release isradipine, do not have a role in reducing BP in the ED. However, these and long-acting agents from other major antihypertensive classes are valuable tools for long-term BP control, which, as mentioned previously is the most important aspect of management in these patients.

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SELF-ASSESSMENT QUESTIONS

1. A patient being evaluated for a routine history and physical is noted to have a blood pressure (BP) of 220/130 mm Hg. He states he feels fine except for nightly reflux. Examination shows fundi with atrioventricular nipping and normal heart sounds. Chest x-ray film is normal; serum creatinine 1.3 mg/dl and urinalysis show rare RBCs. Management should include which of the following?
   - **A.** Immediate hospitalization to intensive care unit with administration of intravenous labetalol
   - **B.** Stat electrocardiogram, cardiac enzymes, and admission to the cardiac care unit
   - **C.** Start oral isradipine 5 mg, let the patient rest in a quiet room, and observe for some hours.
   - **D.** Perform a full workup for secondary causes with plasma metanephrines and catecholamines and aldosterone-renin ratio. Start clonidine, 0.4 mg twice daily
2. A patient presents with an acute hemorrhagic stroke and has a BP of 180/120 mm Hg. You are asked to consult on the patient. Which of the following is the *best* strategy?
   - **A.** Give hydralazine (10 mg IV) to bring the BP down as rapidly as possible.
   - **B.** Initiate nitroprusside therapy and titrate BP down to 140/90 mm Hg over a 1-hour period.
   - **C.** Start nicardipine infusion and reduce BP to 160/90 mm Hg within an hour.
   - **D.** Do not treat the hypertension because it may worsen the stroke.
3. A patient presents with acute chest pain. On examination, BP in the right arm is 190/120 mm Hg but in the left arm is only 160/90 mm Hg. The chest x-ray film shows a widened mediastinum. What is the best initial treatment to lower the BP?
   - **A.** Start a nitroprusside infusion, targeting BP of 140/90 mm Hg in the right arm.
   - **B.** Start a labetalol infusion, targeting blood pressure of 100 mm Hg systolic in the right arm.
   - **C.** Start an esmolol infusion, targeting BP of 120 mm Hg systolic in the left arm.
   - **D.** Do not treat the BP because it is important to preserve cerebral perfusion.

38

Endocrine Causes of Hypertension

Aldosterone

I. David Weiner, Charles S. Wingo

Recent advances in the diagnosis of aldosterone-induced hypertension have led to the recognition that primary aldosteronism is more common than previously thought. Effective diagnostic strategies are available, and treatment regimens are highly efficacious.

ETIOLOGY AND PATHOGENESIS

Aldosterone is a steroid hormone normally produced by the zona glomerulosa of the adrenal glands (Fig. 38.1). Aldosterone synthase, which is encoded by the gene *CYP11B2,* is the generally accepted rate-limiting enzyme in adrenal aldosterone production. Table 38.1 summarizes factors known to stimulate or inhibit aldosterone synthesis. There is circadian variation in serum aldosterone concentrations, greatest in the late morning with peak values about 50% greater than the average concentration. The physiologically most important regulators of aldosterone production include angiotensin II (Ang II), which stimulates aldosterone production through activation of the AT1 receptor, atrial natriuretic peptide (ANP), which is inhibitory, and extracellular potassium concentration (hyperkalemia is stimulatory and hypokalemia is inhibitory).[1,2] A high-salt diet, particularly in the presence of chronic kidney disease (CKD), can suppress aldosterone production; this likely occurs through changes in ANP and renin-dependent Ang II production.

Pathogenesis of Aldosterone-Dependent Hypertension

Aldosterone increases blood pressure (BP) through several mechanisms involving effects on the kidneys, vasculature, central and peripheral nervous system (CNS), and other endocrine hormones (Fig. 38.2). These multiple effects explain why primary aldosteronism can cause refractory hypertension.

First, aldosterone stimulates renal sodium chloride (NaCl) retention by increasing expression of the amiloride-sensitive epithelial sodium channel (ENaC), in the collecting duct, and the chloride-reabsorbing protein, pendrin, in the cortical collecting duct.[3-5] Aldosterone also can acutely stimulate sodium reabsorption in these segments through nongenomic mechanisms.[6] Aldosterone also stimulates NCC, the sodium-chloride cotransporter that is present in the distal convoluted tubule (4). Together, these effects on multiple Na^+ and Cl^- transporters lead to NaCl retention, intravascular volume expansion, and volume-dependent hypertension.

Second, aldosterone alters BP through generation of hypokalemia. Aldosterone increases extrarenal cellular potassium uptake by stimulating the ubiquitous Na^+,K^+-ATPase. As discussed in Chapter 9, potassium depletion raises BP through a variety of mechanisms, including expression of the of the thiazide-sensitive NaCl cotransporter in the distal convoluted tubule, induction of renal interstitial injury, and direct vascular effects.

Third, aldosterone has multiple effects on the vasculature. Aldosterone increases both basal vascular tone and vascular reactivity to circulating vasoconstrictors, including norepinephrine, epinephrine, Ang II, and vasopressin.[7] Aldosterone decreases flow-mediated vasodilation, possibly by decreased nitric oxide (NO) production resulting from decreased endothelial NO synthase expression.[8] In the CNS, aldosterone stimulates CNS-mediated sympathetic nervous tone, which further increases BP.[9] Finally, aldosterone causes perivascular fibrosis and stimulates vascular endothelin expression.[10]

Aldosterone mediates its physiologic and pathophysiologic effects predominantly by activating the mineralocorticoid receptor (MR).[11] The MR is located in the inactive state in the cytoplasm in selectively aldosterone-responsive tissue; aldosterone binding to MR promotes a conformational change and translocation to the nucleus, where it regulates gene transcription.

Other Hormones That Can Cause Hypertension Through Mineralocorticoid Receptor Activation

Cortisol is a naturally synthesized glucocorticoid with an affinity for MR similar to that of aldosterone, but is present in plasma at levels about 100-fold greater than aldosterone. The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is expressed in the aldosterone-sensitive distal nephron and collecting duct and metabolizes cortisol to cortisone, which does not effectively bind to MR, thereby preventing glucocorticoid-dependent MR activation. Either the genetic deficiency of 11β-HSD or the ingestion of inhibitors of this enzyme can result in excessive activation of the MR and development of severe hypertension (see Chapter 47).[12] Aldosterone also has nongenomic effects, but their role in mineralocorticoid-dependent BP regulation remains unclear.[13]

Types of Primary Aldosteronism

Primary aldosteronism can result either from an aldosterone-producing adenoma (APA) or from hyperplasia of the zona glomerulosa (Fig. 38.3). Typically, unilateral disease results from adenoma and bilateral disease from hyperplasia. This association is not absolute, and about 10% of patients with primary aldosteronism have either bilateral APA, which may be microscopic, or unilateral hyperplasia. In general, an APA causes more severe primary aldosteronism than does adrenal hyperplasia, but this association is not sufficiently strong to solely guide clinical decision making.

Most APAs are unilateral and are large enough (≥1 cm) to be identified by computed tomography (CT) (Fig. 38.4). However, APAs also may be microscopic and may be bilateral. Hyperplasia is typically bilateral but occasionally is unilateral, and it may develop asynchronously in the two adrenal glands. Because unilateral adrenal hyperplasia is potentially curable with adrenalectomy, the absence of an identifiable adrenal

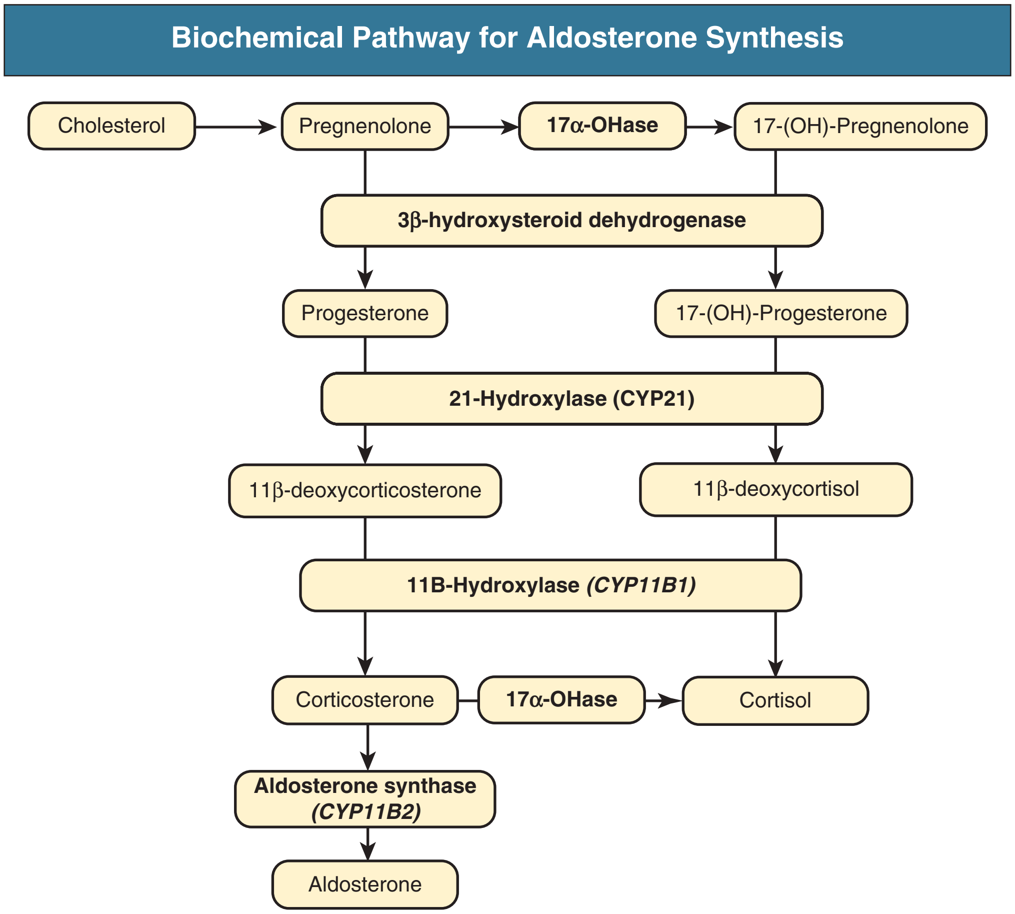
Biochemical Pathway for Aldosterone Synthesis
Cholesterol
Pregnenolone
17α-OHase
17-(OH)-Pregnenolone
3β-hydroxysteroid dehydrogenase
Progesterone
17-(OH)-Progesterone
21-Hydroxylase (CYP21)
11β-deoxycorticosterone
11β-deoxycortisol
11B-Hydroxylase (CYP11B1)
Corticosterone
17α-OHase
Cortisol
Aldosterone synthase (CYP11B2)
Aldosterone

Fig. 38.1 Biochemical pathway for aldosterone synthesis.

TABLE 38.1 Factors That Regulate Aldosterone Release

Stimulatory	Inhibitory
Angiotensin II	*Atrial natriuretic peptide*
*Adrenocorticotropic hormone**	Dopamine
Potassium	Somatostatin
Serotonin	Estrogen (via ERβ receptor)
Vasopressin	
Endothelin-1	
Estrogen (via GPER-1 receptor)	
Parathyroid hormone	
Leptin	

Data from references 1 and 17.
*Acutely, only.
Both extracellular potassium and numerous hormones exert significant effects on aldosterone release. The primary effectors under most clinical circumstances are angiotensin II, potassium, and adrenocorticotropic hormone, and are noted in italics.

adenoma on CT or magnetic resonance imaging does not exclude the possibility of surgically treatable primary aldosteronism.

Familial Forms of Primary Aldosteronism

Multiple familial forms of primary aldosteronism have been identified. In some cases, the clinical presentation suggests the presence of a familial etiology, and in some the presentation is indistinguishable from sporadic forms. With the exception of familial hyperaldosteronism type 1, identification of these familial forms, beyond allowing specific genetic testing of family members of affected individuals, does not alter treatment decisions at this time,

Familial Hypertension Type I

The first identified was *familial hypertension type I* (FH-I), which also is known as *glucocorticoid-remediable aldosteronism* (GRA). In FH-I there is crossover between the *CYP11B1* and *CYP11B2* genes, resulting in a chimeric aldosterone synthase gene, whose expression is regulated by adrenocorticotropic hormone (ACTH), leading to excessive aldosterone release.[14,15] FH-I is transmitted in an autosomal dominant pattern and should be considered in children or young adults with refractory hypertension or in whom there is a family history of hypertension at a young age or history of premature hemorrhagic stroke.[16] If a genetic cause is suspected, genetic testing is the preferred diagnostic approach because of improved sensitivity and specificity over measurement of steroid metabolites or dexamethasone suppression testing.[16] When FH-I is identified, administering corticosteroids at the lowest dose necessary to suppress ACTH release often dramatically improves BP control (see Chapter 47).

Familial Hyperaldosteronism Type II

The clinical presentation of FH-II does not differ from that observed with sporadic forms of primary aldosteronism.[17] Genetic studies have not identified any causative mutations. At present, FH-II is identified by its autosomal dominant clinical presentation and absence of mutations in *CYP11B2*, *KCNJ5*, or *CACNA1H*, the genes responsible for other familial hyperaldosteronism syndromes.

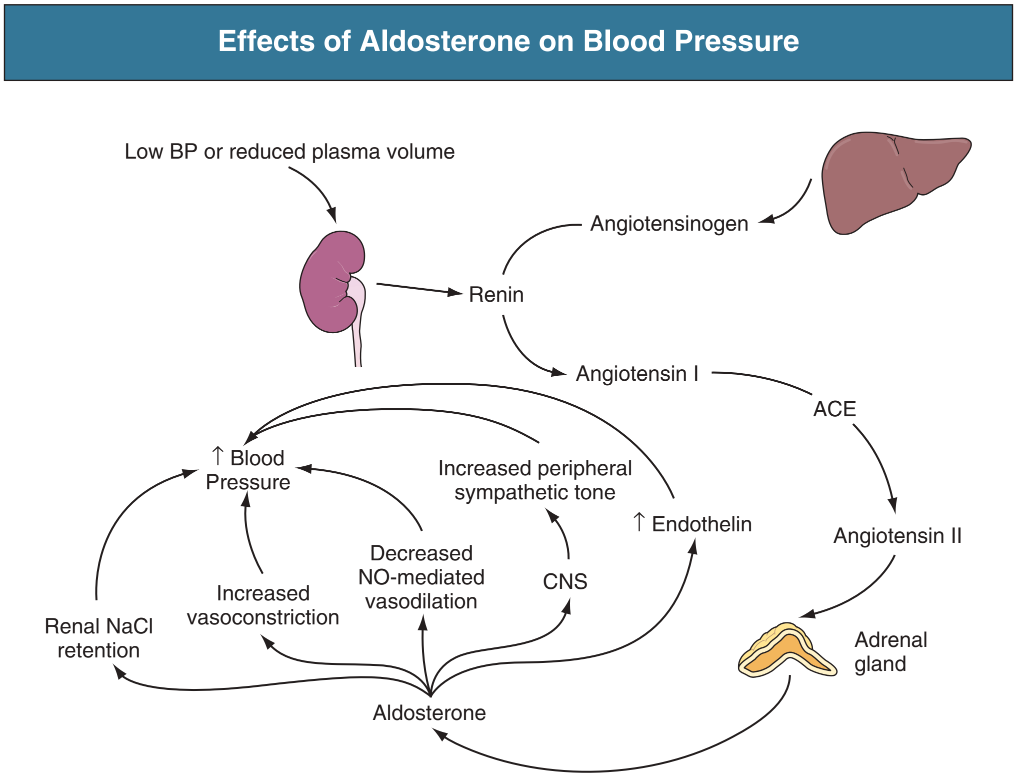
Effects of Aldosterone on Blood Pressure
Low BP or reduced plasma volume
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Adrenal gland
↑ Blood Pressure
Increased peripheral sympathetic tone
↑ Endothelin
Decreased NO-mediated vasodilation
CNS
Increased vasoconstriction
Renal NaCl retention
Aldosterone

Fig. 38.2 **Summary of aldosterone's effects on blood pressure** ***(BP)*** **regulation.** *ACE,* Angiotensin-converting enzyme; *CNS,* central nervous system; *NO,* nitric oxide.

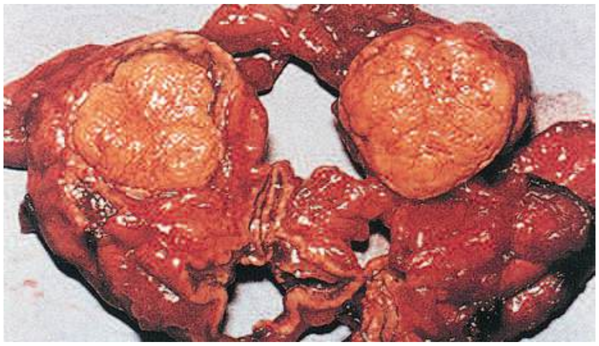

Fig. 38.3 **Adrenal adenoma.** An aldosterone-producing adrenal adenoma with typical cholesterol-rich yellow appearance.

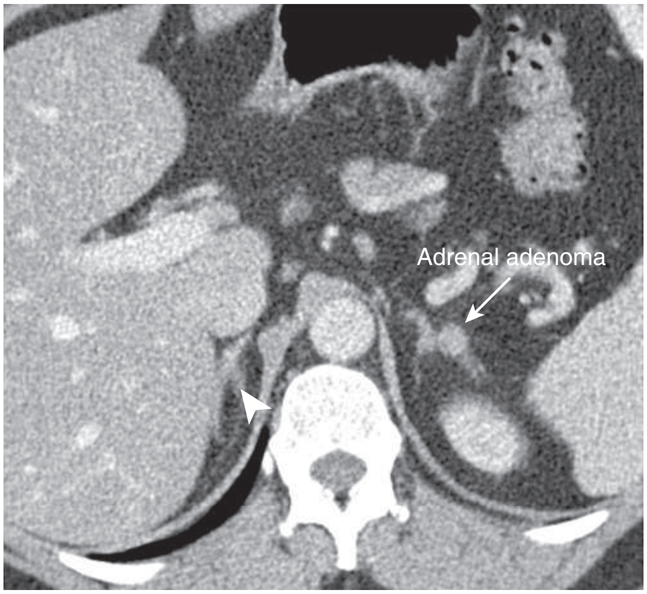
Adrenal adenoma

Fig. 38.4 **Adrenal adenoma by computed tomography scan.** A normal linear image of the right adrenal gland *(white arrowhead)* and expansion of the left adrenal with aldosterone-producing adenoma (~1 cm) *(white arrow).*

Familial Hyperaldosteronism Type III

FH-III was first reported in 2008.[18] Although initial studies characterized FH-III as having a severe, often childhood onset of hypertension, subsequent studies suggest the presentation is more variable.[17] FH-III is the result of germline mutations in the *KCNJ5* gene.[19,20] The *KCNJ5* gene encodes a K^+ channel that is a major determinant of adrenal cortical cell membrane voltage. Mutations observed in FH-III result in loss of K^+ selectivity, leading to Na^+ influx, and membrane depolarization. Consequently, there is voltage-gated Ca^{2+} channel activation, increased cytosolic calcium, and stimulation of aldosterone production and adrenal cell proliferation.

Familial Hyperaldosteronism Type IV

FH-IV is the most recently identified genetic form of primary aldosteronism and generally presents with hypertension and primary aldosteronism before 10 years of age.[21] FH-IV appears to result from mutations in the *CACNA1H* gene, which encodes for a T-type calcium channel ($Ca_V3.2$). These mutations appear to lead to increased Ca^{+2} entry, increased cytosolic calcium, and stimulation of aldosterone production and adrenal cell proliferation. Clinical penetrance of the mutation is incomplete.

Sporadic Forms

Substantial advances have been made recently in our understanding of the factors that lead to sporadic forms of primary aldosteronism. In particular, mutations in the potassium channel gene *KCNJ5* are now recognized as a frequent cause of primary aldosteronism. Somatic mutations are present in about 40% of aldosterone-producing adenomas and may occur in as many as 65% to 80% in certain regions, such as China, Taiwan, and Japan.[19,22] Somatic mutations in the genes *ATP1A1* (encoding the α-subunit of Na^+,K^+-ATPase), *ATP2B3* (encoding a Ca^{2+}-ATPase), and *CACNA1D* (encoding a voltage-gated calcium channel subunit) also have been identified in about 7% of APAs.[17,23] These mutations increase intracellular calcium in adrenal cortical cells, and the increased intracellular calcium is believed to initiate the development of hyperplasia, lead to adenoma formation, and increase expression of the specific genes involved in aldosterone synthesis. Each of these mutations appears to alter intracellular calcium regulation, leading to stimulation of aldosterone production.

Recent advances also have been made in understanding the pathogenesis of primary aldosteronism from bilateral adrenal hyperplasia. Activating autoantibodies directed against the Ang II type I (ATI) receptor may activate the ATI receptor, both directly stimulating adrenal aldosterone secretion and contributing to the hypertension through an aldosterone-independent mechanism involving ATI receptor activation in vascular tissue.[24,25] To date, the presence of these antibodies has been examined in only a limited number of patients. Additional studies are needed to examine how widespread this mechanism is found and what proportion of cases of bilateral adrenal hyperplasia results from this mechanism.

EPIDEMIOLOGY

The apparent incidence of primary aldosteronism varies with the patient population and the diagnostic criteria used. Early studies, which recognized only severe cases, suggested that primary aldosteronism was rare, with an incidence less than 1% to 2%. More accurate diagnosis has now led to the recognition that primary aldosteronism is relatively common. Patients with treatment-resistant hypertension—inadequately controlled hypertension despite treatment with three medications at appropriate dosages, including a diuretic—are highly likely to have primary aldosteronism, with rates typically of 20% to 40% and as high as 67% in some studies (Fig. 38.5).[26]

CLINICAL MANIFESTATIONS

Identifying patients with primary aldosteronism purely on clinical characteristics is difficult. Some patients with primary aldosteronism have features suggestive of secondary hypertension, such as early onset of hypertension or the need for multiple drugs for BP control. Others present with either frank or easily provoked hypokalemia. But many have no distinguishing characteristics that differentiate them from individuals with essential hypertension. The incidence of primary aldosteronism in a hypertensive population parallels the severity of hypertension, although 1% to 2% of those with primary aldosteronism are normotensive (see Fig. 38.5).[27] Table 38.2 summarizes characteristics of those with primary aldosteronism.[28]

Because of this wide variety of presentations, we recommend testing all patients who have characteristics of secondary hypertension, have baseline or easily provoked hypokalemia, or have hypertension not effectively controlled with routine antihypertensive therapy for primary aldosteronism. It is important to recognize that both hypokalemia and metabolic alkalosis are no longer considered hallmarks of primary aldosteronism and are absent in the majority of patients.

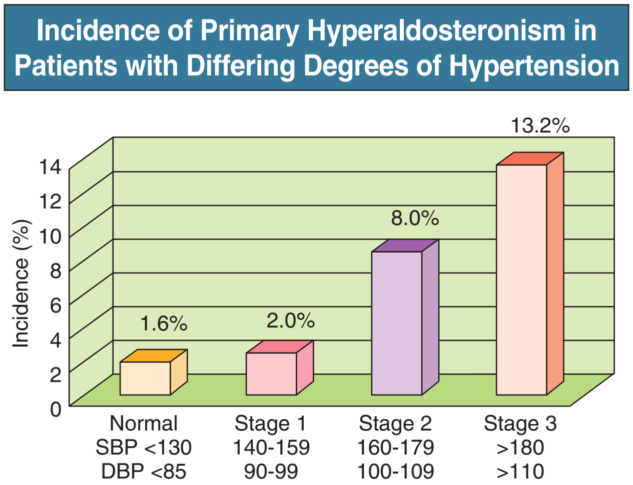

Fig. 38.5 Incidence of primary aldosteronism in patients with differing degrees of hypertension. *DBP,* diastolic blood pressure; *SBP,* Systolic blood pressure. (From reference 27.)

TABLE 38.2 Typical Characteristics of Patients at Diagnosis of Primary Aldosteronism

Patient Factor	Measured Value
Gender (female/male)	43 : 57 (%)
Age (yr)	52 ± 1 (range 29-74)
Hypertension duration (yr)	10 ± 1
Number of hypertensive medications	2.4 ± 0.1 (range 0-4)
Percentage requiring three or more medications	54%
Blood pressure controlled with current medical regimen	20%
Neither hypokalemic nor receiving three or more medications	52%
Plasma aldosterone (ng/dl)	
<15	37%
15-40	54%
>40	9%
Plasma renin activity (ng Ang I/ml/h)	0.39 ± 0.04

Data from reference 17 and 28.

Primary aldosteronism also causes adverse effects that are independent of hypertension and hypokalemia. Untreated primary aldosteronism causes cardiovascular events at rates greater than attributable solely to the hypertension. This includes an increased risk for cardiac arrhythmias, both atrial and ventricular, cerebrovascular events, and coronary heart disease.[29] Diagnosing and treating the primary aldosteronism, whether with adrenalectomy or with MR blockers, as clinically appropriate, substantially reduces, and may even fully correct, this increased risk.[29] Finally, primary aldosteronism is associated with a variety of neuropsychiatric disorders, ranging from depression and anxiety to lethargy, fatigue, and difficulties with concentration. Appropriate treatment of the primary aldosteronism appears to reverse these symptoms.[17]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Who to Screen for Primary Aldosteronism

We recommend that screening for primary aldosteronism should be performed in several groups of patients. The first is the patient with refractory hypertension. The incidence of primary aldosteronism is increased in patients with hypertension and increases with increasing severity of hypertension. The second is the patient with spontaneous or easily provoked hypokalemia. Hypokalemia has significant long-term adverse effects, and identification and treatment of the underlying cause is beneficial. Finally, the patient found to have an adrenal adenoma on abdominal imaging should be considered for screening if under the age of 40 years, where the incidence of a nonfunctional adrenal adenoma is low. In the patient older 40 years, we recommend screening for primary aldosteronism if hypertension requiring therapy with multiple medications is present.

The question as to whether to screen patients with refractory hypertension at all for primary aldosteronism before initiating therapy with MR blockers is not a simple one. MR blockers, when used for the treatment of refractory hypertension, improve BP to a similar extent in those who do and those who do not have primary aldosteronism.[30] Thus screening is not needed to determine whether MR blocker therapy will be effective treatment of the hypertension. We recommend screening for primary aldosteronism before initiating MR blocker therapy because significant diagnostic problems occur if a patient treated with an MR blocker who was not screened for primary aldosteronism is found at a later time to have an adrenal adenoma. Determining whether this is an APA or a nonfunctional adenoma is very difficult in this case because MR blocker treatment can cause false-negative screening test results for primary aldosteronism. If withholding an MR blocker, the length of time it should be withheld to enable effective serologic screening has not been determined; we recommend holding therapy for at least 2 weeks, and preferably 4 weeks. Otherwise, the only way to differentiate a nonfunctional adenoma from an APA is through adrenal vein sampling, with the risks and significant costs associated with this procedure. Accordingly, we recommend screening for primary aldosteronism before initiating antihypertensive therapy with MR blockers. If the screening result is negative, MR blocker therapy should still be used, but there is no need to evaluate for an APA should an adrenal adenoma be identified at a later time.

Evaluation of Suspected Primary Aldosteronism

Evaluation of patients with suspected primary aldosteronism is directed at (1) identifying those who have autonomous aldosterone release and then (2) determining whether treatment should be based on a medical or a surgical approach (Fig. 38.6).

Use of the Aldosterone-Renin Ratio (ARR)

Evidence of Ang II–independent aldosterone release is used to indicate autonomous aldosterone release and therefore primary aldosteronism. Because Ang II cannot be assayed by routine clinical tests, renin is used as a surrogate. A random blood sample is used to measure the ratio of plasma aldosterone to renin (ARR). This sample should be obtained in early morning because of diurnal variations in plasma aldosterone and plasma renin activity. The question as to whether to hold medications that can alter the renin-angiotensin-aldosterone system (RAAS) and, if so, for how long before testing is complex and is discussed in detail later. If the ARR is elevated, this suggests that there is significant Ang II–independent aldosterone release, providing presumptive evidence of autonomous aldosterone production consistent with primary aldosteronism.

Currently, two types of renin assays are in routine clinical use. One measures renin activity, assayed as the rate of conversion of angiotensinogen to Ang I, and the second measures the amount of immunoreactive renin. These two techniques yield results that correlate well with each other, but the units and numerical values obtained differ. For the plasma renin activity, the normal range is 1.9 to 3.7 ng Ang I/ml/h, and the lower level of detectability is 0.1 ng Ang I/ml/h in most clinical laboratories. For the direct renin assay, the normal range is typically 13 to 44 IU/ml and lower level of detectability is 6 to 8 IU/ml. Therefore the typical ARR, for a patient with primary hypertension not receiving drugs that alter the renin-angiotensin system (RAS), is about 10 : 1 when using the plasma renin activity and 1 : 1 with the direct renin assay.

Although an elevated aldosterone value in combination with an elevated ARR strongly suggests primary aldosteronism, an elevated ARR can occur even with suppressed plasma aldosterone production if plasma renin activity (or concentration) is substantially suppressed. In this event, the ARR represents a false-positive screening result. We recommend that the combination of an elevated ARR and a "nonsuppressed" aldosterone level should be used for case-screening for primary aldosteronism. The minimal plasma aldosterone level that may be associated with aldosteronism is unclear. We recommend using a minimal value of 8 ng/dl to make a diagnosis of primary aldosteronism.[31] Others recommend using a cut-off of 15 or even 20 ng/dl.[32,33] We recommend the lower cut-off because about 40% of patients with primary aldosteronism have plasma aldosterone levels between 9 and 16 ng/dl,[27,34] and about 20% of those with unilateral autonomous adrenal aldosterone production have levels less than 15 ng/dl.[34]

Effect of Drugs on Screening for Primary Aldosteronism

Many medicines commonly used for the treatment of hypertension can alter either plasma aldosterone or renin release and thereby alter the ARR.[33,35] β-Adrenergic receptor antagonists (β-blockers) suppress renin release, typically by about 50%. However, β-blockers generally will not result in complete renin suppression that is typically seen in primary aldosteronism.[35] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), along with diuretics, can increase renin release in normal individuals, which theoretically might decrease the sensitivity of ARR measurement. However, the effect of ACE inhibitors and ARBs to increase renin release also can be an advantage. In patients using either an ACE inhibitor or an ARB, suppressed renin in combination with nonsuppressed aldosterone (>8 ng/dl) is highly specific for primary aldosteronism. MR antagonists such as spironolactone and eplerenone can elevate the plasma renin activity and impair the sensitivity of testing. Direct renin inhibitors have been reported to both increase and decrease plasma renin activity in patients who presumably have essential hypertension and decrease plasma aldosterone. Their effect on plasma renin activity and ARR in patients with primary aldosteronism is not known.

When to Withold Drugs That Affect the Renin-Angiotensin-Aldosterone System Before Screening

The decision whether to discontinue drugs that directly interact with the RAAS requires the clinician to balance competing priorities. Doing so can improve the diagnostic accuracy of measurement of aldosterone and plasma renal activity. However, in the patient with poorly controlled hypertension, discontinuing all diuretics, β-blockers, ACE inhibitors, ARBs, and direct renin inhibitors and attempting to control the BP solely with calcium channel blockers (CCBs), α-adrenergic blockers, and direct vasodilators can be problematic because of the risk for worsening already poor BP control. Moreover, the amount of time drugs should be discontinued to completely reverse all of their effects on the adrenal gland is not clear. Acute effects of these drugs will be reversed

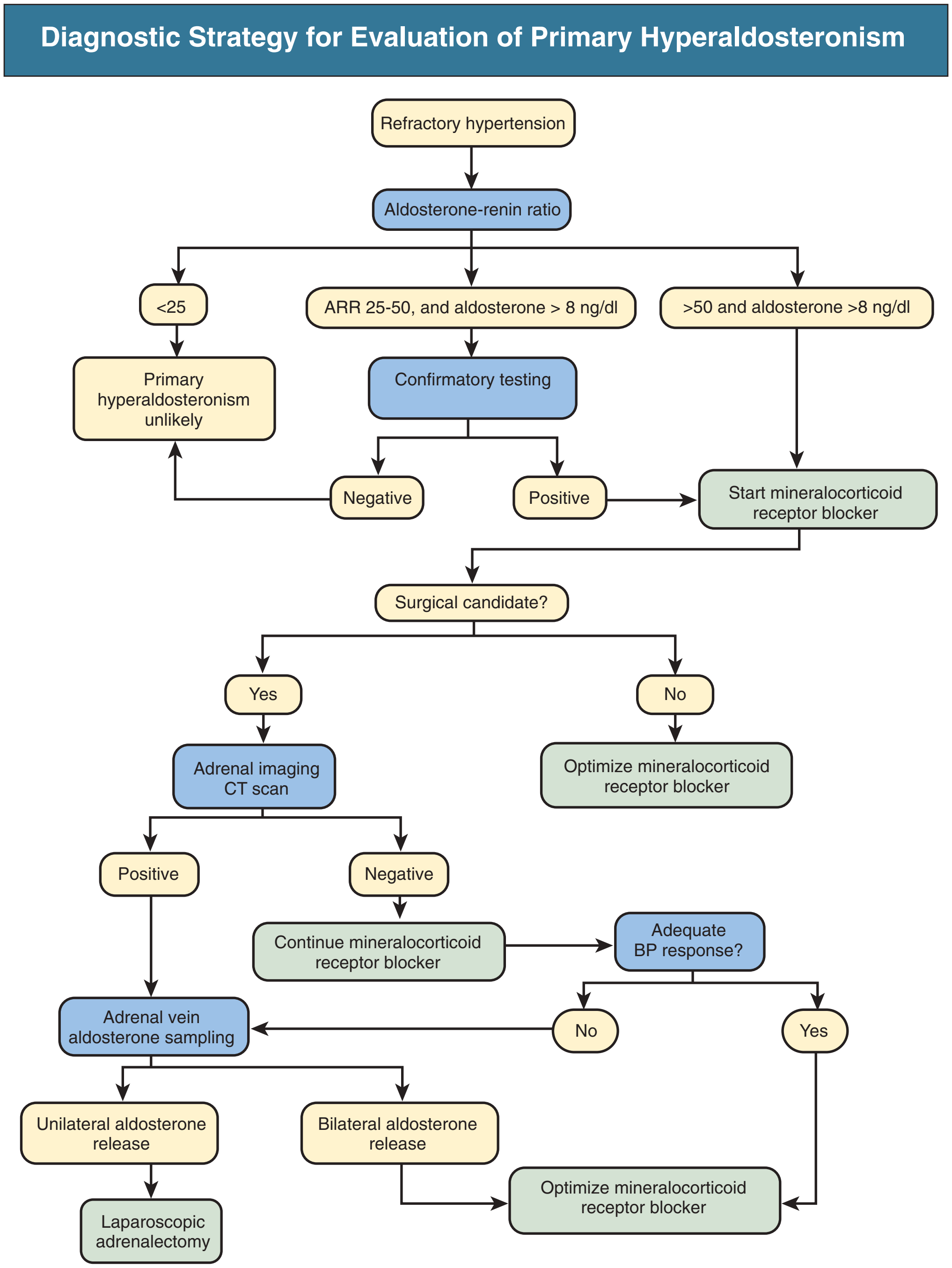
Diagnostic Strategy for Evaluation of Primary Hyperaldosteronism
Refractory hypertension
Aldosterone-renin ratio
<25
ARR 25-50, and aldosterone > 8 ng/dl
>50 and aldosterone >8 ng/dl
Primary hyperaldosteronism unlikely
Confirmatory testing
Negative
Positive
Start mineralocorticoid receptor blocker
Surgical candidate?
Yes
No
Adrenal imaging CT scan
Optimize mineralocorticoid receptor blocker
Positive
Negative
Continue mineralocorticoid receptor blocker
Adequate BP response?
Adrenal vein aldosterone sampling
No
Yes
Unilateral aldosterone release
Bilateral aldosterone release
Optimize mineralocorticoid receptor blocker
Laparoscopic adrenalectomy

Fig. 38.6 **Diagnostic strategy for evaluation of primary aldosteronism.** Aldosterone-renin ratio *(ARR)* is calculated using measurement of plasma renin activity. If direct renin immunoassay is used, the resulting ARR calculation should be multiplied by 10 for use with this diagnostic algorithm. *BP,* Blood pressure; *CT,* computed tomography.

once they are fully metabolized. However, chronic effects that involve AT1 receptor–mediated changes in expression of proteins involved in aldosterone synthesis may be more long-lasting. Finally, requiring discontinuation of these drugs for at least several days, and optimally several weeks, before testing substantially complicates the use of ARR as an easy screening test in patients who may be at only modest risk for primary aldosteronism.

Our practice as to whether to withhold drugs before testing depends on clinical situation. For patients evaluated because of refractory hypertension, we think the time, expense, and risks for more severe hypertension associated with discontinuation of all drugs that can affect the RAS and treatment of the refractory hypertension solely with CCBs, direct vasodilators, and α-blockers, is significant, and that the risk may exceed the benefit of eliminating concern regarding these drugs on the ARR. Indeed, in this population, whether the patient has primary aldosteronism does not predict whether MR blockers will improve BP control; patients with refractory hypertension regardless of whether they have primary aldosteronism respond equally well treatment to MR blockers. The diagnosis of primary aldosteronism is important primarily to direct decisions regarding whether to evaluate further for a potentially surgically curable APA. Because an APA is typically associated with more severe primary aldosteronism, the risk for false-negative testing if medications are not held may be less.

In patients being evaluated because they have an adrenal adenoma and who have minimal clinical symptoms related to possible primary aldosteronism, that is, do not have resistant hypertension and who do not have substantial hypokalemia, our approach is different. In this patient population, we think discontinuation of medications that alter the renin-angiotensin-aldosterone pathway and substitution with CCBs and direct vasodilators, as needed for BP control, is appropriate. In this latter group, the clinical difficulty and risks to the patient from making this medication change is much less substantial.

Confirmatory Testing

If the diagnosis of primary aldosteronism is in doubt, several confirmatory tests can be used. Table 38.3 summarizes the various confirmatory testing methods in routine use. Both the risks and the benefits of confirmatory testing must be considered.[31] None of the confirmatory tests has 100% sensitivity or specificity. Moreover, confirmatory testing has complicating issues associated with its performance. Salt loading, if used for testing, can raise BP and worsen hypokalemia and is problematic in the patient who already has poorly controlled hypertension. Testing requires the patient to not use any medications that interact with the RAAS, which means discontinuation of β-blockers, ACE inhibitors, ARBs, MR blockers, direct renin inhibitors, and diuretics, and this can lead to significant worsening of hypertension control.[31] How long these medications should be held is not clear. Acute effects will dissipate within days as the medications are metabolized, but chronic effects on expression of proteins involved in adrenal aldosterone metabolism may persist longer.

We recommend that confirmatory testing should be used if it will substantially alter management. Patients with resistant hypertension respond well to MR antagonists with significant BP improvement even if they do not have primary aldosteronism.[36,37] Because of this, we do not routinely perform confirmatory testing before initiating treatment with MR blockers in this population. We reserve confirmatory tests for patients with an adrenal adenoma found for unrelated reasons who have minimal clinical symptoms and are being evaluated for possible adrenalectomy. In this latter patient population, the benefits of MR blocker therapy are less clear and the clinical risks associated with holding RAS blockers, discussed earlier, are substantially less. Accordingly, we believe that confirmatory testing before adrenal vein sampling procedure and possible adrenalectomy is appropriate.

Differentiation of Etiology

Selection of Patients for Further Testing

Once primary aldosteronism is diagnosed, the clinician should determine whether there is primarily unilateral aldosterone release, in which case adrenalectomy may be curative. However, this step is important only if the patient is both an appropriate surgical candidate and desires possible surgical intervention. If either condition is not met, further evaluation is not necessary, and the patient can be treated with MR blocker therapy.

Imaging Approaches

Primary aldosteronism most commonly results either from an APA, which is typically unilateral, or from hyperplasia of the zona glomerulosa, which is typically bilateral (see Fig. 38.3). Most APAs are large enough (>1 cm) to be identified by CT (see Fig. 38.4). Adrenal hyperplasia, as a cause of primary aldosteronism, is not detectable with current CT or MR imaging techniques. It is important when imaging for a possible APA to use CT or MR imaging with distances of only 1 to 3 mm between slices. Conventional abdominal CT imaging, which often uses 10-mm slices, can miss small adrenal adenomas. However, the presence or absence of an adrenal adenoma should not be equated with the presence or absence of unilateral or bilateral aldosterone production, respectively. About 10% of patients with primary aldosteronism have either bilateral APA, which may be microscopic and not identifiable by CT or MR imaging, or unilateral hyperplasia. In addition, nonfunctional adrenal adenomas are common and the frequency increases as the patient's age increases. Consequently, the presence of an adenoma on imaging studies does not necessarily indicate the presence of an APA. Overall, an adrenal adenoma in a patient with primary aldosteronism has an approximately 70% to 80% chance that it is functional, that is, that an APA is present, and a 20% to 30% chance that it is a nonfunctional adenoma. In the patient younger than 40 years of age,

TABLE 38.3 **Confirmatory Testing for Primary Aldosteronism**

Test	Method	Evaluation	Limitations
Oral sodium chloride (NaCl) loading	Oral NaCl intake >200 mmol/day for 3 days, with oral KCl as needed to prevent hypokalemia, with subsequent 24-hr urine aldosterone measurement	Urine aldosterone <10 μg/day, diagnosis unlikely; >12 μg/day, diagnosis likely	Avoid if severe uncontrolled hypertension, CKD, CHF, cardiac arrhythmias, or severe hypokalemia
Saline infusion test	Patient in recumbent position for 1 hr before testing and then throughout entire test Begin test between 8 and 9:30 AM. Measure plasma aldosterone, plasma renin activity, cortisol, and potassium at beginning of test and then after infusing 2 l NS IV over 4 hr.	Plasma aldosterone at end of infusion <5 ng/dl, diagnosis unlikely; >10 ng/dl, diagnosis likely; 5-10 ng/dl, indeterminate	Avoid if severe uncontrolled hypertension, CKD, CHF, cardiac arrhythmias, or severe hypokalemia
Fludrocortisone suppression test	Oral fludrocortisone, 0.1 mg every 6 hr for 4 days, plus oral NaCl, 30 mmol 3×/day, and high-salt diet combined with sufficient KCl to avoid hypokalemia	Upright plasma aldosterone on day 4 >6 ng/dl and plasma renin activity <1 ng/ml/h, diagnosis likely	Requires very close follow-up to monitor blood pressure and potassium
Captopril challenge test	Oral captopril, 20-50 mg, given with plasma aldosterone, and plasma renin activity obtained immediately before captopril and then 1-2 hr afterward, with patient seated throughout test	Plasma aldosterone decrease >30%, diagnosis unlikely	Probably more false-positive and false-negative results than other tests

From reference 39.

CHF, Congestive heart failure; *CKD,* chronic kidney disease; *KCl,* potassium chloride; *l NS IV,* liters normal saline intravenously.

the likelihood of a nonfunctional adenoma is less and the likelihood of an APA is greater. If a detectable adrenal adenoma is not found on imaging, the likelihood of unilateral autonomous aldosterone production is substantially less, probably close to 10%.

Adrenal Vein Sampling

Adrenal vein sampling is considered the definitive test for determining whether autonomous aldosterone release is due to unilateral or bilateral disease. Adrenal vein sampling should be used in the patient who has a high pretest likelihood of unilateral disease. This generally means the patient with primary aldosteronism known to have an adrenal adenoma or the patient with severe primary aldosteronism not responsive to medical therapy.

When interpreting adrenal vein sampling results, the first step is to confirm sampling of both the right and left adrenal veins. Because of the small caliber of both adrenal veins and the variable insertion point of the right adrenal vein into the inferior vena cava, successful cannulation is difficult. Confirmation of successful cannulation, particularly of the right adrenal vein, solely on radiologic criteria is unreliable. Accordingly, biochemical confirmation of successful adrenal vein sampling should be employed. Typically this is done by measuring the concentration of a hormone produced in the adrenal gland and demonstrating that the observed concentration is significantly greater than present in the inferior vena cava; cortisol is the most frequently measured analyte, and acute stimulation of cortisol production with ACTH or an analogue is often used. The selectivity index, the ratio of adrenal vein to inferior vena cava (sampled below the renal veins) cortisol concentration, should be determined and should be at least 5 : 1 for each adrenal vein sample to confirm successful adrenal vein cannulation. Alternative approaches using metanephrine levels also may be used.[38] If the selectivity index is not adequate to confirm successful adrenal vein cannulation, results of the aldosterone value in that adrenal vein sample may not be interpretable.

After confirming successful adrenal vein sampling, the lateralization index is calculated to determine whether there is unilateral or bilateral excessive aldosterone production. The ratio of adrenal vein aldosterone to adrenal vein cortisol is calculated for each adrenal vein. The lateralization index is calculated by dividing the greater adrenal vein ratio by the lesser adrenal vein ratio. A lateralization index greater than 2.0 supports a diagnosis of an APA, but it should be noted that this cut-off is not 100% specific. Our practice is to use a lateralization index greater than 2.0 to indicate an APA if this is concordant with the presence of an adrenal adenoma on the same side. If the lateralization index findings are discordant with imaging, then because of the possibility of a false-positive test result with a lateralization index between 2 and 4, we generally do not refer the patient for adrenalectomy unless the lateralization index is greater than 4.0.

Other Testing Options

Many other diagnostic tests have been suggested in the evaluation of primary aldosteronism to differentiate unilateral from bilateral disease, but none has widespread acceptance. Noninvasive physiologic tests, such as the saline suppression test and postural stimulation tests, rely on the association that APA-mediated aldosterone release is typically not stimulated by Ang II, whereas in hyperplastic lesions Ang II–dependent stimulation is generally retained. All medicines that affect the RAS, including diuretics, β-blockers, ACE inhibitors, and ARBs, must be discontinued before testing, but the difficulty in controlling BP in these patients without these medicines often limits the utility of this test. In addition, the association of Ang II–stimulated aldosterone production is discordant with whether aldosterone release is unilateral or bilateral in as many as 20% of cases, leaving this test result insufficiently accurate to determine whether surgical therapy should be used in most cases. Its main role may be in the evaluation of the patient with an adrenal adenoma and unsuccessful adrenal vein sampling.[39]

NATURAL HISTORY

The natural history of untreated primary aldosteronism leads to a variety of significant complications. Clearly, it is a major cause of worsening hypertension, and it also increases the incidence of hypokalemia, with its adverse chronic effects. In addition, it leads to a wide variety of end-organ complications. These end-organ effects include increased risks for coronary heart disease, atherosclerotic peripheral vascular disease, cardiac arrhythmias, left ventricular hypertrophy, low bone mineral density, and development of CKD.[29,40,41] The incidence of these complications appears to be substantial, and twofold to threefold, greater than in patients with essential hypertension of the same magnitude. These effects appear to be related to excessive activation of MRs in these end-organ tissues and therefore reflect a direct and BP-independent disease association. Effective treatment of primary aldosteronism appears to substantially improve these risks. Therefore treatment either with MR blockers or with adrenalectomy is recommended for all patients with primary aldosteronism.

TREATMENT

Adrenalectomy

The appropriate treatment of patients with primary aldosteronism depends on two factors: whether they are candidates for and would consider surgical therapy, and for those who are, whether they have unilateral or bilateral autonomous aldosterone production. This is because patients with unilateral autonomous aldosterone production, typically from an APA, who are acceptable surgical candidates, can have a dramatic response to adrenalectomy. Patients with an APA who undergo adrenalectomy have a 30% to 60% chance of hypertension cure.[42,43] Patients most likely to have their hypertension cured are younger than 50 years of age and have few family members with primary hypertension. Those not cured have a greater than 95% chance for BP improvement.[42,43] The lack of complete cure may reflect microvascular disease that developed as a consequence of the poorly controlled hypertension. Adrenalectomy performed using a laparoscopic approach is associated with a relatively short hospital stay, low postoperative morbidity, and a rather quick return to normal health, at least as compared with a nonlaparoscopic surgical approach. Adrenalectomy should not be performed in patients with bilateral autonomous aldosterone production because unilateral adrenalectomy is not curative and bilateral adrenalectomy is associated with unacceptable long-term complications secondary to the induction of deficiency of other adrenal hormones, such as glucocorticoids and catecholamines.

Mineralocorticoid Receptor Antagonists

Patients who are not candidates for surgical adrenalectomy or who have bilateral aldosterone production should be treated with MR antagonists. Current MR antagonist treatment options are spironolactone and eplerenone. These should be started at modest doses and titrated slowly. Most patients find that the responses are delayed, and monthly dose adjustments should be done until an optimal dose is identified.

The choice of which MR blocker to use involves consideration of effectiveness and side effects. Importantly, the treatment efficacy of these two agents is quite different. Spironolactone appears to be more effective than eplerenone at improving BP, yielding almost twice as great a BP reduction and a substantially greater proportion of patients experiencing a significant BP improvement.[44] Spironolactone has off-target effects on sex-steroid hormone receptors, which can lead to breast enlargement (gynecomastia) in men and breast tenderness (gynecodynia) and menstrual irregularities in women. These side effects are dose-dependent and are typically mild or not present at doses of 100 mg/day or less. Eplerenone is more selective than spironolactone for the MR, and the risk for these side effects is less, but not eliminated.

Based on its greater treatment efficacy, we recommend spironolactone as the preferred initial agent for medical treatment of primary aldosteronism. Treatment can begin with low doses; we typically recommend initial therapy with oral spironolactone 25 to 50 mg/day, with dose titration on a 2- to 4-week basis. Most patients can be treated with maximum dose of 100 mg/day, but occasional patients may require 200 to 400 mg/day, often administered twice a day. Eplerenone can be used at similar doses and with a similar dose escalation pattern, with the exception that the general maximum recommended dose is only 100 mg/day.

Many of the side effects of MR blockers can be easily managed. Muscle cramps occur with both spironolactone and eplerenone. Changing from one MR blocker to the other often allows resolution of the muscle cramps. MR blockers can cause neuropsychiatric side effects that are often nonspecific and can include symptoms of feeling out of touch with reality, difficulty thinking, and decreased attention and performance in various memory tasks.[44,45] In general, these effects are temporary and resolve within a few weeks. Hyperkalemia is common when MR blockers are used for conditions other than primary aldosteronism, such as congestive heart failure,[46,47] but relatively uncommon in patients with primary aldosteronism. However, hyperkalemia can occur late in therapy, often after years of MR blocker administration, and may require either a decrease in the MR dose or addition of diuretics to increase renal potassium excretion.

Treatment with an MR antagonist usually results in dramatically improved BP control. Many patients will respond to a low dose of spironolactone (25 to 50 mg daily) as initial therapy. Both systolic BP and diastolic BP frequently decrease by about 25 mm Hg over a few weeks to months. Dosage of the MR antagonists can be increased as necessary but generally should not be changed more than every 2 to 4 weeks. If present, hypokalemia and metabolic alkalosis typically improve. Potassium supplements often can be discontinued when MR therapy is initiated, or the dose can be tapered rapidly. Because changes in potassium supplement requirement to avoid either hypokalemia or hyperkalemia exhibit significant inter-patient variability after MR initiation, we suggest close follow-up of serum potassium after initiating MR therapy, particularly in patients previously treated with large doses of potassium. With time, BP can be controlled in many patients with an MR antagonist and a single alternative agent. We typically use ACE inhibitors or ARBs because renin activity, which is suppressed initially, typically increases after starting MR antagonist therapy. Synergistic use of an ACE inhibitor or ARB may prevent development of a renin-stimulated, Ang II–dependent component of hypertension. However, many antihypertensive combinations can be used successfully with the MR antagonist.

Other MR blockers are in development and may become available for use in the near future. Finerenone is a novel, selective, nonsteroidal MR blocker that may have less effect on serum potassium.[48] This may make this medication particularly useful in treatment of a number of patients, such as those with CKD and primary aldosteronism, with CKD and glomerular disease, and with CKD and congestive heart failure (CHF), in whom MR blocker–induced hyperkalemia is often a limiting factor in MR blocker therapy. Multiple other nonsteroidal MR blockers are also in development.

Non–Mineralocorticoid Receptor Blocker Therapy

In occasional patients, high doses of MR blockers will not be sufficient to block the effects of aldosterone on BP and potassium. In this case, addition of a medication that specifically blocks aldosterone's effect on renal NaCl reabsorption can be helpful. Aldosterone specifically stimulates the distal epithelial cell Na^+ transporter, ENaC, which contributes to the volume expansion and resulting hypertension. Use of ENaC inhibitors, such as amiloride or triamterene, in combination with MR blockers may be helpful. We typically use oral amiloride, starting at 5 mg/day and titrating as needed.

Aldosterone synthase inhibitors are a new treatment option in development.[49] These medications directly inhibit adrenal aldosterone synthesis, leading to decreased plasma aldosterone levels and leading to improvements in BP control. Because they do not target MR, their side-effect profile is likely to differ from that observed with MR blockers, although the development of hyperkalemia is not likely to differ.

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SELF-ASSESSMENT QUESTIONS

1. The most common genetic cause of primary aldosteronism resulting from an aldosterone-producing adenoma (APA) is related to a mutation in which protein?
   - **A.** Aldosterone synthase
   - **B.** Mineralocorticoid receptor
   - **C.** AT1 receptor
   - **D.** Potassium channel (KCNJ5)
   - **E.** Sodium channel
2. Based on recent comparative studies, which of the following mineralocorticoid receptor (MR) antagonists for primary aldosteronism is preferred and for what reason?
   - **A.** Eplerenone, because of greater efficacy
   - **B.** Eplerenone, because of fewer side effects and less drug discontinuation
   - **C.** Spironolactone, because of greater efficacy
   - **D.** Spironolactone, because of fewer side effects and less drug discontinuation
3. Which of the following is the preferred first-line test for identification of primary aldosteronism?
   - **A.** Serum potassium
   - **B.** Plasma aldosterone
   - **C.** Plasma renin activity
   - **D.** Aldosterone-renin ratio (ARR) in combination with absolute level of plasma aldosterone
   - **E.** Urinary sodium and potassium excretion rate

39

Other Endocrine Causes of Hypertension

A. Mark Richards

Endocrine hypertension often remains undiagnosed. However, primary aldosteronism may be present in 10% of patients with newly diagnosed hypertension, and, overall, an endocrine contribution to high blood pressure (BP) may be present in more than 12% of all hypertension cases.[1]

Endocrine hypertension frequently occurs in the absence of readily observed signs and symptoms or abnormalities in routine biochemical tests. However, certain features should trigger consideration of endocrine hypertension (Fig. 39.1) because diagnosis may offer the chance for cure and simple therapies that ameliorate other elements of the disease beyond BP control. Chapter 38 discusses aldosteronism; this chapter describes other types of endocrine hypertension.

CUSHING SYNDROME

Definition

This syndrome of sustained glucocorticoid excess is most often secondary to production of adrenocorticotropic hormone (ACTH) by a pituitary adenoma (Cushing disease). Less frequently, Cushing syndrome is the result of cortisol overproduction from an adrenal adenoma, adrenal nodular hyperplasia, or carcinoma, and rarely it may be secondary to ectopic ACTH (corticotrophin) secretion from tumors.[1-3] Approximately 0.5% of patients with bronchogenic carcinoma (more common in men than women) develop ectopic ACTH syndrome. The Carney complex, an autosomal dominant disorder featuring cardiac myxomas and pigmented skin/mucosal lesions is a rare cause of Cushing syndrome. Ectopic corticotropin-releasing hormone (CRH) from tumors is a rare cause of hypercortisolism. Cushing syndrome also can result from exogenous corticosteroid administration. The incidence of endogenous Cushing syndrome is 5 to 10 cases per 1 million population per year. Cushing disease and cortisol-secreting adrenal tumors are four times more common in women than in men.

Etiology, Pathogenesis, and Epidemiology

Hypertension is present in 80% of patients with Cushing syndrome (less often when caused by exogenous synthetic corticosteroid administration) and results from an increase in both cardiac output and total peripheral resistance. The mechanisms underlying these hemodynamic changes are complex.[4]

In some patients, Cushing syndrome may be caused by concurrent overproduction of mineralocorticoids such as aldosterone, 11-deoxycorticosterone, and corticosterone. Although cortisol can bind the mineralocorticoid receptor (MR), usually it does not because of the renal enzyme 11β-hydroxysteroid dehydrogenase type 2 (β-HSD2), which inactivates cortisol to corticosterone, thereby preventing its binding to the MR. However, in the patient with low β-HSD2 activity or extremely high cortisol levels (e.g., ectopic ACTH syndrome), there may be sufficient excess cortisol that MR binding occurs. Furthermore, alterations in oxidation-reduction (redox) status, potentially triggered by metabolic disturbance and cytokines, may alter the effects of corticosteroids at the MR function, converting cortisol from its receptor antagonist role in health to an agonist in inflammation.[5]

Subsequent cardiac and vascular MR activation may foster cardiovascular inflammatory, hypertrophic, and fibrotic changes. Inhibition of the vasodilator nitric oxide (NO) by cortisol may contribute to the hypertension, along with enhanced pressor responsiveness to catecholamines and angiotensin II (Ang II), heightened cardiac inotropic sensitivity to β-adrenergic stimulation, and increased plasma volume.[4] The sympathetic nervous system and renin-angiotensin system (RAS) may be suppressed, even though circulating levels of renin substrate are increased.[,] Adipokines, including leptin and resistin, plus release of pro-inflammatory cytokines (tumor necrosis factor α, interleukin-6) also may contribute to the increased cardiovascular (CV) risk observed in Cushing syndrome.[1-3,6-8]

Successful treatment of Cushing disease or removal of an underlying adrenal adenoma usually results in BP reduction and partial return of the previously impaired nocturnal fall in arterial pressure, although hypertension persists in a sizable minority of patients.[8]

Clinical Manifestations

Clinical features in Cushing disease result from elevated circulating levels of pro-opiomelanocortin hormones, including ACTH (increased pigmentation) and cortisol (central adiposity, insulin resistance or diabetes, muscle wasting/weakness, plethoric facies, purple striae [Fig. 39.2], easy bruising, osteoporosis, psychological problems). In some patients, androgen effects are observed (hirsutism, acne, virilization) and may be striking in those with adrenal adenoma or carcinoma. Ectopic ACTH syndrome caused by small cell bronchial carcinoma or other tumors (e.g., bronchial or thymic carcinoid) manifests typically as a wasting disease, often with hyperpigmentation and hypokalemia. Hypertension is often associated with left ventricular hypertrophy, which can be disproportionate to BP, and frank cardiac failure is occasionally the presenting feature.[1,4] In up to 15% of patients with Cushing syndrome, clinical features occur only periodically; this is known as *cyclical Cushing syndrome*.[1]

Differential Diagnosis

Pseudo–Cushing syndrome can occur with a sustained high intake of alcohol by inducing augmented cortisol secretion and reduced cortisol metabolism caused by hepatic damage. Routine diagnostic tests are

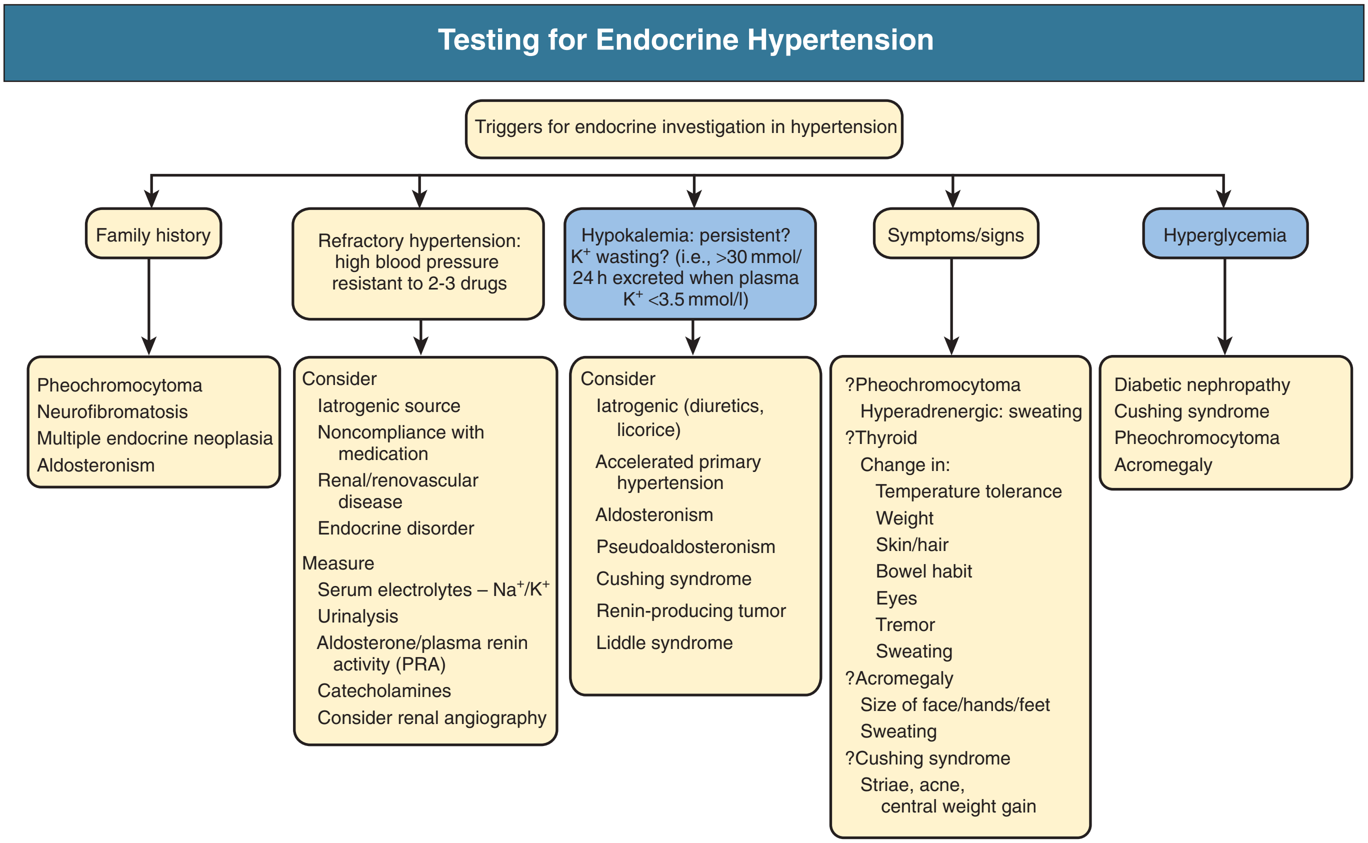
Testing for Endocrine Hypertension
Triggers for endocrine investigation in hypertension
Family history
Refractory hypertension: high blood pressure resistant to 2-3 drugs
Hypokalemia: persistent? K+ wasting? (i.e., >30 mmol/ 24 h excreted when plasma K+ <3.5 mmol/l)
Symptoms/signs
Hyperglycemia
Pheochromocytoma
Neurofibromatosis
Multiple endocrine neoplasia
Aldosteronism
Consider
Iatrogenic source
Noncompliance with medication
Renal/renovascular disease
Endocrine disorder
Measure
Serum electrolytes – Na+/K+
Urinalysis
Aldosterone/plasma renin activity (PRA)
Catecholamines
Consider renal angiography
Consider
Iatrogenic (diuretics, licorice)
Accelerated primary hypertension
Aldosteronism
Pseudoaldosteronism
Cushing syndrome
Renin-producing tumor
Liddle syndrome
?Pheochromocytoma
Hyperadrenergic: sweating
?Thyroid
Change in:
Temperature tolerance
Weight
Skin/hair
Bowel habit
Eyes
Tremor
Sweating
?Acromegaly
Size of face/hands/feet
Sweating
?Cushing syndrome
Striae, acne, central weight gain
Diabetic nephropathy
Cushing syndrome
Pheochromocytoma
Acromegaly

Fig. 39.1 **Testing for endocrine hypertension.** Clinical observations suggesting investigation into endocrine causes of hypertension in hypertensive patients.

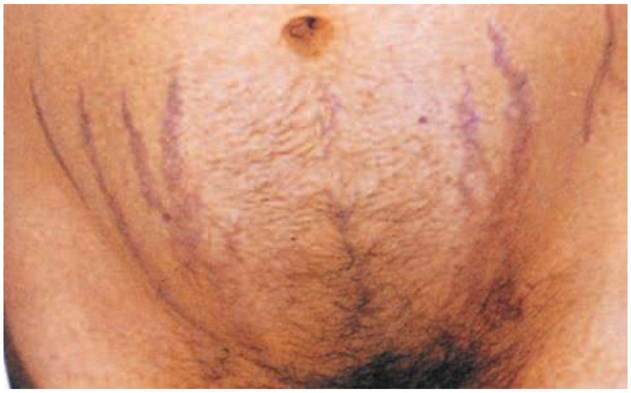

Fig. 39.2 Striae and central obesity in a patient with Cushing syndrome.

unable to distinguish alcoholic pseudo–Cushing syndrome from true Cushing syndrome, and reassessment after alcohol withdrawal may be required.[9] Depression is associated with an increased cortisol level. Careful psychological and physical evaluation will usually differentiate these patients from those with Cushing syndrome.

Diagnosis

Initial evaluation should test for one or more of the following: (1) an elevated 24-hour urinary free cortisol excretion (at least two samples), (2) increased late night salivary cortisol, (3) absence of suppression of 8 AM plasma cortisol after a dose of dexamethasone (1 mg at midnight), and (4) failure of suppression of cortisol on low-dose dexamethasone (0.5 mg four times daily) for 48 hours. Random plasma cortisol measurements are not reliable.

A positive test result should trigger involvement of an endocrinologist. Further key investigations include computed tomography (CT) and magnetic resonance imaging (MRI) of the pituitary and adrenal glands and plasma ACTH (suppressed in cortisol-secreting adrenal tumors but elevated in pituitary adenoma and ectopic ACTH syndrome). Further tests may include a high-dose dexamethasone suppression test that partially suppresses ACTH in patients with pituitary tumors but not with ectopic ACTH. The response of plasma ACTH to a dose of corticotrophin-releasing hormone (≥20% rise in response to CRH points to a pituitary source) may help distinguish pituitary from adrenal or ectopic tumors. Simultaneous bilateral inferior petrosal sinus sampling for ACTH measurements is useful in differentiating Cushing disease from ectopic ACTH syndrome, when the previous tests give equivocal results. Imaging of the thorax, abdomen, and pelvis is indicated when ACTH-producing carcinoid tumors are suspected. When other tests are equivocal, an indium-111 octreotide radio-ligand scan, highlighting tissue with somatostatin receptors, may secure the location of ectopic ACTH production.

Treatment and Prognosis

Untreated patients with Cushing syndrome have 50% 5-year mortality because of CV risk from hypertension, along with glucose intolerance, insulin resistance, hyperlipidemia, and obesity.[4,10]

Cure rates in treatment of Cushing disease are 80% to 90% by selective removal of a pituitary microadenoma and 50% for pituitary macroadenomas. Cushing syndrome caused by adrenal adenoma is almost always cured by unilateral adrenalectomy. However, in adrenal carcinoma, median survival is less than 2 years. The prognosis is also poor when Cushing syndrome results from ectopic ACTH syndrome caused by small cell bronchial carcinoma. If the ACTH-producing tumor is benign and can be located, however, complete removal usually leads to cure and reduction of mortality to match that in the general population. After cure of Cushing syndrome, approximately 30% of patients have persistent hypertension.[11]

No evidence supports the use of any antihypertensive class over another. Potassium-losing diuretics can exacerbate both hypokalemia and glucose intolerance, whereas potassium-sparing diuretics, usually in combination with other antihypertensive agents, may correct hypokalemia and reduce edema while lowering BP.

PHEOCHROMOCYTOMA

Definition

Pheochromocytoma can mimic a wide spectrum of other disorders, and the diagnosis is frequently delayed or missed altogether.[12]

Pheochromocytoma refers to a dusky tumor whose cells stain brown with chromium salts. Such tumors arise most frequently within the adrenal glands (Fig. 39.3), but approximately 10% are extra-adrenal (paraganglioma). Although the majority of pheochromocytomas are benign, 10% to 15% of adrenal pheochromocytomas and 20% to 50% of paraganglionomas are malignant. Histologic features are not a reliable guide to malignant behavior. The tumors secrete norepinephrine, epinephrine, and dopamine, with patterns differing among patients. Few paragangliomas produce epinephrine. Very high dopamine production is associated with malignant disease or a large tumor mass.

Etiology, Pathogenesis, and Epidemiology

The prevalence of pheochromocytoma in patients with hypertension in general medical outpatient clinics is 0.1% to 0.6%.[13] However, the prevalence may be considerably higher because the diagnosis is often made postmortem.[12,13]

Pheochromocytomas can be sporadic or familial.[14] Whereas sporadic cases are usually unicentric and unilateral, familial pheochromocytomas are often multicentric and bilateral. At least one third of all pheochromocytomas result from germ-line gene mutation; 14 genes have been identified thus far.[12,15] Variants in the *RET* gene result in multiple endocrine neoplasia (MEN) type 2; in the *VHL* gene, the von Hippel–Lindau syndrome; in the neurofibromatosis type 1 *(NF1)* gene in von Recklinghausen disease; and variants in the genes encoding the B and D subunits of mitochondrial succinate dehydrogenase (*SDHB* and *SDHD*) are associated with familial paragangliomas and pheochromocytomas. The high prevalence of inherited disease and the fact that the *SDHB* variants lead to metastatic disease in 40% of cases, makes genetic testing important once pheochromocytoma is diagnosed.[12,15] For patients with apparently sporadic pheochromocytomas, an underlying germ-line mutation of the genes mentioned may be present in about 20% of cases and should be considered in younger patients (<50 years) and those with multifocal or extra-adrenal tumors.[12,15,16] Patients with a germ-line mutation should be identified for appropriate guidance of medical management for them and their families.

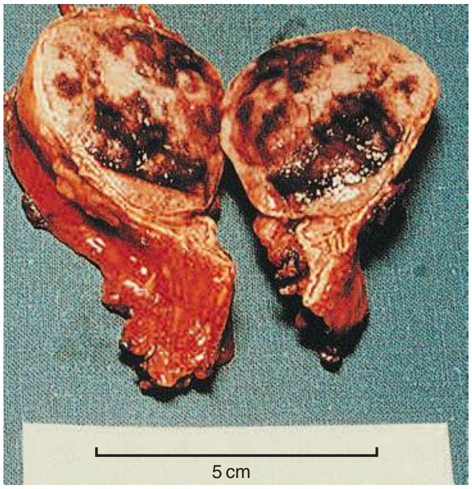

Fig. 39.3 Large adrenal pheochromocytoma with areas of hemorrhagic necrosis.

Clinical Manifestations

Table 39.1 outlines clinical features of syndromes associated with pheochromocytoma. Clinical features of pheochromocytoma reflect episodic or continuous overproduction of catecholamines and depend in part on which catecholamine dominates. Symptoms include headache, sweating, palpitations, anxiety, and pallor (Fig. 39.4).[17] Hypertension or diabetes mellitus, with or without symptoms, may be the initial manifestation. Less than 1% of resistant hypertension cases are due to pheochromocytoma. Pheochromocytoma also may manifest as a tumor mass, usually an enlarging primary lesion in the abdomen or a paraganglioma in the neck, ear, thorax, or abdomen. On occasion, a metastatic lesion may be the presenting sign. About 4% of adrenal incidentalomas are pheochromocytomas. Physical examination may reveal labile (66%) or persistent (33%) hypertension, sometimes with strikingly reciprocal changes in BP and heart rate when the tumor secretes predominantly norepinephrine.[18] The patient may have cool, mottled extremities and a low-grade fever with tachycardia and postural hypotension. Hypertensive crisis with or without heart failure may be precipitated by emergency surgery, general anesthesia, or on exposure to radiocontrast material. This also may occur after minor or major trauma, at delivery, and apparently from sudden spontaneous release of catecholamines from the tumor or on hemorrhage into it. Pheochromocytoma in pregnancy presents particular difficulties in diagnosis and management.[19]

Diagnosis

Diagnosis of pheochromocytoma is based on clinical suspicion and biochemical confirmation (Fig. 39.5). Measurement of plasma free metanephrines or urinary fractionated metanephrines is the investigation of choice for diagnosis or exclusion of pheochromocytoma. Levels are relatively independent of renal function and provide some guidance for tumor size and location.[12] When analysis of plasma free metanephrines is not available, plasma or urinary catecholamines or their other metabolites may be used and typically are 5- to 10-fold greater than normal. When catecholamine levels are less than 3 to 4 times the upper limit of normal, it is useful to undertake a suppression test with clonidine, which suppresses plasma norepinephrine into the normal range in health but fails to do so in patients harboring a pheochromocytoma.[20]

Once the biochemical diagnosis is secured, the lesion must be localized (see Fig. 39.5). MRI or CT scan (with nonionic contrast) of the abdomen and pelvis, concentrating first on the adrenals, is successful in most patients, but additional investigations may be required if no lesion is detected. These may include metaiodobenzylguanidine (MIBG) scanning, In-111–labeled octreotide scanning, or positron emission tomography (PET); with any of these imaging modes potentially coupled with selective venous sampling from vena cava (or veins draining specific organs) to detect a step-up in catecholamine levels (preferably including measurements of plasma free metanephrines.[21] MIBG scanning is generally recommended to corroborate the diagnosis and exclude multisite

TABLE 39.1 Clinical Features of Syndromes Associated With Pheochromocytoma

Associated Syndrome	Clinical Manifestations
Von Hippel–Lindau Syndrome	
Type 1 (no pheochromocytoma)	Renal cell cysts and carcinomas
	Retinal and CNS hemangioblastomas
	Pancreatic neoplasms and cysts
	Endolymphatic sac tumors
	Epididymal cystadenomas
Type 2 (with pheochromocytoma)	2A. Retinal and CNS hemangioblastomas
	Pheochromocytomas
	Endolymphatic sac tumors
	Epididymal cystadenomas
	2B. Renal cell cysts and carcinomas
	Retinal and CNS hemangioblastomas
	Pancreatic neoplasms and cysts
	Pheochromocytomas
	Endolymphatic sac tumors
	Epididymal cystadenomas
	2C. Pheochromocytomas only
Multiple Endocrine Neoplasia (MEN) Type 2*	
Type 2A (MEN-2A)	Medullary thyroid carcinoma
	Pheochromocytoma
	Hyperparathyroidism
	Cutaneous lichen amyloidosis
Type 2B (MEN-2B)	Medullary thyroid carcinoma
	Pheochromocytoma
	Multiple neuromas
	Marfanoid habitus
Other Syndromes	
Neurofibromatosis type 1	Multiple fibromas on skin and mucosa
	Café-au-lait skin spots
	Pheochromocytomas
Paraganglioma syndromes	Head and neck tumors (carotid body tumors; vagal, jugular, and tympanic paragangliomas)
	Pheochromocytomas
	Abdominal or thoracic paragangliomas (or both)

*A third type of MEN type 2 consists of familial medullary thyroid carcinoma only (without pheochromocytoma).
CNS, Central nervous system.

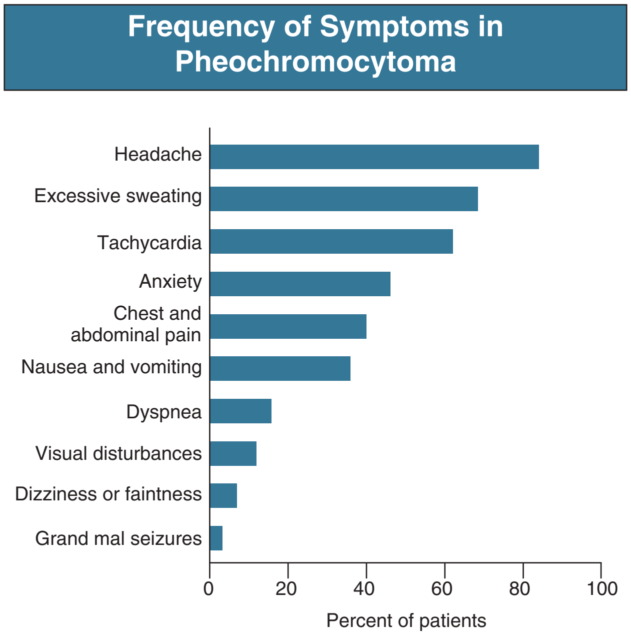

Fig. 39.4 Frequency of symptoms in 324 patients with pheochromocytoma. (Modified from reference 17.)

or metastatic disease. Removal of a pheochromocytoma-containing adrenal gland can result in compensatory medullary hyperplasia in the contralateral adrenal gland, potentially giving a false-positive MIBG scan on follow-up scanning, so the clinician must be cautious with interpretation.[22] Diagnosis of a pheochromocytoma should trigger exclusion of associated syndromes, including von Hippel–Lindau syndrome, von Recklinghausen disease, and familial paraganglioma.

Treatment

Once the pheochromocytoma has been localized, the patient should be prepared for surgery with a collaborative team approach by the surgeon, anesthesiologist, and physician. Traditionally, preoperative management has included 7 to 21 days of α-adrenoceptor blockade (usually with phenoxybenzamine), repletion of salt and water volume, and the later addition of β-blockade (if necessary to control BP and tachycardia). β-Blocker monotherapy is contraindicated because unopposed α-adrenergic stimulation can cause hypertensive crisis. Alternative drugs that have been used successfully before surgery include prazosin (α-blocker) and labetalol (combined α- and β-blocker). Metyrosine, a tyrosine hydroxylase inhibitor, blocks catecholamine synthesis; frequent side effects have led to limitation of its use for large tumors or where other measures have failed to achieve control of the BP.

Longer preoperative treatment has been recommended in cases with cardiomyopathy, myocardial infarction, and/or vasculitis. However, the need for prolonged presurgical pharmacologic control is still debated, with an emerging view that improved anesthetic management, skilled use of short-acting vasoactive drugs, and careful intraoperative handling of the tumor usually will allow safe progression to early surgery, with perioperative mortality close to zero in recent series.[12,14, 23]

A laparoscopic approach to surgical removal of adrenal pheochromocytomas and some extra-adrenal tumors has gained widespread acceptance, but open adrenalectomy is preferred for large tumors, difficult dissection, invasion, adhesions, or surgical inexperience.[24] Laparoscopic surgery also has been used successfully for hereditary bilateral or recurrent pheochromocytoma. Intraoperative manipulation of the tumor causes volatile elevations in BP. Agents used to achieve intraoperative BP control include phentolamine, sodium nitroprusside, and magnesium sulfate.

Hypotension and hypoglycemia are potential postoperative problems. In most patients, surgical removal of pheochromocytoma normalizes plasma catecholamine levels and previously suppressed central sympathetic outflow. Plasma or urinary metanephrines should be checked no sooner than 10 days after surgery. Follow-up should include life-long biochemical monitoring at least annually and in the event of symptoms suggestive of recurrence.

BP usually improves with removal of a pheochromocytoma, but especially in those with persistent hypertension versus episodic, BP will remain elevated in 25% of cases, necessitating long-term antihypertensive therapy. For malignant pheochromocytoma, consideration should be given to aggressive surgical resection, particularly when there is a single

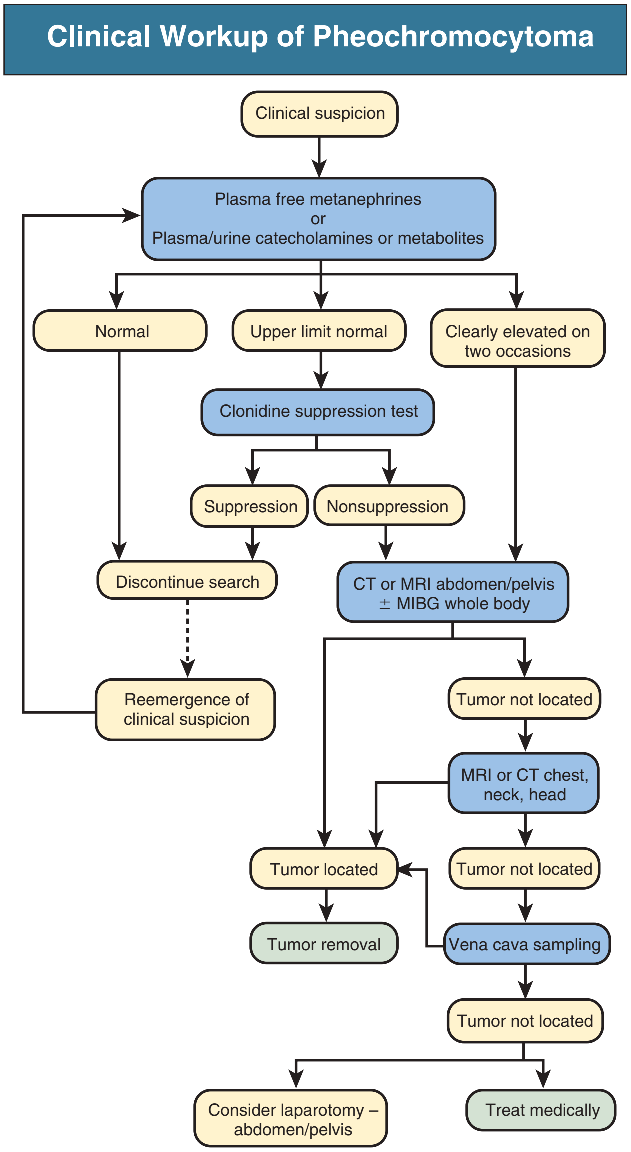
Clinical Workup of Pheochromocytoma
Clinical suspicion
Plasma free metanephrines or Plasma/urine catecholamines or metabolites
Normal
Upper limit normal
Clearly elevated on two occasions
Clonidine suppression test
Suppression
Nonsuppression
Discontinue search
CT or MRI abdomen/pelvis ± MIBG whole body
Reemergence of clinical suspicion
Tumor not located
MRI or CT chest, neck, head
Tumor located
Tumor not located
Tumor removal
Vena cava sampling
Tumor not located
Consider laparotomy – abdomen/pelvis
Treat medically

Fig. 39.5 Clinical workup of pheochromocytoma. *CT,* Computed tomography; *MIBG,* metaiodobenzylguanidine; *MRI,* magnetic resonance imaging.

metastatic lesion. Hepatic metastases are readily resected. The standard chemotherapeutic regimen for malignant pheochromocytoma includes cyclophosphamide, vincristine, and dacarbazine. Other chemotherapeutic options include doxorubicin, cisplatin, VP-16, etoposide, carboplatin, ifosfamide, temozolomide, imatinib, tamoxifen, bevacizumab, sorafenib, and prednisone. Targeted molecular treatment includes the antiangiogenic tyrosine kinase receptor inhibitor sunitinib. Everolimus inhibits the pro-proliferative, proangiogenic mammalian target of rapamycin (mTOR) pathways.

Several other treatment options are available. Radionuclide treatment with I-131 MIBG at high dose offers treatment targeted to the tumor. Somatostatin-like drugs coupled with radioisotopes such as yttrium-90 and letetium-177 offer alternative modes of radiotherapy.

External beam radiation therapy can be useful for bone metastases. Tumor embolization and ablation procedures using radiofrequency ablation, cryoablation, and ethanol injection have been successful as palliation or for longer term control of metastatic disease in selected cases.[14]

Progression of malignant pheochromocytoma is extremely variable. Although median survival is approximately 5 years, survival for decades has been recorded in some cases.

ADRENAL INCIDENTALOMA

Definition and Epidemiology

Incidentaloma refers to the incidental discovery of an adrenal mass of 1 cm or greater in diameter in the course of investigation for other conditions in the absence of any prior suspicion of adrenal disease.[25] The increasing use and sophistication of abdominal imaging for a wide range of indications frequently leads to the incidental discovery of an adrenal mass. Current prevalence of unsuspected adrenal masses is reported in 4% to 7% of adults undergoing high-resolution CT or MRI abdominal studies (<1% in those younger than 30 years, rising to 7% in those older than 70 years).[25-27]

Hypertension is more common in those with incidentalomas (40%) than in the general population. In a substantial series of more than 1000 incidentalomas, about 75% proved to be nonsecretory benign adenomas. However, an important minority show endocrine activity, including aldosteronoma (frequently normokalemic), pheochromocytoma (>4%, with half normotensive), and, most often, cortisol-secreting tumors. Between 5% and 30% of patients with incidentalomas have subclinical hypercortisolism, which is more common among those with bilateral rather than unilateral incidentaloma.[28,29] The formal definition of subclinical Cushing syndrome (SCS) is yet to be finally agreed upon but will include plasma cortisol after dexamethasone suppression over a threshold at some level between 1.8 and 5.0 µg/dl and a basal ACTH value below 10 pg/ml. SCS is frequently complicated by hypertension (~65% of cases), diabetes (~33%), obesity, and osteoporosis and carries increased risk for CV events and related mortality.[30] Adrenal carcinoma accounted for 4% of cases in a large, well-documented series of incidentalomas. Although a rare malignancy in the general population at 3 to 17 per million, 2% of masses up to 4 cm in diameter, 6% of those 4 to 6 cm in diameter, and 25% of those larger than 6 cm are adrenal carcinomas. Adrenal carcinomas may or may not be functional. The prognosis is poor, with 5-year survival of less than 20%.

Management

Investigation and management should address two key issues: whether the tumor is malignant and whether it is hormonally active. CT appearances consistent with malignancy and tumors greater than 4 cm in diameter without benign imaging features should be surgically resected.[25,29,31] Biochemical screening should be undertaken for pheochromocytoma (plasma free metanephrines or urinary free metanephrines), glucocorticoid excess (ratio of urinary free cortisol to creatinine and early-morning plasma cortisol concentration after 1 mg dexamethasone given the night before), or primary aldosteronism (plasma and 24-hour urinary potassium levels and ratio of plasma renin to aldosterone), as outlined here and in Chapter 38. It is reasonable to resect functional tumors. In nonfunctional tumors of benign appearance, annual biochemical follow-up for 5 years together with repeat imaging has been recommended if the tumor is larger than 3 cm. Incidentalomas increasing in size by more than 0.8 cm per year should be considered for resection.[27,30,31]

RENIN-SECRETING TUMOR

Definition

Primary renin-secreting tumors are rare, and fewer than 200 cases have been reported.[32] Diagnostic criteria include an elevated plasma renin or prorenin level, which decreases on removal of the tumor, and demonstration of renin within the tumor. Most renin-secreting tumors are caused

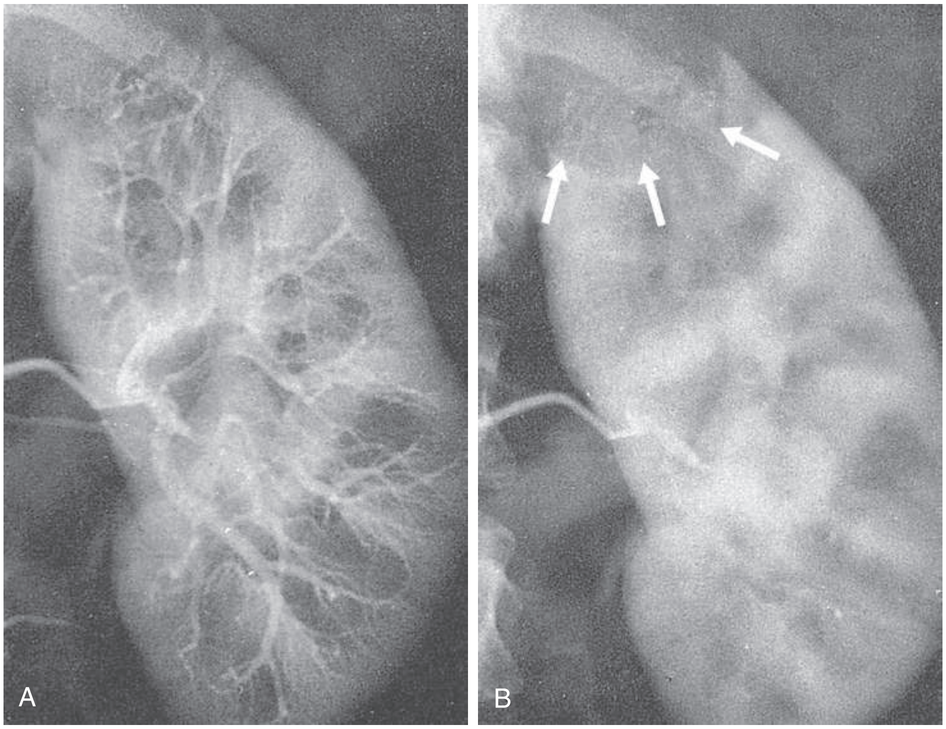

Fig. 39.6 Renin-secreting tumor. Left renal angiography arterial (A) and (B) phases revealing a 2.5-cm juxtaglomerular cell tumor with a circumscribed and relatively avascular appearance at the upper pole *(arrows)*. (Modified from reference 34.)

by benign renal juxtaglomerular cell tumors (JGCT) ranging from 5 mm to 6 cm in diameter (typically 2 to 4 cm). These tumors occasionally occur with nephroblastomas, renal cell carcinomas, and extrarenal neoplasms (bronchial or pancreatic carcinoma, ovarian tumors, carcinoma of ileum or colon, soft tissue sarcomas, orbital hemangiopericytoma).

Etiology and Pathogenesis

Autonomous hypersecretion of renin results in high circulating levels of Ang II that increase arterial pressure. Secondary hyperaldosteronism and hypokalemia result from stimulation of the adrenal glomerulosa by Ang II. High Ang II levels also induce hyponatremia in a minority of patients, by stimulation of thirst and arginine vasopressin (AVP) secretion, together with a direct renal water-retaining action of the peptide.[32]

Clinical Manifestations

Cases show female predominance; 75% of patients are younger than 30 years, presenting usually with severe, occasionally paroxysmal hypertension (average 206/131 mm Hg), hypokalemia (<3.0 mmol/l in ~70% of cases), proteinuria (>0.4 g/day in ~50% of patients), and in a minority, hyponatremia.[33] Glomerular filtration rate (GFR) is normal or high. BP may decrease substantially with the first dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

Pathology

Renin-secreting tumors are encapsulated and tan or grayish yellow, with scattered hemorrhages. These masses consist largely of polygonal or spindle cells in close contact with capillary and sinusoidal vessels and contain cytoplasmic renin granules.[32]

Diagnosis and Differential Diagnosis

Patients presenting with hypertension and hypokalemia together with elevated renin (and prorenin) and aldosterone levels may harbor a renin-secreting tumor, most often a JGCT.

CT or MRI angiography or renal arteriography typically identify JGCTs as radiolucent, expansile, homogeneous, solid renal cortical neoplasms that typically measure 2 to 4 cm in diameter (Fig. 39.6).[33] CT and MRI scans showing an isodense or hypodense lesion with little or no enhancement after injection of contrast material have proved helpful in the provisional localization of these tumors. Bilateral, simultaneous renal vein sampling may enable lateralization of the tumor. Because renal blood flow to the culprit kidney is not impaired, however, a renin ratio of more than 1.2 : 1 between the two renal veins may not be present, in contrast to unilateral renal artery stenosis, in which reduced blood flow to the stenosed kidney and renin oversecretion often lead to an elevated renal vein renin ratio. Selective segmental renal vein renin sampling may help localize the tumor. When no renal lesion can be visualized and lateralization of renin secretion is not evident, an extrarenal renin-secreting lesion must be considered and sought by appropriate radiographic investigations and venous sampling for renin measurements.

Apart from renal artery stenosis or occlusion, it may be necessary to exclude other renin-producing lesions, including Wilms tumor, renal carcinoma, neuroblastoma, hepatocellular carcinoma, and pheochromocytoma, which can either secrete renin or stimulate renal renin production.

Treatment

Preoperative control of arterial pressure is based on an ACE inhibitor or ARB, introduced with caution to avoid first-dose hypotension. For JGCTs, local excision, where possible, is advisable to preserve nephrons. When doubt exists, an intraoperative frozen section will differentiate a benign JGCT from malignant lesions and guide surgery. Removal of a JGCT results in the return of renin and aldosterone levels to normal. BP decreases rapidly, but not always to normal if there is a background of primary hypertension or established hypertensive vascular damage.[34]

ACROMEGALY

Definition and Epidemiology

Acromegaly is caused by excessive circulating growth hormone (GH) originating sporadically from a somatotroph adenoma of the pituitary in over 95% of cases. Rare causes of acromegaly include hypothalamic or neuroendocrine tumors secreting GH-releasing factor (GHRH) and, rarely, hemopoietic, breast, bronchial, and abdominal tumors secrete GH. MEN syndrome type 1 may feature GH-secreting tumors. Acromegaly may appear in other familial settings (e.g., McCune-Albright syndrome, Carney complex) or as an isolated disorder in familial isolated pituitary adenoma.[35]

Acromegaly is rare, with an incidence of 5 cases per 1 million population per year and a prevalence of 36 to 60 cases per million. Hypertension is more common (~40%) in persons with acromegaly than in the general population, with an estimated 35% of patients with acromegaly having diastolic BP above 100 mm Hg with higher frequencies in female and older patients.[36] Patients with acromegaly who have additional hypopituitarism or advanced cardiomyopathy may have BP reduction masking prior hypertension. Most pituitary adenomas causing acromegaly are macroadenomas resulting in some pituitary destruction and one or more hypopituitary features in 75% of cases.

The pathogenesis of hypertension in acromegaly is complex but reflects sodium retention and volume expansion associated with an inappropriate response of hormonal systems to counteract these effects. Total exchangeable sodium, total body water, and extracellular fluid volume are increased. Volume expansion should suppress plasma renin levels, but although levels are low, they are not consistent with the sodium status. Aldosterone levels are also normal or only slightly suppressed. The kidneys are enlarged and GFR is increased, but sodium balance is not corrected unless the acromegaly is cured.

Clinical Manifestations

Excess circulating GH stimulates production of insulin-like growth factor 1 (IGF-1) from the liver. IGF-1 mediates the biologic effects of GH. Acromegaly is characterized by enlargement of the skull (Fig. 39.7), hands (Fig. 39.8), and feet. Other symptoms result from local effects of an expanding pituitary tumor and include visual field defects and headache. The manifestations of disease are gradual, slowly progressing over many years, and diagnosis may be delayed until dysmorphic features are well developed, typically in the fourth to fifth decade. Other signs and symptoms include headache (40%), excessive sweating (50%), loss of libido (35%), amenorrhea (45%), carpal tunnel syndrome (25%), diabetes mellitus (19%), and visual field defects (5%).[35] Thyroid enlargement occurs in 50% of patients and thyrotoxicosis in 6%. Hirsutism occurs in 24% of women and galactorrhea in 10%. Other complications of acromegaly include cardiac hypertrophy, systolic and diastolic dysfunction, heart failure, arrhythmia, sleep apnea, osteoarthritis and osteopenia, and disturbed calcium metabolism.[37] Through uncertain mechanisms, acromegaly is associated with increased rates of subsequent neoplasia, best demonstrated in a twofold increase in colorectal cancer.

Diagnosis

Clinical suspicion should be raised by symptoms and signs. Box 39.1 lists appropriate tests for acromegaly. Elevated plasma levels of IGF-1 and GH, especially with lack of suppression of GH on oral glucose tolerance testing, are strongly suggestive of the diagnosis. Visual field assessment and MRI of the pituitary fossa are necessary to define the tumor and exclude supra-tentorial extension.

Treatment

Trans-sphenoidal adenomectomy is the treatment of choice. Surgery is curative for microadenoma in 80% to 90% of cases. At least half of macroadenomas are not cured surgically. Surgical cure (defined by normalization of plasma IGF-1 and a nadir oral glucose tolerance test GH of <2 μg/l) is achieved in 81% to 100% of microadenomas and

BOX 39.1 Diagnostic Tests for Acromegaly

- Serum growth hormone
- Serum growth hormone responses to glucose tolerance test
- Serum insulin-like growth factor 1
- Lateral skull x-ray film
- Magnetic resonance imaging of the pituitary fossa
- Visual field measurements
- Assessment of other pituitary functions (e.g., thyroid function tests, thyroid-stimulating hormone, prolactin level, adrenocorticotropic hormone, and cortisol)

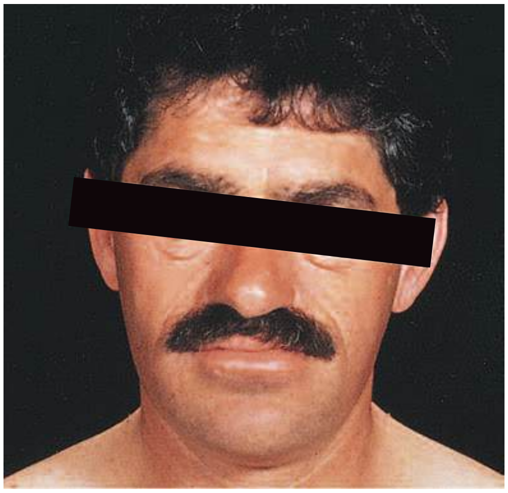

Fig. 39.7 Facial features of acromegaly with enlargement of brow, nose, and jaw.

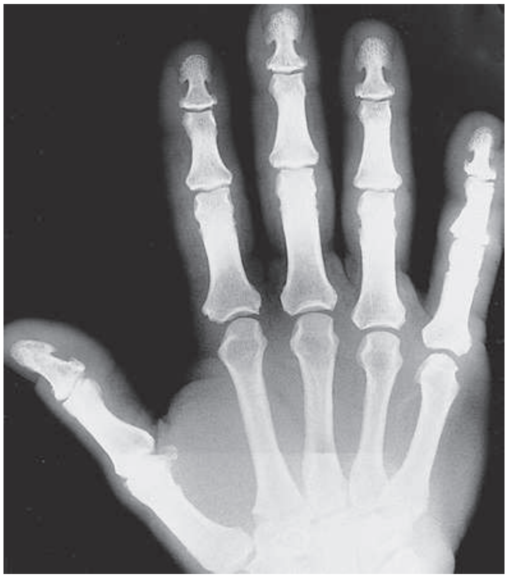

Fig. 39.8 Radiograph of the hand in acromegaly. "Arrowhead" distal phalanges, expanded joint spaces, and increased soft tissue can be seen.

45% to 68% of macroadenomas.[35] Irradiation and drug therapy are valuable when complete removal of tumor tissue is not possible (approximately one third of acromegalic cases overall) and when surgery is contraindicated. Dopaminergic agents, such as bromocriptine and cabergoline, and the somatostatin analogue octreotide, reduce serum GH in acromegaly. Bromocriptine may induce tumor shrinkage and improve diabetes. The GH receptor antagonist pegvisomant also has been shown to be safe and effective.[35,38] In view of long-term side effects, radiation therapy is employed only when necessary in cases with persistent active disease despite all other treatment. Radiotherapy may not exert its full effect for months or years. Hypopituitarism may occur late after treatment and necessitate endocrine replacement for ACTH, thyroid-stimulating hormone (TSH), or gonadotropin deficiency. Therefore regular monitoring of pituitary function is required after treatment. Overall, 75% to 94% of cases are controlled.[35]

Management of Hypertension in Acromegaly

Surgical removal of the pituitary adenoma with normalization of GH levels may reduce BP to some extent, but most patients with acromegaly will continue to require antihypertensive therapy. Antihypertensive treatment requires a diuretic, given the volume-expanded state. Additional antihypertensive agents are frequently required, and both calcium channel blockers and ACE inhibitors may be effective. β-Blockers also may be used, although theoretically such agents may increase GH concentration.

HYPOTHYROIDISM

Definition and Epidemiology

It is estimated that hypertension is 1.5 to 2 times more common in hypothyroid patients than in the general population.[39] The pathogenesis of the hypertension is multifactorial and associated with both increased total body sodium and increased peripheral vascular resistance. Even in euthyroid patients, serum free thyroxine index (FTI) is lower and TSH is higher in hypertensive than in normotensive patients and FTI also independently predicts BP response to increments in dietary sodium in both normotensive and hypertensive individuals.[40]

Hypothyroidism is associated with increased aortic stiffness, loss of sensitivity to vasoconstrictors, and impaired endothelial function with loss of endothelial-dependent vasodilation plus reduced vasodilatory responses to NO donors.[41] Observations of short-term hypothyroidism have confirmed increases in arterial pressure, plasma catecholamines, aldosterone, and cortisol, all reversible with thyroid hormone treatment.[42,43,44] The relationship between plasma catecholamine levels and BP is enhanced in hypothyroidism.[45] Hypertension develops despite a low cardiac output.

Thyroid replacement therapy corrects the electrolyte, hemodynamic, and hormone changes and cures the hypertension in most patients.

Clinical Features

Symptoms and signs can be protean. Bradycardia, mild hypertension with narrowed pulse pressure, and muffled heart sounds are the most frequent signs in overt hypothyroidism. Other features include weakness, dry skin, lethargy, slow slurred speech, cold intolerance, thick tongue, facial puffiness (Fig. 39.9), coarse and thinning hair, failing memory, constipation, and weight gain with reduced appetite. In extreme cases, myxedema and coma ensue. Coronary heart disease is common, with dyslipidemia and hypertension accelerating the atherogenic process.

Diagnosis

Hypothyroidism should be considered in any patient with hypertension. Because the clinical manifestations of hypothyroidism are often difficult to elicit, especially in elderly patients, thyroid function tests, including TSH when FTI is equivocal, should be performed. In patients with primary hypothyroidism in whom normotension is not achieved by full thyroxine replacement therapy, primary hypertension is a likely concomitant disorder. For those with gross or long-standing hypothyroidism, replacement thyroxine therapy should be cautious to minimize the chances for exacerbating latent myocardial ischemia.

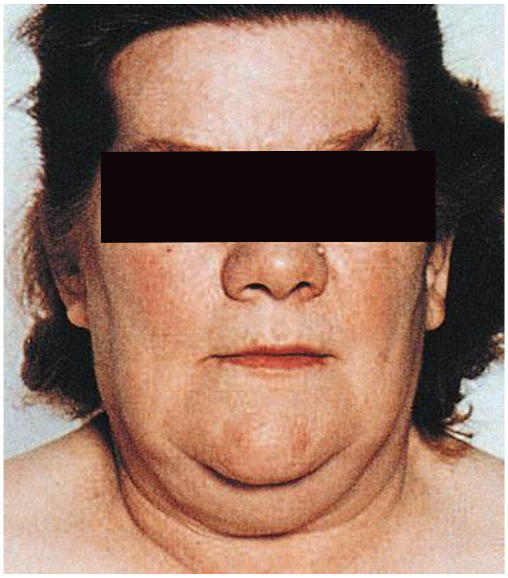

Fig. 39.9 Hypothyroid facies.

HYPERTHYROIDISM

Definition and Epidemiology

Hypertension is common in hyperthyroidism, with a prevalence of 60% in toxic adenoma and approximately 30% in Graves disease.[1]

Clinical Features

The clinical features depend on the underlying cause of the hyperthyroidism, severity of the disorder, rapidity of onset, age of the patient, and concomitant disease. Abnormalities may be evident in the cardiovascular system (tachyarrhythmias, heart failure), skin (increased sweating, increasing pigmentation with vitiligo), eyes (lid lag, exophthalmos), nervous system (hypertension, nervousness), alimentary system (increased appetite yet weight loss, diarrhea), and muscles (proximal weakness).

Hypertension in hyperthyroidism is associated with an increased pulse pressure with elevated systolic BP and normal or low diastolic BP. It may be observed in both postpartum thyrotoxicosis and neonatal thyrotoxicosis. Elevation of diastolic BP is unusual unless there is concomitant primary hypertension.

The hemodynamic characteristics in hypertension of thyrotoxicosis are an increased cardiac output (by 50% to 300%), increased myocardial contractility, tachycardia, decreased peripheral vascular resistance, and expanded blood volume. These indices return to normal in most patients on achieving the euthyroid state. Interestingly, catecholamine levels tend to be low (inversely to hypothyroid hypertension) and there is no heightened activity of the sympathetic system. The RAS tends to be activated and the aldosterone levels increased in hyperthyroidism, which may contribute to the development of systolic hypertension. Suspicion of hyperthyroidism should be high in the elderly patient with hypertension and a high pulse pressure, particularly if there is also atrial fibrillation. Such patients are prone to developing cardiac failure, in which case the increased systolic arterial pressure will diminish, masking previous hypertension. Hypertension with a high pulse pressure, although typical of hyperthyroidism, is observed in many elderly patients with primary hypertension because of the loss of compliance of the aorta with aging.

Diagnosis and Treatment

Diagnosis of hyperthyroidism is confirmed by thyroid function tests, including measurement of TSH. β-Blockers are often effective first-line therapy for hyperthyroidism-associated hypertension. Treatment of hyperthyroidism, whether by antithyroid drugs, surgery, or radioiodine, often will promptly normalize the increased systolic arterial pressure, although not necessarily in elderly patients with concomitant primary hypertension.

PRIMARY HYPERPARATHYROIDISM

The incidence of primary hyperparathyroidism (PHPT) is approximately 20 per 100,000 person-years.[1,46] Full-blown PHPT may feature severe hypercalcemia, nephrolithiasis, acute and chronic renal disease, and fractures, but more commonly patients are asymptomatic. The prevalence of hypertension is increased in PHPT, approaching 50% with an independent association between plasma ionized calcium levels and the presence of hypertension. Generally, mild PHPT is not an indication for parathyroidectomy and management comprises serial follow-up in an endocrine service with monitoring of plasma calcium, renal function, and bone density. Coincident hypertension is not an accepted indication for parathyroidectomy and is managed according to standard guidelines with the notable difference that thiazide diuretics (which may increase plasma calcium) should be avoided. There is some evidence that surgical cure of PHPT and restoration of eucalcemia restores vascular function and BP toward normal.[46]

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SELF-ASSESSMENT QUESTIONS

1. Each form of endocrine hypertension:
   A. Always manifests typical signs and symptoms
   B. Can always be cured if correct specific therapies are applied
   C. Is usually familial
   D. May present as hypertension resistant to multiple drugs
2. Initial screening tests for Cushing syndrome include which of the following?
   A. Computed tomography or magnetic resonance imaging of pituitary and adrenal glands
   B. Measurement of late night salivary cortisol
   C. High-dose dexamethasone suppression test
   D. Bilateral inferior petrosal sinus sampling for ACTH
3. Adrenal incidentalomas are:
   A. Usually hormonally active
   B. Associated with subclinical hypercortisolism in about 30% of cases
   C. Adrenal carcinomas in over 5% of cases
   D. Are not associated with any higher prevalence of hypertension than in the general population without incidentaloma

40

Neurogenic Hypertension, Including Hypertension Associated With Stroke or Spinal Cord Injury

Venkatesh Aiyagari, Mohamed Osman, Philip B. Gorelick

An intimate relationship exists between the nervous system and blood pressure (BP).[1] It is well recognized that the elevated BP response to stressors is mediated by the sympathetic nervous system (SNS). However, the role of the SNS in long-term regulation of BP and the initiation and maintenance of hypertension is now better delineated. Several studies of serum catecholamine levels, renal norepinephrine spillover, microneurography, and heart rate variability suggest that sympathetic activation plays a major role in hypertensive patients.[2] The SNS also has an important role in hypertension after neurologic injury. In this chapter, we discuss the physiology and management of hypertension in such injury.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Neural Control of Blood Pressure

The brainstem, especially the ventral medulla, has a key role in the maintenance of BP (Fig. 40.1). BP is controlled by the nucleus tractus solitarius, which receives inhibitory baroreceptor afferents, and the rostral ventrolateral medulla and rostral ventromedial medulla, which are the source of excitatory descending bulbospinal pressor pathways. In addition, a depressor center in the caudal ventrolateral medulla composed of γ-aminobutyric acid (GABA)-containing neurons receives afferents from the nucleus tractus solitarius and projects to the rostral ventral medulla. These inhibitory GABA-containing neurons are tonically active, and reduced activity of these neurons leads to hypertension.[3-5]

The ultimate effector units are the sympathetic neurons located in the intermediolateral cell column of the spinal cord and the parasympathetic neurons found in the dorsal motor nucleus of the vagus and nucleus ambiguus located in the medulla. In addition, impulses from the limbic system, cerebral cortex, and hypothalamus directly or indirectly project to the intermediolateral cell column of the spinal cord and influence BP regulation.

The factors that lead to increased sympathetic activation in hypertension are poorly understood. However, there is strong evidence linking hypertension with increased levels of circulating inflammatory markers such as tumor necrosis factor α, interleukin-6, C-reactive protein, monocyte chemoattractant protein 1, and adhesion molecules such as P-selectin and intercellular adhesion molecule 1. Angiotensin II (Ang II) and aldosterone also play a crucial role in vascular inflammation, and treatment with both candesartan and mineralocorticoid antagonists decrease the levels of inflammatory markers. In addition, Ang II–mediated hypertension is associated with brain microglial activation and increased brain levels of inflammatory cytokines and reactive oxygen species. An increase in reactive oxygen species may directly activate or sensitize sympathetic neurons and scavenge nitric oxide, which tonically inhibits sympathetic outflow. Thus a dysfunction of the neural-immune-vascular triad leading to an increase in central oxidative stress may drive sympathetic activation, which then increases Ang II and promotes further inflammation and vascular dysfunction.[6]

Cerebrovascular Autoregulation

Under normal conditions, cerebral blood flow (CBF) of the adult brain is 50 ml/100 g/min. CBF is regulated by the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR):

$$\text{CBF} = \text{CPP}/\text{CVR}$$

CPP is the difference between the mean arterial blood pressure (MAP) and the intracranial pressure (ICP). If ICP is increased, systemic BP must also increase to maintain CPP and CBF.

Cerebrovascular autoregulation maintains a constant blood flow over a wide range of CPP. Normally, changes in CPP have little effect on CBF because of compensatory changes in CVR. An increase in CPP produces vasoconstriction and a decrease produces vasodilation, thus keeping the CBF constant (Fig. 40.2). Autoregulation is effective for a range of CPP from about 60 to 150 mm Hg. In chronically hypertensive individuals, the cerebral arterioles develop medial hypertrophy and lose the ability to dilate effectively at lower pressures. This leads to a shift of the autoregulatory curve to the right.[7] In these individuals, a rapid reduction of BP may lead to a drop in CBF even though the BP might still be “normal.” With effective control of hypertension for several months, the normal range for autoregulation can be reestablished.[8]

Above the upper limit of autoregulation, there is breakthrough vasodilation leading to damage of the blood-brain barrier, cerebral edema, and possibly cerebral hemorrhage. Below the lower limit of autoregulation, decreases in CPP lead to a decrease in CBF. Under these circumstances, increased extraction of oxygen and glucose maintains normal cerebral metabolism and brain function. When the CBF decreases to less than 20 ml/100 g/min, increases in oxygen extraction are no longer able to supply the metabolic needs of the brain, leading to impairment of brain function.

SPECIFIC SYNDROMES

Hypertension After Stroke

Epidemiology

BP is commonly elevated in patients with stroke. In a large retrospective analysis that examined 276,734 patients presenting to the emergency department with acute ischemic stroke, the incidence of elevated BP was 76.5%.[9] The Chinese Acute Stroke Trial (CAST) and the International Stroke Trial (IST), each enrolling approximately 20,000 patients with

Neural Pathways Involved in the Control of Blood Pressure

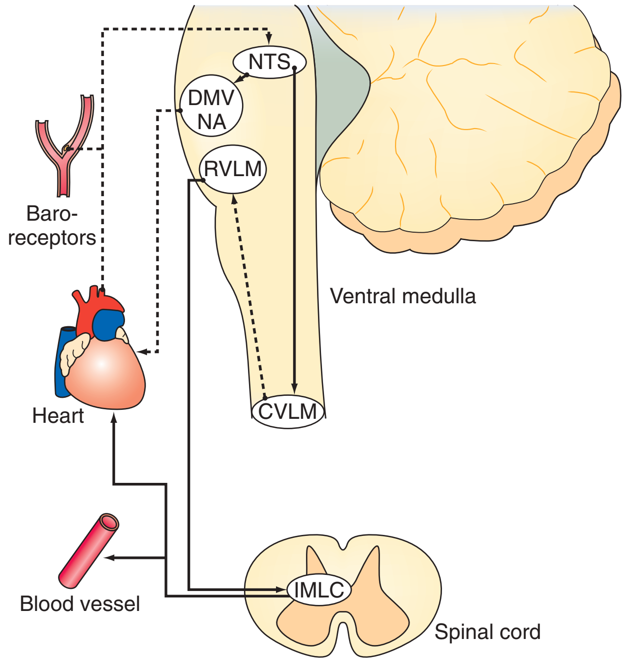

Fig. 40.1 **Neural pathways involved in the control of blood pressure.** The ventral medulla has a key role in generating both excitatory *(solid line)* and inhibitory *(dotted line)* pathways, largely through the rostral ventrolateral medullary neurons *(RVLM)* and nucleus tractus solitarius *(NTS)*, respectively. Ultimate effector control is provided by sympathetic activation originating in the intermediolateral cell column *(IMLC)* and parasympathetic action through the nucleus ambiguus *(NA)* and dorsal motor nucleus of the vagus nerve *(DMV)*. *CVLM*, Caudal ventrolateral medullary neurons.

ischemic stroke, reported systolic BP (SBP) above 140 mm Hg in 75% and 80% of patients and severely elevated SBP of greater than 180 mm Hg in 25% and 28%, respectively.[10,11]

Hypertension is the most important modifiable risk factor for stroke, and reduction in BP is effective in the primary prevention of both ischemic and hemorrhagic stroke; BP reduction also decreases the risk for a recurrent ischemic or hemorrhagic stroke.[12] Combined data from 40 trials show that a 10% reduction in SBP lowers stroke risk by one third.[13] A 5-mm reduction in diastolic pressure together with a 9-mm lower SBP confers a 33% lower risk for stroke, and a 10-mm lower diastolic BP (DBP) together with an 18- to 19-mm lower SBP confers more than a 50% reduction in stroke risk.[14] In patients who have had a stroke, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed that BP reduction was associated with reductions of 28% in stroke recurrence and 26% in major coronary and vascular events, even in normotensive subjects. This study also demonstrated a reduction of absolute rates of hemorrhagic stroke from 2% to 1% over a mean of 3.9 years of follow-up.[15]

However, the management of BP in the immediate aftermath of a stroke is controversial.[16] A high proportion of patients have elevated BP immediately after a stroke, but BP spontaneously decreases over 1 to 2 weeks to the prestroke baseline in most patients. Some of the postulated causes of elevated BP are listed in Box 40.1. An increased BP after stroke is associated with a higher mortality. Nonetheless, it is uncertain whether this increase directly contributes to poor outcome and whether immediate lowering of BP will lead to better outcomes.

Cerebral Autoregulation Curve

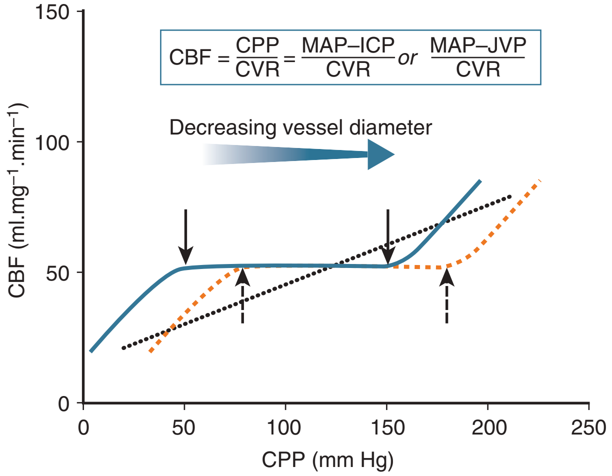

Fig. 40.2 **Cerebral autoregulation curve.** In the normal state *(solid line)*, the cerebral blood flow *(CBF)* is held constant across a wide range of cerebral perfusion pressure *(CPP)* (60 to 150 mm Hg). In chronic hypertension *(dashed line)*, the autoregulation curve shifts to the right. In the presence of acute cerebral ischemia *(dotted line)*, cerebral autoregulation may be impaired, and the CBF becomes dependent on the CPP. *CVR*, Cerebral venous resistance; *ICP*, intracranial pressure; *JVP*, jugular venous pressure; *MAP*, mean arterial pressure. (Reproduced with permission from reference 17.)

BOX 40.1 Postulated Causes of Hypertension After Stroke

- Preexisting hypertension
- "White coat" effect
- Stress of hospitalization
- Cushing reflex*
- Catecholamine and cortisol release
- Lesion of brainstem or hypothalamus
- Nonspecific response to brain damage

*A hypothalamic response to raised intracranial pressure or ischemia consisting of hypertension with bradycardia.

SBP variability is significantly associated with the risk for cerebrovascular events independent of the mean BP. Home BP monitoring and ambulatory BP monitoring are useful in monitoring BP variability. Normally, BP is highest in the morning and gradually falls to reach its lowest level during sleep. Several alterations in this pattern, including a lack of nighttime decline in BP (nondippers), a rise in nighttime BP (reverse dippers), and a more than 20% fall in nighttime BP (extreme dippers), are associated with increased risk for vascular complications, including stroke. These findings also have a bearing on the choice of the antihypertensive agent for stroke prevention. Calcium channel blockers (CCBs) and nonloop diuretics appear to decrease SBP variability, whereas β-blockers, angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme (ACE) inhibitors have the opposite effect.

Pathophysiology

An understanding of cerebrovascular pathophysiology is essential to understand the pros and cons of treating hypertension in these patients (Table 40.1).

TABLE 40.1 Acute Treatment of Hypertension in Stroke: Advantages and Disadvantages

Advantages	Disadvantages
Acute Ischemic Stroke	
Might lower mortality	BP decreases on its own
Might decrease stroke progression	No proven benefit
Might decrease hemorrhagic transformation (especially after tPA)	Ongoing ischemia around infarct (ischemic penumbra)
Might decrease cerebral edema formation	Altered autoregulation from chronic hypertension, ischemia
Might be helpful for systemic reasons (e.g., associated myocardial ischemia)	Large-vessel stenosis might have resulted in reduction of perfusion Chance of propagating thrombus
Patients likely to be more compliant with antihypertensive use if treatment initiated in hospital	Anecdotal case reports and trial results demonstrating deterioration with BP decrease Principle of "do no harm" *(primum non nocere)*
Acute Intracerebral Hemorrhage	
Might lower mortality	BP decreases on its own
Might decrease hematoma expansion	No proven benefit
Might decrease cerebral edema formation	Possible zone of ischemia around intracerebral hematoma
Might be helpful for systemic reasons (e.g., associated myocardial ischemia)	Chronically hypertensive patients require higher CPP, because of shift in autoregulatory curve.
Patients likely to be more compliant with antihypertensive use if treatment initiated in hospital	ICP may be elevated, and lowering BP reduces what could be marginal CPP Principle of "do no harm" *(primum non nocere)*
Aneurysmal Subarachnoid Hemorrhage	
Might decrease rebleeding rate	No proven benefit
Might help if there is cardiac ischemia (stunned myocardium)	ICP may be elevated, and lowering BP reduces what could be marginal CPP. Might lead to cerebral ischemia in presence of vasospasm.

BP, Blood pressure; *CPP,* cerebral perfusion pressure; *ICP,* intracranial pressure; *t-PA,* tissue plasminogen activator.

In patients with an ischemic stroke, vascular occlusion leads to a central region of irreversibly ischemic brain surrounded by an ischemic zone where blood flow is reduced but brain tissue is still viable. After 2 or 3 days, the ischemic areas either recover completely or undergo infarction. In the first few days, perfusion of the area surrounding that destined to infarction is marginal and a further decrease in blood flow might lead to infarction there as well. Because cerebral autoregulation is impaired with acute ischemic stroke, a fall in BP could lower blood flow and extend infarction. On the other hand, a very high BP could exacerbate cerebral edema or lead to hemorrhagic transformation, especially if thrombolytic agents have been given.

In patients with intracerebral hemorrhage (ICH), the considerations are different.[17] Hematoma expansion occurs in 73% of patients within 24 hours, and significant expansion (>33% increase in volume) occurs in nearly 40% of patients.[18] Hematoma expansion is frequently associated with decline in neurologic status and is an independent predictor of mortality and poor functional outcome. Therefore BP is often lowered in these patients in the hope that this might decrease hematoma expansion. However, it is not often clear if the elevation in BP is the cause or the consequence of hematoma expansion. The suggestion that there may be perihematomal ischemia around an ICH has not been supported by recent studies.[19] Furthermore, some patients with ICH might have increased ICP because of the hematoma volume or associated hydrocephalus. In such a situation, lowering of BP is not warranted because it might critically lower CPP. Monitoring of ICP and CPP may be helpful in choosing the appropriate BP target in these circumstances.

In patients with aneurysmal subarachnoid hemorrhage (SAH), there is a significant risk for rebleeding from aneurysmal re-rupture and therefore early BP control is recommended to decrease the re-bleeding risk. Some patients with SAH have associated myocardial dysfunction ("stunned myocardium"), in which case high BP might worsen myocardial function. Similar to patients with ICH, in patients with hydrocephalus or an associated ICH, ICP and CPP monitoring can help guide BP management. However, many patients develop vasospasm of the intracranial arteries at 4 to 12 days after SAH, and reduction of BP may lead to worsening of cerebral ischemia in this situation. Therefore, once the aneurysmal rupture has been adequately treated with surgical clipping or coiling, BP is usually maintained at a normal or slightly elevated level in these patients.

Diagnosis and Treatment

Acute management of hypertension in stroke is highly dependent on the type of stroke (ischemic vs. hemorrhagic) and for ischemic stroke the use of thrombolysis. The benefits of lowering BP to prevent hematoma expansion in the setting of ICH or hemorrhagic transformations of ischemic stroke should be balanced with the risk for abrupt reduction of CBF in chronically hypertensive patients with shifted cerebrovascular autoregulation, especially if increased ICP and cerebral edema are present.

It is important to distinguish between hypertensive encephalopathy, in which lowering of BP is clearly indicated, and ischemic stroke with hypertension, in which urgent lowering of BP may not be warranted. The level of consciousness, the presence of focal neurologic deficits, and the funduscopic examination can help in making this distinction. Hypertensive encephalopathy is a syndrome of global neurologic dysfunction, usually with papilledema. Focal neurologic deficits are usually less prominent. In acute ischemic stroke, the focal neurologic deficit is prominent and the symptoms and neurologic signs often can be mapped to the vascular territory supplied by a specific cerebral blood vessel. Early alterations of consciousness are less common except with brainstem strokes or when there is "malignant" brain edema secondary to a massive hemispheric infarction.

Several recent studies assess the benefits and risks of BP lowering after ischemic and hemorrhagic stroke. A Cochrane review on this topic concluded that more research is needed to evaluate and identify the candidates most likely to benefit from management of BP in the acute phase of stroke, and the timeframe for such intervention.[20]

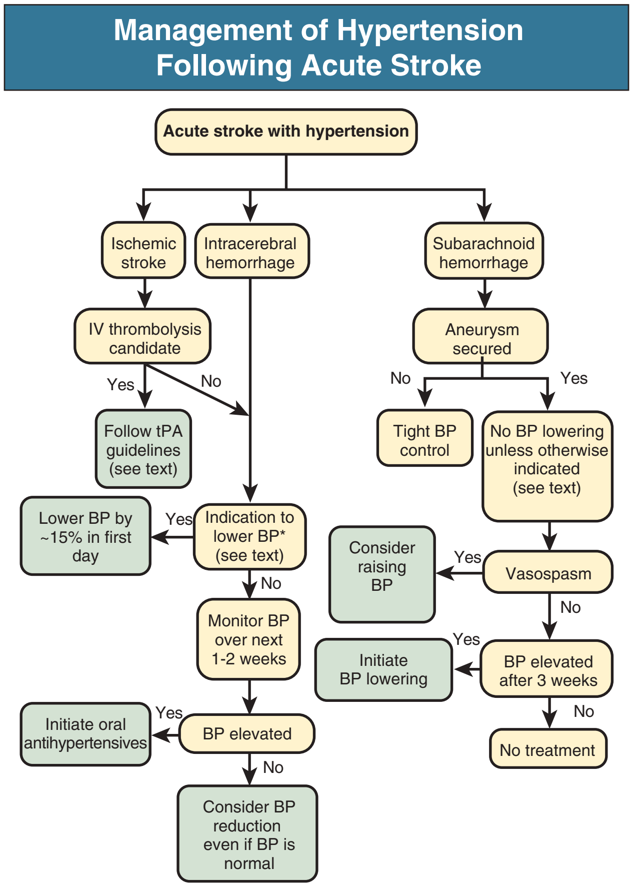
Management of Hypertension Following Acute Stroke
Acute stroke with hypertension
Ischemic stroke
Intracerebral hemorrhage
Subarachnoid hemorrhage
IV thrombolysis candidate
Yes
No
Follow tPA guidelines (see text)
Aneurysm secured
No
Yes
Tight BP control
No BP lowering unless otherwise indicated (see text)
Lower BP by ~15% in first day
Yes
Indication to lower BP* (see text)
No
Consider raising BP
Yes
Vasospasm
No
Monitor BP over next 1-2 weeks
Initiate BP lowering
Yes
BP elevated after 3 weeks
No
Initiate oral antihypertensives
Yes
BP elevated
No
No treatment
Consider BP reduction even if BP is normal

Fig. 40.3 Management of hypertension after acute stroke. *Indication for treatment includes systolic BP above 220 mm Hg or diastolic BP above 120 mm Hg for ischemic stroke, the presence of associated conditions such as aortic dissection or myocardial infarction, and, in cases of cerebral hemorrhage, systolic BP above 180 mm Hg or mean arterial pressure above 130 mm Hg. *BP,* Blood pressure; *IV,* intravenous; *tPA,* tissue plasminogen activator.

An overview of recommendations for treating BP in different clinical situations is outlined in Fig. 40.3.

Acute ischemic stroke. Several large prospective trials of BP lowering in acute ischemic stroke have been completed and are summarized in Table 40.2.[21-29]

The current guidelines of the American Heart Association/American Stroke Association (AHA/ASA) and the European Stroke Organisation (ESO) for BP management in acute ischemic stroke recommend a cautious approach to lowering BP in acute ischemic stroke. Patients receiving thrombolytic therapy should have their BP lowered to less than 185/110 mm Hg before the administration of the thrombolytic agent and maintained at a level of less than 180/105 mm Hg for at least the first 24 hours after thrombolytic treatment. Patients not receiving thrombolytic agents should have antihypertensive medications withheld unless the SBP is greater than 220 mm Hg or the DBP is greater than 120 mm Hg, in which case a 15% reduction in BP in the first 24 hours appears reasonable. Recommendations are summarized in Table 40.3.

Thus the available evidence does not support immediate BP reduction after an acute ischemic stroke. Based on the limited data and natural history of BP after ischemic stroke, treatment of newly diagnosed previously untreated hypertension or resumption of long-term antihypertensive medication can be initiated or resumed gradually after the first 24 hours. Reduced dosage and/or number of agents from the prestroke regimen should be used to avoid rapid reduction of BP in the case of prior outpatient noncompliance.

Intracerebral hemorrhage. Hypertension is the most important modifiable risk factor for ICH. Although long-term benefit in lowering BP in patients with ICH is widely accepted, it remains unclear if elevated BP should be lowered in the acute phase. In recent years, a few randomized trials have attempted to address the issue of acute BP lowering in ICH and are summarized in Table 40.4.[30-34]

The currently recommended guidelines of the AHA/ASA and the European Stroke Initiative (ESI) for BP management in acute ICH are summarized in Table 40.5.[35,36] It should be noted that these guidelines were published before the publication of the results of Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 (ATACH 2). Similar to the case in acute ischemic stroke, the current evidence does not demonstrate lower rates of mortality or severe disability with aggressive BP reduction in patients with cerebral hemorrhage. If elevated ICP is of concern, such as in patients with large hemorrhages or with hydrocephalus, ICP should be monitored to ensure that the CPP is appropriate before significant BP reduction. In other instances, it is reasonable to keep the SBP below 180 mm Hg. Definitive evidence to support lower BP targets (e.g., <140 mm Hg) in the acute setting is currently lacking.

Subarachnoid hemorrhage. Before definitive treatment of the ruptured aneurysm, SBP is usually kept below 160 mm Hg, although there is no conclusive evidence that higher BPs increase rebleeding rates. In patients with suspected elevation of ICP, it is important to monitor ICP and keep the CPP above 70 mm Hg. The AHA/ASA guidelines recommend monitoring and control of BP to balance the risk for stroke, hypertension-related bleeding, and maintenance of CPP. An SBP goal of less than 160 mm Hg is considered reasonable.[37] The ESO recommends keeping the SBP below 180 mm Hg but keeping the MAP greater than 90 mm Hg.[38] After the ruptured aneurysm has been secured, aggressive treatment of BP should be avoided, and in the setting of cerebral vasospasm, BP is usually elevated using vasopressors until the neurologic deficits resolve, often as high as an SBP of 200 to 220 mm Hg.

Hypertension After Carotid Endarterectomy and Endovascular Procedures

Definition, Incidence, and Clinical Features

Hemodynamic disturbances such as hypotension, bradycardia, and hypertension are common (10% to 40%) after carotid endarterectomy and endovascular procedures such as angioplasty and stenting. A small percentage of these patients develop carotid hyperperfusion (or reperfusion) syndrome. This syndrome occurs in the first week after surgery or angioplasty-stenting and manifests as transient or permanent contralateral neurologic signs, ipsilateral pulsatile headache, seizures, ICH, or reversible cerebral edema.[39-41] Some subjects with postrevascularization cerebral hyperperfusion may not manifest clinical signs acutely but may later develop cortical neuronal loss and cognitive impairment.[42]

After carotid endarterectomy, the incidence of postoperative severe hypertension is reported as 19% and that of carotid hyperperfusion syndrome as 1%. Most cases occurred in the first week and the average time to symptoms was the fifth postoperative day. Seizures (36%), hemiparesis (31%), or both (33%) were the common presenting features, and 59% of patients had headache.[43]

Pathophysiology

Preexisting hypertension, baroreceptor impairment after surgical manipulation, and elevated catecholamine levels after cerebral hypoperfusion during intraoperative cross-clamping may contribute to postoperative hypertension that contributes to cerebral hyperperfusion. The hyperperfusion syndrome may be due, in part, to impaired autoregulation from chronic vasodilation of the distal vascular bed ipsilateral to a hemodynamically significant internal carotid artery stenosis.[44] Other postulated mechanisms include activation of the trigeminovascular axon reflex and derangement of the carotid baroreceptors.[45] Subjects at risk

TABLE 40.2 Major Trials of Acute Blood Pressure Reduction in Ischemic Stroke

Trial	Study Design	Study Arms	Number of Patients	Results
Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS)[21]	Prospective, double-blind, placebo-controlled, randomized, multicenter, phase 2	Candesartan versus placebo	342	Lower 12-month mortality and vascular events in the candesartan group, but no significant difference in BP between the two arms
Scandinavian Candesartan Acute Stroke Trial (SCAST)[22]	Prospective, double-blind, placebo-controlled, randomized, multicenter	Candesartan versus placebo	2029 (274 had cerebral hemorrhage)	During 6 months of follow-up, the risk of the composite vascular end-point did not differ between treatment groups. Analysis of functional outcome suggested a higher risk for poor outcome in the candesartan group.
Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS)[23]	Prospective, double-blind, placebo-controlled, randomized, multicenter	Labetalol versus lisinopril versus placebo	179 (25 had cerebral hemorrhage)	No difference in death or dependency at 2 weeks, early neurologic deterioration, or serious adverse event.
Continue Or Stop post-Stroke Antihypertensive Collaborative Study (COSSACS)[24]	Prospective, open, multicenter, randomized, blinded-end-point trial	Continue versus stop preexisting antihypertensive drugs	763 (38 had cerebral hemorrhage)	Continuation of antihypertensive drugs did not reduce 2-week death or dependency, cardiovascular event rate, or mortality at 6 months.
Glycine Antagonist in Neuroprotection (GAIN International)[25]	Prospective, double-blind, placebo-controlled, randomized, multicenter	Gavestinal versus placebo	1445	A 30% drop in mean arterial pressure from baseline was not associated with poor outcome.
Intravenous Nimodipine West European Stroke Trial (INWEST)[26]	Prospective, double-blind, placebo-controlled, randomized, multicenter	Placebo versus low-dose versus high-dose nimodipine	265	Patients with a DBP reduction of ≥20% in the high-dose group had a significantly increased adjusted odds ratio for the compound outcome variable death or dependency.
Chinese Antihypertensive Trial in Acute Ischemic Stroke (CATIS)[27]	Prospective, single-blind, randomized, blinded end-point, multicenter	Antihypertensive treatment versus discontinuing all antihypertensives	4071	BP reduction with antihypertensive medications, compared with the absence of hypertensive medication, did not reduce the likelihood of death and major disability at 14 days or hospital discharge.
Efficacy of Nitric Acid in Stroke (ENOS)[28]	Prospective, multicenter, randomized, placebo-controlled, patient-masked, outcome-assessor-masked, parallel-group trial	Glyceryl trinitrate versus no treatment; subset taking antihypertensive medications on admission randomized to taking versus stopping them	4011 (629 had cerebral hemorrhage)	Transdermal glyceryl trinitrate lowered BP and had acceptable safety but did not improve functional outcome. There was no evidence to support continuing prestroke antihypertensive drugs in patients in the first few days after acute stroke.
Valsartan Efficacy on Modest Blood Pressure Reduction in Acute Ischemic Stroke (VENTURE)[29]	Prospective, multicenter, randomized, open-label, blinded-end-point trial	Valsartan versus no treatment	393	Early reduction of BP with valsartan did not reduce death or dependency and major vascular events at 90 days, but increased the risk for early neurologic deterioration.

BP, Blood pressure; *DBP,* diastolic blood pressure.

for development of this syndrome are those with extensive microvascular disease, preoperative hypoperfusion and impaired autoregulation, or postoperative hyperperfusion.

Diagnosis and Treatment

Cerebral hyperperfusion represents a postoperative increase in CBF of more than 100% compared with preoperative flow. However, this increase in blood flow may be only approximately 20% compared with the contralateral side.[46] Making a diagnosis based on CBF doubling alone may lead to a significant overestimation of the incidence, and the following four criteria have been suggested: (1) Occurrence within 30 days post–carotid endarterectomy; (2) evidence of hyperperfusion (on transcranial Doppler, single-photon emission computed tomography, or computed tomography (CT)/magnetic resonance (MR) perfusion imaging) or SBP greater than 180 mm Hg; (3) clinical features such as new headache, seizures, hemiparesis, Glasgow coma scale less than 15, or radiologic features such as cerebral edema or ICH; and (4) no evidence of new cerebral ischemia, postoperative carotid occlusion, or metabolic or pharmacologic cause to explain the findings.[43]

Because of the risk for development of carotid hyperperfusion syndrome after carotid endarterectomy or stenting, all patients should have continuous intraoperative and postoperative BP monitoring. Most authors advocate strict BP control (SBP <120 mm Hg) from the time of intraoperative internal carotid artery unclamping or angioplasty, particularly in high-risk patients.[47] If high-risk features are absent, aiming for SBP of 140 to 160 mm Hg or preoperative SBP (if lower) in the postoperative period is reasonable. Elevated BP should be treated with intravenous labetalol or clonidine. Vasodilators such as nitroglycerin

TABLE 40.3 Guidelines for Blood Pressure Management After Acute Ischemic Stroke

AHA/ASA	ESO
Patients Eligible for Thrombolytic Therapy ***Before Thrombolytic Therapy*** Lower BP if SBP >185 or DBP >110 mm Hg. ***After Thrombolytic Therapy*** Lower BP if SBP >180 or DBP >105 mm Hg.	Routine BP lowering is not recommended. Cautious BP lowering is recommended in patients with extremely high BP (>220/120 mm Hg) on repeated measurements, or with severe cardiac failure, aortic dissection, or hypertensive encephalopathy. Abrupt BP lowering should be avoided. BP must be below 185/110 mm Hg before, and for the first 24 hours after, thrombolysis.
Patients Not Eligible for Thrombolytic Therapy Patients with markedly elevated BP may have their BP lowered. Lowering BP by ~15% in these patients is reasonable. Antihypertensive drugs should be withheld unless SBP >220 or DBP >120 mm Hg.	

AHA/ASA, American Heart Association/American Stroke Association; *BP,* blood pressure; *DBP,* diastolic blood pressure; *ESO,* European Stroke Organisation; *SBP,* systolic blood pressure.

TABLE 40.5 Guidelines for Blood Pressure Management After Acute Cerebral Hemorrhage

AHA/ASA	ESO
For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe (Class I; Level of Evidence A) and can be effective for improving functional outcome (Class IIa; Level of Evidence B).	In acute ICH within 6 hours of onset, intensive BP reduction (SBP target <140 mm Hg in <1 hour) is safe and may be superior to SBP target of <180 mm Hg. No specific agent can be recommended. (Quality of evidence: Moderate; Strength of recommendation: Weak).
For patients with ICH presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring (Class IIb; Level of Evidence C).	

AHA/ASA, American Heart Association/American Stroke Association; *BP,* blood pressure; *CPP,* cerebral perfusion pressure; *DBP,* diastolic blood pressure; *ESO,* European Stroke Organisation; *ICP,* intracranial pressure; *MAP,* mean arterial pressure; *SBP,* systolic BP.

TABLE 40.4 Major Trials of Acute Blood Pressure Reduction in Cerebral Hemorrhage

Trial	Study Design	Study Arms	Number of Patients	Results
Koch et al.[30]	Prospective, randomized	Target MBP <110 or 110-130 mm Hg	42	No significant differences in early neurologic deterioration, hematoma and edema growth, and clinical outcome.
INTERACT[31]	Prospective, randomized, blinded end-point assessment	Target SBP <140 or <180 mm Hg	404	No significant difference in hematoma growth between the two tiers after adjustment for baseline hematoma volume and time to CT scan.
INTERACT 2[32]	Prospective, randomized, blinded end-point assessment	Target SBP <140 or <180 mm Hg	2839	No significant reduction in the rate of primary outcome of death or severe disability with intensive lowering of BP. Improved functional outcomes with lower BP target on ordinal analysis of modified Rankin Scale score.
ATACH[33]	Prospective, Phase I dose-escalation	Target SBP 110-140 or 140-170 or 170-200 mm Hg	60	Observed proportions of neurologic deterioration and serious adverse events below the prespecified safety thresholds; 3-month mortality rate lower than expected in all tiers.
ATACH 2[34]	Prospective, randomized, multicenter, open-label trial	Target SBP 110-140 or 140-179 mm Hg	1000	BP reduction to a target SBP of 110 to 139 mm Hg did not result in a lower rate of death or disability than a target of 140 to 179 mm Hg. The rate of renal adverse events within 7 days after randomization was significantly higher in the group with the lower BP target.

BP, Blood pressure; *CT,* computed tomography; *MAP,* mean arterial blood pressure; *SBP,* systolic BP.

and sodium nitroprusside should be avoided. Because this syndrome may occur after patients have been discharged from the hospital, it is important for physicians to ensure that BP is appropriately controlled even after the immediate postoperative period.

Hypertension After Spinal Cord Injury

Definition and Epidemiology

Autonomic dysreflexia occurs in up to 70% of persons after spinal injury, most often during the first 2 to 4 months after injury. It is defined as an increase in SBP by at least 20%, associated with a change in heart rate and accompanied by at least one sign (sweating, piloerection, facial flushing) or symptom (headache, blurred vision, stuffy nose).[48] If it is unrecognized, it can result in serious sequelae, such as posterior leukoencephalopathy, ICH, SAH, seizures, arrhythmia, pulmonary edema, retinal hemorrhage, and, rarely, coma or death.[49]

Pathophysiology and Diagnosis

Autonomic dysreflexia is most commonly seen in patients with complete spinal cord injury in which there is loss of all neurologic function below the level of the lesion. The spinal cord lesion is typically at or above the sixth thoracic spinal level. Immediately after the injury, there is initial loss of supraspinal sympathetic control similar to the initial period of muscle flaccidity. This often leads to hypotension and bradycardia (spinal shock). After a few weeks to months, there is extrajunctional sprouting of the α-receptors, denervation hypersensitivity, and impaired presynaptic uptake of norepinephrine. In addition, there may be derangement of spinal glutaminergic interneurons. Noxious stimuli below the neurologic level of the lesion trigger a spinal reflex arc that results in increased sympathetic tone and hypertension.[50] The most common inciting events are an overdistended urinary bladder and fecal impaction. However, it may be secondary to other precipitants, including infections, pressure ulcers, urologic and endoscopic procedures, sympathomimetic medications, and sildenafil citrate used for sperm retrieval.[51]

Clinical symptoms include pulsatile headache, blurred vision, anxiety, nasal congestion, nausea, and sweating above the involved spinal level. The flushed, sweaty skin above the lesion level is due to brainstem parasympathetic activation. At and below the lesion, the skin remains pale, cool, and dry. Heart rate can be quite variable from bradycardia to tachycardia. The hallmark physical finding is elevated BP. However, because BP may normally be quite low after spinal cord injury, baseline BP readings may be within the normal range but elevated for a given individual, making clinical suspicion and reliance on other clinical signs and symptoms paramount in the diagnosis if baseline BP is not known.[50]

Treatment

Vigilant preventive measures for autonomic dysreflexia include proper bowel, bladder, and skin care. However, expeditious treatment of elevated BP is critical to avoid the potentially life-threatening consequences. Placement of the patient upright with the legs lowered to reduce BP and removal of any possible noxious stimuli (such as binding clothing and devices) are the initial treatments. It is also important to look for and appropriately treat other common triggers such as urinary retention or constipation.

Pharmacologic treatment with rapid-acting, short-lived agents may be indicated for SBP elevation of 150 mm Hg or greater that persists after the preceding interventions. Nitroglycerin is often used to treat hypertension associated with autonomic dysreflexia. However, to avoid precipitating hypotension, nitrate-containing agents should not be given for 24 hours before the use of sildenafil or similar agents to facilitate sperm retrieval or treat erectile dysfunction in spinal cord injury. CCBs and ACE inhibitors also have been reported to be effective.[52] However, these agents might exacerbate resting hypotension and therefore should be used with caution. Prazosin has been reported to be effective in reducing the severity of autonomic dysreflexia without significantly lowering the resting BP. If the bladder is empty and the BP is below 150 mm Hg, fecal disimpaction with topical anesthetic should be attempted. If dysreflexia is refractory or associated with severe clinical presentation, other precipitants should be sought and hospitalization may be indicated.[53]

Up to 90% of pregnant women with upper spinal cord injury experience autonomic dysreflexia during labor and delivery. Appropriate epidural or spinal anesthesia techniques can ameliorate the risk.[54]

Cerebrovascular Effects of Antihypertensive Agents

Different classes of antihypertensive agents have different direct effects on the CBF, ICP, and autoregulation. The ideal drug would not increase ICP or decrease blood flow to ischemic regions. In addition, in treatment of hypertension in the acute setting, drugs that can be given intravenously, have a short half-life and do not cause sedation are preferable. In the chronic phase after a stroke, adequate BP lowering is key and there is no clear evidence favoring one class of antihypertensive agent over another; however, one may consider avoiding the use of nonselective β-blockers that may increase SBP variability.

The advantages and disadvantages of various classes of antihypertensive agents after acute stroke are summarized in Table 40.6.

β-Adrenergic antagonists (e.g., esmolol) and combined α- and β-adrenergic receptor antagonists (e.g., labetalol) do not increase ICP or affect cerebral autoregulation. They are suitable for treatment of hypertension in the setting of acute cerebral ischemia or increased ICP. However, bradycardia secondary to increased ICP is a relative contraindication.

Vasodilators (e.g., hydralazine, sodium nitroprusside, nitroglycerin) cause cerebral arterial dilation and venodilation and can theoretically

TABLE 40.6 Preferred Antihypertensive Agents in the Treatment of Stroke-Associated Hypertension

Drug	Mechanism of Action	Intravenous Dose	Advantages	Disadvantages
Labetalol	α_1-, β_1-, and β_2-Receptor antagonist	Test dose 5 mg, then 20- to 80-mg bolus every 10 min up to 300 mg; IV infusion 0.5-2 mg/min	Does not lower CBF Does not increase ICP	May exacerbate bradycardia
Esmolol	β_1-Receptor antagonist	500-mcg/kg bolus, then 50-300 mcg/kg/min	Does not lower CBF Does not increase ICP	May exacerbate bradycardia
Sodium nitroprusside	Vasodilator	0.25-10 mcg/kg/min	Potent antihypertensive	May increase ICP Can cause cerebral steal Potential for cyanide toxicity
Nitroglycerin	Vasodilator	5-200 mcg/min	Can be helpful for concomitant cardiac ischemia	May increase ICP Can cause cerebral steal
Hydralazine	Vasodilator	2.5- to 10-mg bolus	Can be given as IV bolus when labetalol is contraindicated because of bradycardia	May increase ICP Can cause cerebral steal
Nicardipine	L-type CCB	5-15 mg/h	Does not decrease CBF	May increase ICP Long duration of action
Enalaprilat	ACE inhibitor	0.625-1.25 mg every 6 hr	Does not decrease CBF	Variable response Long duration of action

ACE, Angiotensin-converting enzyme; *CBF,* cerebral blood flow; *CCB,* calcium channel blocker; *ICP,* intracranial pressure.

increase ICP and cause a cerebral steal phenomenon in patients with acute cerebral ischemia. Other disadvantages of sodium nitroprusside are tachyphylaxis, the need to shield the medication from light because of its photosensitivity, and the danger of cyanide and thiocyanate toxicity that may be difficult to detect in patients with brain injury. However, they may be used in patients with small and moderate-sized ICH and in patients with SAH if increased ICP is not a concern.

CCBs have varying effects on cerebral autoregulation. Nifedipine can lead to severe reduction in BP and is not recommended. Nimodipine is used routinely in patients with SAH because it has been shown to improve outcome, possibly due to a neuroprotective effect. Nicardipine has been used in patients with acute ICH without any change in CBF and is often used in patients with SAH. It is becoming quite popular in neurocritical care units because of its efficacy, ease of titration, predictable response, and favorable cerebral hemodynamic effects.

ACE inhibitors and the ARB candesartan have been used in patients with acute cerebral ischemia and have no effect on CBF. However, short-acting parenteral forms of these drugs are not available. ACE inhibitors and ARBs shift the lower limit of cerebral autoregulation toward lower BP in rats and humans. However, these agents have a long half-life, which is not desirable in treatment of hypertension in the acute phase.

Similarly, because of its long half-life and sedative effect, the α_2-adrenergic agonist clonidine is not preferred.

The cerebrovascular effects of the newer parenteral antihypertensives such as fenoldopam, a peripheral dopamine-1 receptor agonist, and clevedipine, a CCB, have not been extensively studied. However, in small studies, fenoldopam has been shown to decrease global CBF and increase ICP in patients with impaired intracranial compliance.[55] In a small single-center study, clevedipine was found to be safe and effective in perioperative neurosurgical patients with hypertension.[56]

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SELF-ASSESSMENT QUESTIONS

1. A 55-year-old man with long-standing hypertension presents with acute right hemiplegia. The onset of symptoms was 45 minutes before presentation. His blood pressure (BP) on presentation is 200/110 mm Hg and his noncontrast head CT scan is normal. He is given 10 mg labetalol and his BP is now 175/105 mm Hg. Intravenous tPA is administered for acute ischemic stroke. An hour later, his BP is noted to be 170/110 mm Hg. Which of the following statements best characterizes BP management in this case?
   A. The patient should not have been given intravenous tissue plasminogen activator (tPA) because his BP (175/105 mm Hg) was too high.
   B. The patient's current BP of 170/110 mm Hg needs to lowered with intravenous labetalol or nicardipine.
   C. Sublingual nifedipine is the drug of choice in the acute management of elevated BP in the setting of an acute stroke.
   D. BP should be increased using vasopressors to augment cerebral perfusion.
   E. None of the above.
2. A 60-year-old man with poorly controlled BP presents to the emergency department with left hemiparesis that was first noticed 2 days ago. He is awake, fully alert, and oriented. His strength on the right side is normal. His head CT scan shows a 2- × 2-cm right putaminal hemorrhage with no hydrocephalus or intraventricular extension. His BP is 150/85 mm Hg. Which of the following statements best characterizes BP management in this case?
   A. This patient has a >50% chance of clinically significant expansion of his ICH over the next 48 hours if his BP is not lowered acutely.
   B. BP should be lowered immediately to <120/80 mm Hg with intravenous nicardipine to prevent hematoma expansion.
   C. He should have an intracranial pressure monitor inserted to measure intracranial pressure.
   D. There is an area of ischemia surrounding an ICH that may increase in size with additional BP lowering.
   E. None of the above.
3. Which of the following features best characterizes carotid hyperperfusion syndrome after a carotid endarterectomy?
   A. Headache
   B. Intracerebral hemorrhage
   C. Increase in cerebral blood flow ipsilateral to the endarterectomy
   D. Seizures
   E. All of the above

41

Renovascular Hypertension and Ischemic Nephropathy

Barbara A. Greco, Kausik Umanath

NORMAL RENOVASCULAR ANATOMY

The clinical presentations of renovascular disease are influenced by the acuity, nature, and site of renal vascular compromise. In most individuals, the kidney has a single renal artery (RA) with a lumen diameter of 3 to 7 mm. The main RA branches in a double or triple fork pattern or, less commonly, a ladder pattern.[1] The incidence of multiple RAs is about 31%, with bilateral supernumerary arteries in 11%.[2] The right RA usually passes posterior to the inferior vena cava (IVC), but rarely can be precaval. The collaterals to the kidney, depicted in Fig. 41.1, can maintain renal parenchymal viability in the face of main RA occlusion. The factors determining the development and caliber of these vessels are poorly understood but include individual anatomy, status of the aorta, rate of progression of main RA narrowing, and condition of the intrarenal perforating arteries.

CLINICAL SYNDROMES ASSOCIATED WITH RENAL VASCULAR DISEASE

Reduction or loss of renal arterial or venous blood flow is associated with one or more distinct clinical syndromes. These are summarized in Box 41.1. Discussion of these syndromes as distinct entities is meant to help with recognition and understanding. However, more often in clinical practice there is significant overlap. The first section will focus on the three most common clinical presentations of RA stenosis: renovascular hypertension (RVH), ischemic renal disease (IRD), and unstable cardiac syndromes. The second section will address the distinct clinical presentations of renal infarction, atheroembolic disease, and renal vein thrombosis.

RENOVASCULAR HYPERTENSION

A seminal observation in blood pressure (BP) regulation is the observation that a reduction in renal perfusion pressure activates a series of hormonal and neuronal responses that raise systemic arterial pressure to restore RA perfusion pressures.[3] RVH is defined as a syndrome of elevated BP (systolic and/or diastolic) produced by any condition that leads to reduced perfusion of the kidneys.

Central to the pathogenesis of RVH is activation of the renin-angiotensin-aldosterone system (RAAS) with release of renin from the juxtaglomerular apparatus. This is mediated in part by stimulation of neuronal nitric oxide (NO) synthase and cyclooxygenase-2 in the macula densa. Blockade of RAAS during creation of an experimental RA stenosis prevents development of hypertension.[4] Studies in transgenic mice without receptors for angiotensin confirm that development of RVH requires an intact RAAS.[5] In the absence of RAAS blockade, systemic arterial pressures increase until renal perfusion is restored. Studies in experimental models and humans indicate that additional mechanisms contribute to long-term BP elevation in the presence of RA stenosis, including activation of the sympathetic nervous system, impairment of NO generation, release of endothelin, and hypertensive microvascular injury to the kidney.[6]

Mechanisms responsible for sustained RVH differ depending on whether one or both kidneys are affected and have been studied in animal models in which RA perfusion is reduced by clipping the vessel proximally. The nomenclature distinguishes between a situation in which one clip is present with a normal contralateral unclipped kidney (“1-clip–2-kidney hypertension”) and a situation in which the entire renal mass is affected (“1-clip–1-kidney hypertension”). Both these situations begin with impaired renal perfusion and initial activation of RAAS with sodium retention. However, in the 1-clip–2-kidney hypertension model, the elevated pressure generated by RAAS activation mediates a pressure natriuresis in the nonstenotic kidney. This restores plasma volume and results in sustained hypoperfusion of the poststenotic kidney and RAAS activation. This sequence of events produces angiotensin II (Ang II)-dependent hypertension (Fig. 41.2A).

By contrast, 1-clip–1-kidney hypertension represents a model in which the entire renal mass is exposed to reduced perfusion pressure. As a result, sodium retention leads to expanded blood volume and sustained elevation in pressure, which then restores renal perfusion pressure beyond the stenosis and inhibits RAAS activation (see Fig. 41.2B).

Box 41.2 lists causes of RVH based on these mechanisms. Some screening tests for RVH rely on comparison of the different physiologic responses of the two kidneys to maneuvers and are less sensitive in the setting of bilateral renovascular disease. Also, 1-clip–1-kidney hypertension is typically more volume than Ang II dependent. It may be less responsive to RAAS blockade than 1-clip–2-kidney hypertension.

A fall in renal perfusion pressure sufficient to activate the RAAS occurs when luminal stenosis is relatively severe, usually in the range of at least 60% to 80% cross-sectional diameter reduction (Fig. 41.3). In experimental models, the relative importance of pressor mechanisms, including measurable activation of the RAAS, changes with time. Levels of circulating plasma renin activity tend to decrease. Several mechanisms have been proposed to explain such changes, including a slowly developing pressor action of Ang II, transition to alternative

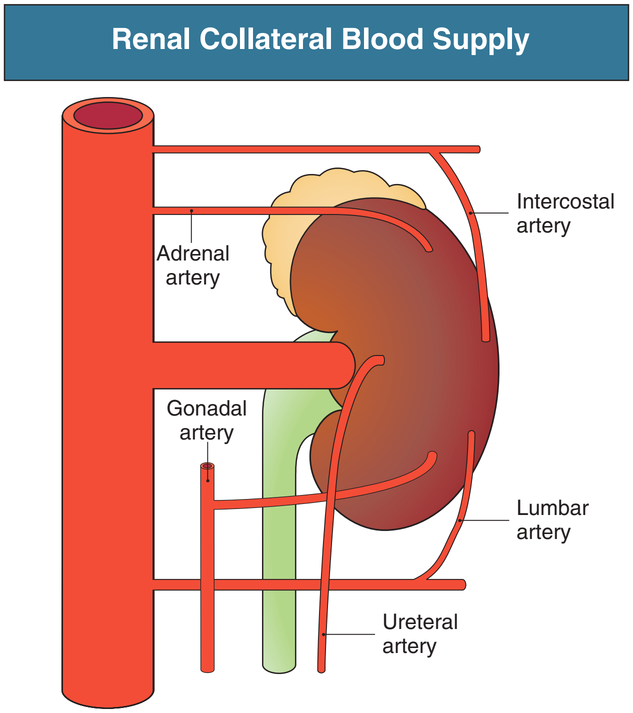
Renal Collateral Blood Supply
Intercostal artery
Adrenal artery
Gonadal artery
Lumbar artery
Ureteral artery

Fig. 41.1 **Renal collateral circulation.** Diagrammatic representation of the potential collateral arterial vessels to the kidney.

pressor mechanisms, and hypertensive injury to the nonstenotic kidney. In experimental models, this translates into a time limit for reversibility of RVH by removal of the clip. Clinically, this makes it difficult to determine when patients are most likely to benefit from endovascular or surgical RA revascularization.

Recent guidelines emphasize the need for effective population-wide BP control while limiting the cost of evaluation and management. As a result, most patients with hypertension simply are treated and subjected to few laboratory investigations. For those who reach target BP, no further studies are performed. Widespread application of RAAS blockers in the management of hypertension, congestive heart failure (CHF), and diabetic and other proteinuric nephropathies has increased the exposure of individuals with undetected RVH to these agents. Therefore many cases of RVH go undiagnosed unless hypertension becomes more difficult to control or kidney dysfunction develops. Patients who typically undergo diagnostic evaluation for RA stenosis are a subset of patients with more severe or resistant hypertension or those presenting with unstable renal or cardiac syndromes.

BOX 41.1 Clinical Syndromes Associated With Renovascular Disorders

- Renovascular hypertension
- Ischemic renal disease
- Unstable cardiac syndromes
- Renal infarction
- Atheroembolic renal disease
- Renal vein thrombosis

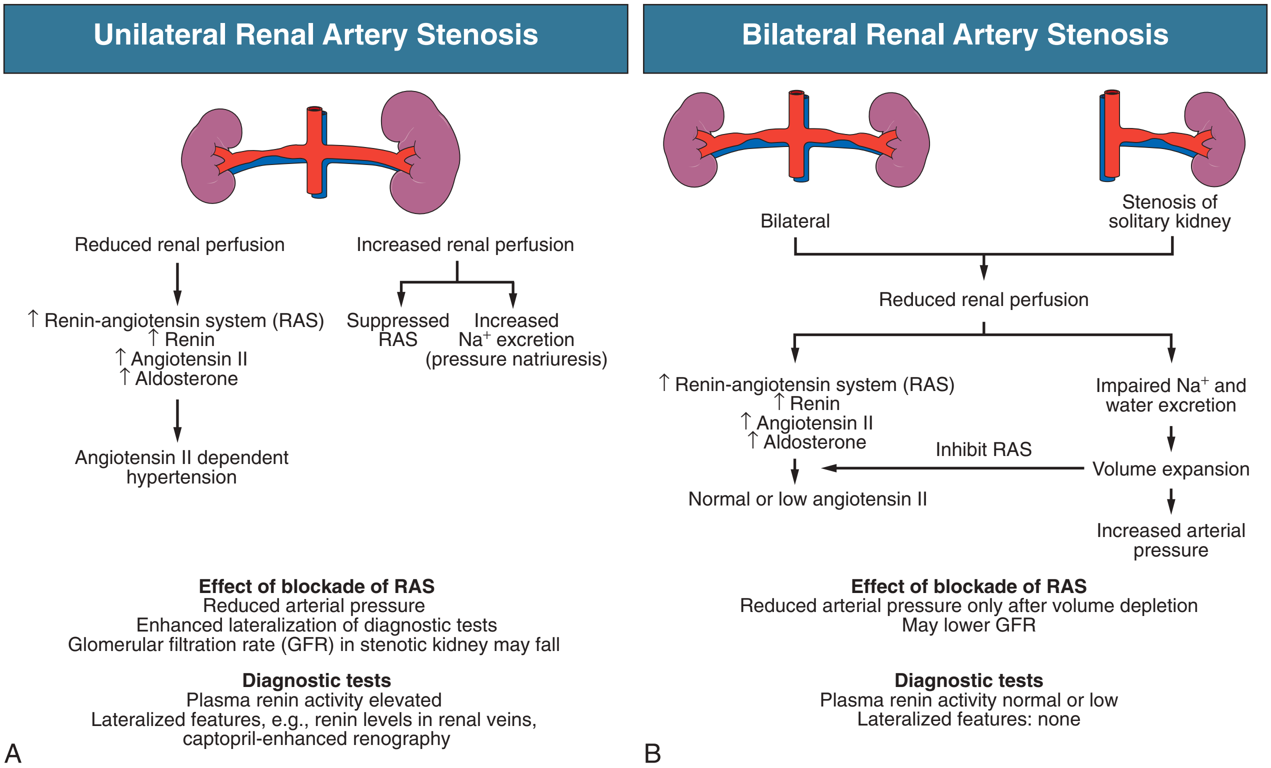
Unilateral Renal Artery Stenosis
Reduced renal perfusion
Increased renal perfusion
↑ Renin-angiotensin system (RAS)
↑ Renin
↑ Angiotensin II
↑ Aldosterone
Suppressed RAS
Increased Na⁺ excretion (pressure natriuresis)
Angiotensin II dependent hypertension
Effect of blockade of RAS
Reduced arterial pressure
Enhanced lateralization of diagnostic tests
Glomerular filtration rate (GFR) in stenotic kidney may fall
Diagnostic tests
Plasma renin activity elevated
Lateralized features, e.g., renin levels in renal veins, captopril-enhanced renography
A
Bilateral Renal Artery Stenosis
Bilateral
Stenosis of solitary kidney
Reduced renal perfusion
↑ Renin-angiotensin system (RAS)
↑ Renin
↑ Angiotensin II
↑ Aldosterone
Impaired Na⁺ and water excretion
Inhibit RAS
Volume expansion
Normal or low angiotensin II
Increased arterial pressure
Effect of blockade of RAS
Reduced arterial pressure only after volume depletion
May lower GFR
Diagnostic tests
Plasma renin activity normal or low
Lateralized features: none
B

Fig. 41.2 Pathogenesis of renovascular hypertension in one-kidney versus two-kidney model. (A) In unilateral stenosis with two kidneys, opposing forces between the stenotic kidney, which has reduced perfusion pressures, and the nonstenotic contralateral kidney, which has increased perfusion pressures, result in laboratory and clinical features of angiotensin-dependent hypertension. (B) In unilateral stenosis with a solitary functioning kidney or in a patient with bilateral critical renal artery stenosis, reduced perfusion pressure to the stenotic kidney in the absence of a normal kidney excreting sodium leads to sodium and volume retention, ultimately associated with hypertension without persistent activation of the RAS.

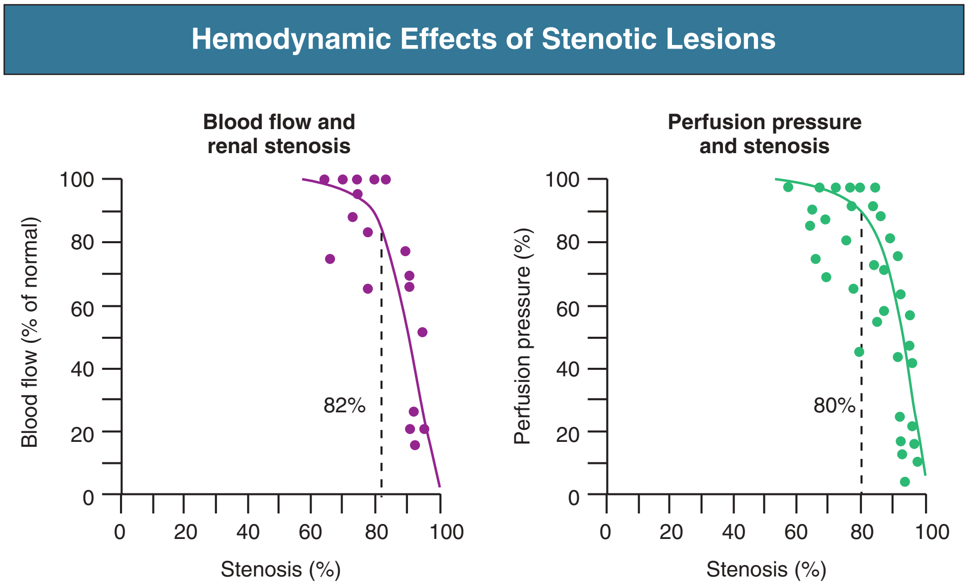

Fig. 41.3 **Hemodynamic effects of stenotic lesions.** Changes in blood flow and arterial pressure across a carefully quantitated arterial lesion are barely detectable until cross-sectional area diminishes by 75% to 80%.

BOX 41.2 Classification of Renovascular Hypertension

Two-Kidney Hypertension*

- Unilateral fibromuscular dysplasia
- Unilateral atherosclerotic renovascular disease
- Renal artery aneurysm
- Renal artery embolism and infarction
- Traumatic arterial occlusion
- Arteriovenous fistula
- Renal artery dissection or thrombosis
- Aortic dissections with compromise to renal ostium
- Page kidney
- Takayasu arteritis
- Metastatic tumor compressing renal parenchyma
- Pheochromocytoma compressing renal artery
- Phakomatosis pigmentovascularis type IIb
- Neurofibromatosis
- Behçet disease
- Covering of origin of renal artery by aortic stent graft
- Renal artery spasm

One-Kidney Hypertension†

- Stenosis to solitary kidney
- Bilateral arterial stenosis or dissection
- Coarctation of the aorta
- Vasculitis involving renal arteries
- Congenital vascular anomalies
- Atheroembolic renal disease

*Two-kidney hypertension implies that a contralateral, nonaffected kidney is present.

†One-kidney hypertension implies that the entire renal mass is beyond the vascular lesion, either bilateral disease or a solitary functioning kidney.

BOX 41.3 Clinical Features of Renovascular Hypertension

- Activation of renin angiotensin system (early)
- Early-onset (<30 years) or late-onset (>60 years) hypertension
- Activation of sympathetic nervous system
- Abnormal circadian rhythm: Loss of nocturnal fall
- Secondary aldosteronism: Hypokalemia
- Accelerated target organ damage
- Microvascular disease
- Left ventricular hypertrophy
- Renal injury
- Hyponatremic hypertensive syndrome
- Unstable cardiac syndromes
- Rarely, nephrotic range proteinuria

Clinical differentiation of RVH and primary hypertension is difficult, and they may be superimposed. RVH secondary to unilateral RA stenosis, for example, often can be easily controlled with the use of RAAS blockers. Certainly, some cases of RVH present with accelerated, resistant, or hypertension urgency or emergency. Clinical studies suggest that for any level of BP, patients with RVH have higher nocturnal pressures ("nondippers") and have more severe target organ manifestations such as left ventricular hypertrophy (LVH) and albuminuria, than patients with essential hypertension.[7] Patients with RVH may present with hypokalemia and metabolic alkalosis, clues to secondary aldosteronism. Clinical suspicion for RVH arises when hypertension develops either very early (<30 years) or later in life (>70) or when BP that was previously easily or well controlled becomes more resistant. Some cases of RVH may rarely be associated with renin-mediated and hemodynamically induced nephrotic range proteinuria that regresses with treatment. A syndrome of polydipsia associated with hyponatremia attributed to the dipsogenic action of Ang II also has been observed in patients with RVH. Clinical features of RVH are summarized in Box 41.3.

Renal Artery Stenosis

The most common cause of RVH is RA stenosis. RA fibromuscular dysplasia (FMD) and atherosclerotic disease are the two most common causes of RVH. The unique clinical presentations of inflammatory arteritides as exemplified by Takayasu arteritis (TA) and aortic coarctation also will be discussed.

Fibromuscular Dysplasia

FMD is a noninflammatory, nonatherosclerotic arteriopathy characterized by arterial medial smooth muscle cell proliferation and fibrosis. It is the most common cause of RVH in children and young adults. FMD is defined by pathognomonic arteriographic aberrancies involving the middle to distal RA or branches. The vascular distribution of FMD involves primarily the renal and cerebral arteries. RAs are involved with FMD in 65% to 80% of cases. Bilateral RA involvement is seen in 25% to 35% of adult cases, in up to 78% of syndromic childhood FMD, and in most familial cases.[8] Cerebrovascular involvement is present in up to 65% of adult cases with renovascular FMD.[9] Less common extrarenal sites of involvement with FMD include coronary, mesenteric, celiac, splenic, aortic, and peripheral vasculature.

The prevalence of clinically apparent renovascular FMD is estimated at 4 in 1000.[10] Data from screening angiography in potential kidney donors suggest that the prevalence may be higher, with FMD observed in 3.8% to 6.6% of individuals.[11] About 90% of FMD cases occur in women. Of those enrolled in the U.S. registry of patients with FMD, 95% are White, and the mean age of onset of hypertension is 43 years.[12] This racial predilection could represent recruitment or geographical bias. Familial FMD occurs in approximately 10% of patients and has been associated with subclinical evidence of carotid flow abnormalities in first-degree relatives, consistent with an autosomal dominant inheritance pattern.[13] FMD also may complicate hereditary and collagen vascular syndromes.

The pathophysiology of FMD is unknown. It is likely that numerous disturbances in vascular collagen and structural processes can result in the FMD angiographic phenotypes. No unifying genetic mutation has been identified. Other factors implicated in the etiology of FMD include cigarette smoking, hormonal influences (based on the female predilection), and vascular trauma or stretching of the RA during development.[14]

Histologically, abnormal vascular wall structure is associated with irregular bands of collagen deposits and in some cases disruption of the elastic membrane. In up to two thirds of cases more than one arterial wall layer is involved. The histologic features coincide with the arteriographic phenotypes outlined in Table 41.1. The most common variant of FMD is medial fibroplasia, accounting for 85% to 100% of cases. Here, alternating thin and thick ridges of collagen and elastic tissue deposits result in discrete stenoses alternating with aneurysmal sections characterized by fragmented internal elastic lamina. This produces the recognizable "string of beads" appearance on angiography as shown in Fig. 41.4. The loss of elastic structural integrity leads to ballooning or beading of the vessels such that the diameter of the beaded segment is larger than the diameter of the artery lumen. RA aneurysms may develop in patients with FMD, and 17% of patients with an aneurysm at any vascular site have more than one vascular site involved, with some having up to four. FMD generally involves the segment of RA beyond the first 2 cm from the ostium. FMD and atherosclerotic renovascular disease may coexist.[15]

The most common adult clinical presentation is early-onset hypertension in young to middle-aged women. Cerebrovascular lesions may manifest with headaches, pulsatile tinnitus, and bruits over the carotid arteries, epigastrium, or femoral regions. FMD should be considered in younger patients presenting with hypertension and stroke, transient ischemic attacks, subarachnoid hemorrhage, or amaurosis fugax. Clinical presentations of FMD and associated disorders are shown in Box 41.4.

The natural history of FMD has not been adequately studied. Progression of disease may manifest with new focal lesions within the same arterial bed, worsening arterial luminal narrowing within a specific lesion, involvement of a new vascular territory, or development or enlargement of arteriovenous fistulas or aneurysms. Up to 37% of patients may demonstrate angiographic progression of FMD.[16] This appears to be limited to younger patients, with few patients developing new or progressive lesions after the age of 40 years. Progression may be associated with kidney cortical thinning, but rarely causes advanced kidney failure.

Atherosclerotic Renal Artery Stenosis

Atherosclerotic RA stenosis is the most common cause of RVH in patients over the age of 50. Estimates of the prevalence of atherosclerotic RA stenosis depend on the population screened. One population-based study of 870 patients older than 65 screened with RA duplex ultrasound found a 6.8% prevalence of atherosclerotic RA stenosis defined as greater than 60% stenosis.[17] Autopsy series report an overall prevalence of 4% to 20%, with progressively higher rates for those older than 60 years (25% to 30%) and 75 years (40% to 60%). It has been estimated that atherosclerotic RA stenosis is a contributor to the development of end-stage renal disease (ESRD) in up to 22% of incident ESRD. Among patients with chronic CHF, RA stenosis has been reported in up to 50%.[18]

Atherosclerotic RA stenosis generally occurs in patients with more generalized atherosclerosis involving the aorta, peripheral vasculature, and coronary arteries.[19] In patients undergoing coronary angiography, coexistent RA stenosis is found in 11% to 16% and in up to 42% of

TABLE 41.1 Histologic Classification of Fibromuscular Dysplasia and Angiographic Phenotypes

Type	Frequency (%)	Histology	Angiographic Appearance
Medial			"String of beads"
Medial fibroplasia	85-100, most common	Alternating ridges of collagen/loss of elastic membrane	Medial: Bead diameter is larger than lumen diameter
Perimedial fibroplasia	Rarer (10-15)		Perimedial: Bead diameter is smaller than lumen diameter
Medial hyperplasia	Rarest	True smooth muscle hyperplasia: No fibrosis	Medial hyperplasia: Smooth stenosis without beads
Intimal	<10	Circumferential deposition of collagen in intima: Fragmented or duplicated internal elastic lamina	Concentric smooth stenosis: Long smooth narrowing
Adventitial	<1	Dense collagen replaces fibrous tissue in adventitia and surrounding tissue	Smooth stenosis or diffuse attenuation of vessel lumen

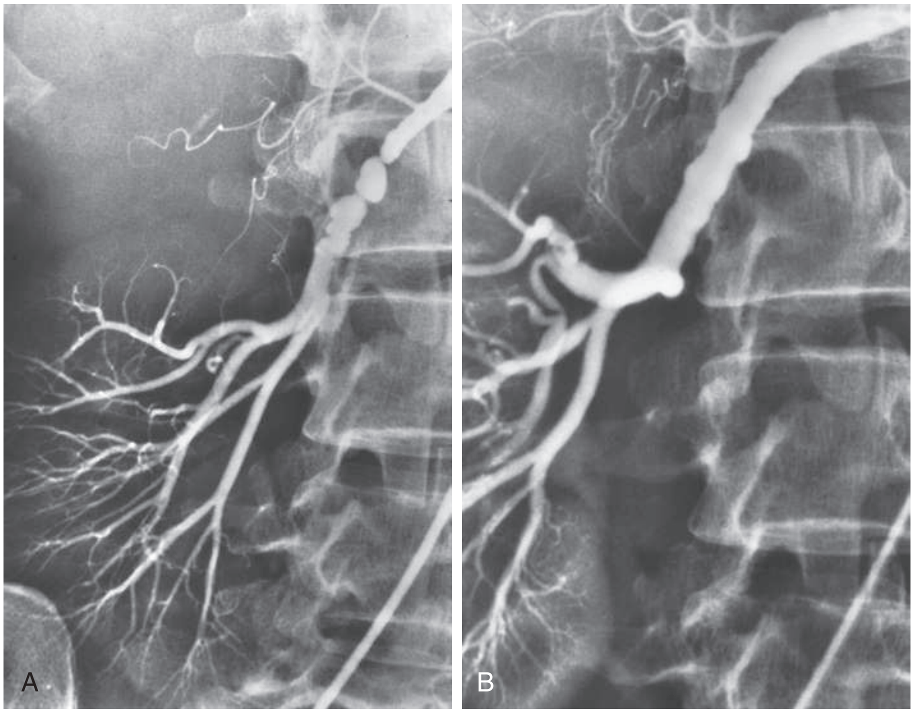

Fig. 41.4 Fibromuscular dysplasia. (A) Selective renal arteriogram illustrating the beaded appearance of fibromuscular dysplasia with multiple webs characteristic of medial fibroplasia in a 39-year-old woman. (B) Selective injection of the same renal artery after technically successful percutaneous transluminal renal angioplasty. (Courtesy Michael McKusick, MD, Mayo Clinic, Rochester, Minn.)

BOX 41.4 Clinical Manifestations and Disorders Associated With Fibromuscular Dysplasia

Clinical Manifestations

- Incidental finding (e.g., living kidney donors)
- Renovascular hypertension
- Renal infarction
- Loin or flank pain
- Hematuria
- Retroperitoneal hemorrhage
- Cerebrovascular accident (stroke)
- Transient ischemic attack
- Headaches
- Pulsatile tinnitus
- Horner syndrome
- Neck pain
- Dizziness
- Imaging finding of aneurysm dissection
- Amaurosis fugax
- Myocardial infarction
- Ischemic chest pain/dyspnea
- Postprandial abdominal pain
- Weight loss
- Hemobilia
- Claudication

Associated Disorders

- Tuberous sclerosis
- Marfan syndrome
- Ehlers-Danlos syndrome
- Cystic medial necrosis
- Coarctation of the aorta
- Alport syndrome
- Renal agenesis or dysgenesis
- α_1-Antitrypsin deficiency
- Medullary sponge kidney
- Pheochromocytoma
- Infantile myofibromatosis
- Ergotamine preparation, methysergide
- Cigarette smoking
- Collagen III glomerulopathy
- Atherosclerotic renovascular disease
- Alagille syndrome
- Ask-Upmark kidney
- Celiac disease
- Cocaine exposure—intrauterine
- Crohn disease
- Homocystinuria
- Macrophagic myofasciitis
- Neurofibromatosis
- Williams syndrome

patients undergoing peripheral angiograms.[20] Predictors of RA stenosis include a history of hypertension, presence of CKD, coexisting peripheral vascular or coronary artery disease, the presence of abdominal bruits, and a history of smoking. Atherosclerotic RA stenosis is bilateral in 20% to 40% of patients. In many of these cases, the degree of stenosis is below the threshold to cause activation of RAAS or have other clinical implications. Given its association with older age and more diffuse atherosclerosis, atherosclerotic RA stenosis is associated with increased cardiovascular and mortality risk.[21] Accordingly, the identification of atherosclerotic disease should prompt clinical attention to cardiovascular risk factors, including the use of high-dose statin therapy, efforts to promote smoking cessation, and optimal control of BP and metabolic syndrome.

Some patients with atherosclerotic RA stenosis will experience progressive RA luminal narrowing and develop RVH or other clinical syndromes described later. Progression is usually defined as a greater than 25% further luminal diameter narrowing or progression to vascular occlusion. Prospective studies between 1990 and 1997 using Doppler ultrasound in patients with atherosclerotic RA stenosis indicated progression in 30% over 3 years, varying by degree of initial stenosis, with progression more common in those with more than 60% stenosis. Total occlusion is rare, reported in only 3%.[22] Statins appear to reduce the risk for progression and occasionally induce regression of stenosis.[23] There are few prospective data assessing progression in patients treated with optimal medical therapy targeting atherosclerotic risk factors in the modern era. Atherosclerotic RA stenosis often presents as RVH but also is associated with other clinical syndromes that will be described later.

Takayasu Arteritis

Initially described in 1761, TA, often termed *pulseless disease*, is one of several inflammatory disorders involving the renal vasculature causing

RVH. Though rare in the United States, its prevalence varies geographically, with reports as high as 1 in 3000 in Japan.[24] TA usually presents between the ages of 25 and 41 years but, like FMD, can present in childhood. It most often presents as RVH and should be considered in any child or young adult with hypertension and/or asymmetric peripheral pulses or bruits. Concomitant inflammatory aortic coarctation may be present. In half of cases, identification of arterial stenosis is preceded by a prodromal illness characterized by fever, night sweats, malaise, and weight loss. Inflammatory markers are often elevated during this phase. After this active inflammatory phase, vascular stenoses can lead to sequelae including RVH, kidney dysfunction, stroke, cerebral hemorrhage, myocardial infarction, or CHF, depending on sites of involvement.

Diagnostic criteria are still somewhat controversial. The diagnosis requires arteriographic narrowing or occlusion of a vascular territory of the aorta, its branches, or large arteries not attributable to atherosclerosis, middle aortic syndrome, or FMD. One distinguishing angiographic feature of TA is the presence of inflammatory thickening or edema of the vascular wall seen on magnetic resonance angiography (MRA), computed tomographic angiography (CTA), or duplex or positron emission tomography.[25]

The pathophysiology of TA is unclear. Theories include autoimmunity and hypersensitivity response to a variety of proposed antigens, including heat shock protein and *Mycobacterium tuberculosis*. Histologically, granulomatous inflammation involves all layers of the vessel wall during the active phase of disease, followed by fibrotic stenosis.

Treatment is controversial but generally starts with corticosteroids or other immunomodulatory therapy during the inflammatory phase of disease followed by medical or interventional treatment to reduce organ ischemic injury.[24,26]

Coarctation and Middle Aortic Syndrome

Coarctation occurs in about 1 in 1550 births and accounts for about one third of all causes of RVH in infants. Yet, only 35% of isolated coarctation cases present during the first year of life, and milder forms may be missed in childhood. Furthermore, cases treated in childhood can develop restenosis of the coarct segment later in life. It is estimated that 1 in 150 adults have congenital heart disease, with aortic coarctation comprising 5% to 10%.

Adult presentations of RVH associated with coarctation include signs and symptoms of collateral development. Bruits may be heard over the carotids, and intercostal pulses may be palpable. A radial-femoral pulse delay is a sensitive physical examination finding. Present in only about 50% of cases, a harsh systolic blowing murmur is heard best over the posterior thorax. Although echocardiography with Doppler flow analysis with special attention to the aortic arch provides excellent diagnostic accuracy in infants, MRA or CTA is necessary to confirm coarctation in adults. Indications for the treatment of coarctation in adults include upper limb hypertension and a greater than 20 mm Hg systolic BP gradient across the stenosis with evidence of significant collateral flow. These patients have a fivefold risk for cerebral aneurysms, and screening cerebrovascular CTA or MRA is recommended. Current guidelines recommend multispecialty consultation among cardiologists, interventionalists, and surgeons to determine the optimal approach (endovascular vs. surgical) to repair. Success rates in terms of cure of hypertension range from 69% to 80%, with highest chance for cure and best survival data when treated in childhood under the age of 10. In adults with prior coarctation, the risk for late-onset hypertension exceeds that in the general population. Causes of this late hypertension include vascular noncompliance, reduced aortic arch baroreceptor sensitivity, early kidney injury with sustained RAAS activation, and, in some cases, development of restenosis of the repaired coarct segment.[27]

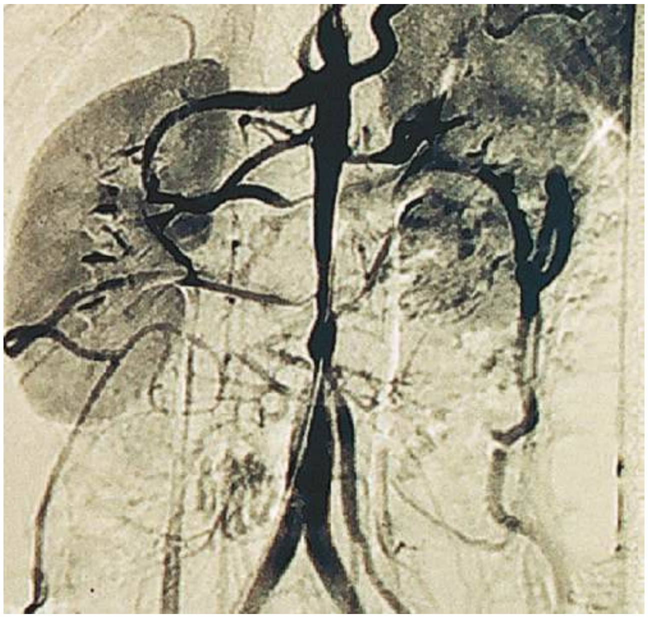

Fig. 41.5 Middle aortic syndrome. Angiogram showing typical smooth narrowing of the aorta. Bilateral stenosis of paired renal arteries is present. (From Panayiotopoulos YP, Tyrrell MB, Koffman G, et al. Mid-aortic syndrome presenting in childhood. Br J Surg. 1996;83:235-240.)

A rare entity, middle aortic syndrome is a segmental or diffuse narrowing of the abdominal or distal descending aorta, causing RVH usually noted in infancy (Fig. 41.5). Concomitant proximal RA stenosis occurs in up to 80% of cases, with variants including RA atresia, hypoplasia, or dysplasia.[28] The cause is congenital in many cases, but associations with FMD, congenital anomalies, neurofibromatosis, Williams syndrome, and TA have been reported and these cases can present later in life. Middle aortic syndrome can cause claudication of the lower extremities as well as mesenteric ischemia. Angioplasty and stenting of stenotic segments, surgical bypass grafting, and autotransplantation of ischemic organs are among the approaches to treatment of this disorder.

Renal Artery Aneurysms

RA aneurysms are a rare cause of RVH that is present in up to 75% of cases. Aneurysms are associated with atheromatous, fibromuscular, and vasculitic RA disease. Thrombosis within an aneurysm can lead to distal emboli and renal infarcts. Aneurysms with diameters of more than 1.5 cm have a higher risk for rupture. Elective repair of large renal aneurysms should be considered in women of childbearing age because of the risk for rupture during the third trimester of pregnancy. Other complications of RA aneurysms include vessel dissection and arteriovenous fistula formation.

ISCHEMIC RENAL DISEASE

Activation of the RAAS can occur without loss of kidney function. However, a common clinical scenario in patients with atherosclerotic RA stenosis is the presence of both hypertension and kidney dysfunction. In recent randomized controlled trials evaluating treatment options for atherosclerotic RA stenosis, 40% to 50% of the enrolled patients had concomitant CKD. In clinical practice, it remains difficult to distinguish CKD secondary to hypertensive nephrosclerosis from reduced kidney function resulting from atherosclerotic RA stenosis, sometimes called IRD.

The term IRD has been used to describe both the hemodynamic and structural consequences of reduced RA perfusion on the kidney. Critical RA stenosis or occlusion can lead to reduced glomerular filtration rate (GFR) by reducing renal blood flow and hence glomerular capillary pressure below the level of renal autoregulatory compensation. GFR improves once perfusion pressure is restored. The term *ischemic* is a misnomer in this context. Indeed, basal kidney energy requirements are met with less than 10% of renal blood flow. When there is reduced perfusion to a kidney, energy delivery tends to match filtration and transport functions. Reductions in GFR and associated energy-dependent solute transport allow adaptation to reduced blood flow without development of tissue hypoxia. Studies using blood oxygen level–dependent magnetic resonance imaging (MRI) indicate that, despite reductions in blood flow and GFR, many patients with RA stenosis maintain normal renal cortical and medullary tissue oxygenation.[29] Thus many poststenotic kidneys have no more ischemia than normal kidneys. These observations explain the relative stability and infrequent progression of kidney injury in prospective trials of medically treated patients with atherosclerotic RA stenosis.

However, under more chronic conditions of reduced blood flow with persistent filtration and tubular function, levels of deoxygenated hemoglobin may increase in the renal medulla, representing true medullary hypoxia beyond that which is physiologic.[30,31] When more severe vascular occlusion develops beyond the limits of functional adaptation, ischemia develops.

Reduced renal perfusion and ischemia ultimately activate numerous mechanisms of tissue injury.[32] This results in macrophage accumulation with progressive tubular cell loss and fibrosis.[33] Glomeruli are usually preserved but often appear collapsed. The ischemic kidney develops microvascular rarefaction contributing to ongoing irreversible structural and functional changes.[34] Often, the kidney atrophies with time. The term IRD comprises both the potentially reversible hemodynamic component and these adaptive and structural changes, some of which will not be reversible by merely revascularizing the kidney.

Clinical presentations that should prompt consideration of the presence of IRD are outlined in Box 41.5. IRD can present as CKD or acute kidney injury (AKI). IRD should be considered in the setting of unexplained CKD in patients with generalized atherosclerosis, resistant or accelerated hypertension, or small or asymmetric kidneys. Unilateral atherosclerotic RA stenosis may lead to atrophy of the poststenotic kidney. The contralateral kidney with a patent RA often hypertrophies and compensates with hyperfiltration. However, over time, this kidney develops parenchymal injury mediated by the combined effects of high pressure and Ang II. In some cases, the kidney with the patent RA has worse function than the poststenotic kidney.[35]

The diagnosis of IRD always should be considered in patients with known RA stenosis who present with rapidly declining renal function or episodes of AKI. In patients with high-grade RA stenosis, AKI can follow normalization of systemic BP with any agent. The sudden reduction in systemic BP can reduce RA pressure below levels needed to sustain GFR. With the use of RAAS inhibitors, these alterations in glomerular hemodynamics may be more common or pronounced.[36] Normally, activation of Ang II causes efferent arteriolar vasoconstriction, which preserves transcapillary filtration pressures at the glomerulus when preglomerular pressures are reduced, thereby maintaining GFR. The loss of this compensatory mechanism induced by agents that inhibit or block the RAAS can result in functional AKI. This typically occurs within a few days from the start of therapy and is usually, but not always, reversible. This change in GFR after initiation of RAAS inhibitors is not specific for the presence of RA stenosis and is seen frequently in patients with cardiac or hepatic dysfunction or patients with intravascular volume depletion because, in these settings, maintenance of GFR is also Ang II dependent.[37]

BOX 41.5 Clinical Presentations of Ischemic Renal Disease Associated With Atherosclerotic Renal Artery Stenosis

- Acute kidney injury with control of blood pressure: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
- Acute kidney injury with aggressive diuresis in patients with congestive heart failure
- Chronic kidney disease otherwise unexplained in atherosclerotic age range
- Chronic kidney disease with asymmetric renal size
- Acute or chronic kidney disease and renovascular hypertension
- Acute on chronic kidney injury with episodes of “flash” pulmonary edema
- Unexplained rapid decline in glomerular filtration rate in chronic kidney disease
- Oligo-anuric kidney failure not otherwise explained in a patient with atherosclerosis and hypertension

HEART FAILURE AND UNSTABLE CARDIAC CONDITIONS

Some patients with RA stenosis present with recurrent episodes of relatively sudden onset “flash” pulmonary edema.[38] This has been attributed in part to rapid loss of contractile strength of the left ventricle caused by sudden increases in afterload. Many of these patients have hypertensive urgency or emergency, hypervolemia resulting from aldosterone excess and effects of Ang II on sodium reabsorption, and echocardiographic evidence of diastolic dysfunction.[39] Such patients have increased mortality and hospitalization rates compared with those who have CHF without renovascular disease.[40] Case series and retrospective reviews suggest that renal revascularization can facilitate fluid volume management, reduce hospitalizations, and improve GFR and cardiac function in this high-risk subgroup of patients with atherosclerotic RA stenosis.[41,42] However, in two large prospective trials comparing medical therapy to RA stenting in atherosclerotic RA stenosis, endovascular treatment did not confer a protective effect on cardiovascular endpoints, including hospitalizations for CHF.[43,44] However, this cohort of patients was underrepresented in randomized controlled trials. Some believe that chronic stimulation of the RAAS secondary to RA stenosis contributes to the abnormal left ventricular remodeling in patients with chronic systolic heart failure as well as the frequency of episodes of decompensation.[45]

Finally, some patients with RA stenosis and LVH can present with chest pain syndromes with no significant lesions in the coronary arteries (although microvascular disease may be present).

IMAGING RENOVASCULAR HYPERTENSION AND RENAL ARTERY STENOSIS

Conventional direct angiography remains the reference standard to define the RA anatomy against which other screening modalities are compared. Noninvasive screening options include RA duplex (or Doppler) ultrasound, CTA, and MRA, each with their limitations and strengths.

RA duplex scanning is often used to identify and follow hemodynamic effects of RA stenoses. It is relatively inexpensive and carries no risk. It is most effective in detecting lesions of the main RA near the ostium and thus is better for identifying atherosclerotic RA stenosis than FMD. The reliability of duplex ultrasound depends on the skill and experience of the operator and the body habitus of the patient.

Duplex ultrasound provides little functional information regarding the kidney beyond the vascular lesion, although structural features such as kidney size and echogenicity can be determined. The duplex diagnostic criteria for hemodynamically significant RA stenosis consider the comparative rates of blood flow in the stenotic area to that in the remaining segments of the RA and the aorta. Parameters measured include peak systolic velocity (PSV) at various sites along the RA and in the suprarenal aorta; the renal aortic ratio (RAR), which compares the PSVs at these segments; acceleration time and index, which help evaluate the RA wave form; and the intrarenal resistive index (see Chapter 5). The resistive index has been associated with intrinsic small vessel renal disease, and a value greater than 80 has a strong negative predictive value on likelihood of BP response to intervention.[46] Normal PSV in the RA will depend on the lumen diameter of the vessel and ranges from about 120 to 160 cm/sec. PSV readings greater than 200 to 220 cm/sec and a RAR greater than 3.5 usually indicate RA stenosis of greater than 60% narrowing.[47,48] Clinicians should be aware of the significant heterogeneity among vascular laboratories in terms of how the data are reported. Most laboratories provide assessment of whether parameters support at least 60% luminal diameter narrowing. More precise assessments are not usually provided. Generally, the higher the PSV, the more severe is the stenosis. Clinicians should be familiar with aortic and RA velocities and waveforms to evaluate the validity of these interpretations. For example, a very blunted RA waveform can represent critical RA stenosis in the absence of an elevated PSV. RA duplex allows for serial testing, hence monitoring for progression and changes in kidney size. It is the preferred test for evaluating for restenosis of a stented RA segment.

Three-dimensional MRA with gadolinium enhancement provides excellent visualization of the arteries and functional information about the kidneys (Fig. 41.6). Limitations include interobserver variability, a tendency to overestimate luminal narrowing, interference by motion and breathing artifact, and limited sensitivity for middle and distal vascular lesions and small accessory vessels. MRA is less sensitive than CTA for the diagnosis of FMD.[49] It has the advantage of avoiding radiation exposure. Caution is advised in the use of gadolinium agents in patients with reduced GFR, based on reports of nephrogenic systemic fibrosis in patients with advanced CKD exposed to these agents. Some centers have reported success in the use of modified steady-state free precession MRA pulse sequences without contrast for visualization of RA stenoses.

CTA with vascular reconstruction provides imaging definition nearly equal to that of conventional angiography but requires significantly more contrast, usually 100 to 125 ml. Focal vascular calcification often obscures accurate assessment of stenoses. CTA is highly sensitive for identifying lesions in the mid and branch vessels often associated with FMD and is a good screening test for these patients who generally have good kidney function.

Angiography remains the gold standard for defining the degree of stenosis associated with atherosclerotic RA stenosis and for confirmation of FMD or other arteritides. It is the most reliable modality for identifying distal and branch or small vessel disease, which may be missed by other screening modalities. Aortography provides the opportunity to measure pressure gradients across a stenosis, an aide in determining the hemodynamic significance of a lesion. When there is complete proximal arterial occlusion, direct aortography can identify distal reconstitution by collateral and a renal "blush" confirming parenchymal viability. Limited selective renal angiography can be performed with as little as 20 ml of contrast. In cases at highest risk for contrast-induced AKI, carbon dioxide can be used instead of nonionic iodinated contrast.

In cases of unilateral RA disease, captopril renography provides functional information regarding the size and excretory capacity of the kidney and demonstrates the rate of isotope appearance as an index of renal blood flow and filtration. It detects the presence of a differential role of Ang II on GFR between the kidneys. This test has a high negative predictive value for the presence of RVH when completely normal.[50] Fig. 41.7 illustrates a captopril-enhanced renogram in a patient with RA stenosis. This examination provides no direct image of the renal vessel. Many intrinsic renal abnormalities unrelated to the main RA may change these curves, which limits its value in the presence of reduced kidney function.

Renal vein renin measurements may help predict the BP response to renal revascularization. Previous studies indicated that lateralization of renal vein levels (>1.5 : 1 stenotic-to-nonstenotic kidney ratio) predicts a favorable BP response for more than 90% of patients. Because failure to lateralize also carried a favorable response in almost half of patients, the negative predictive value is limited. Some clinicians use these measurements to verify the role of a pressor kidney before undertaking nephrectomy.

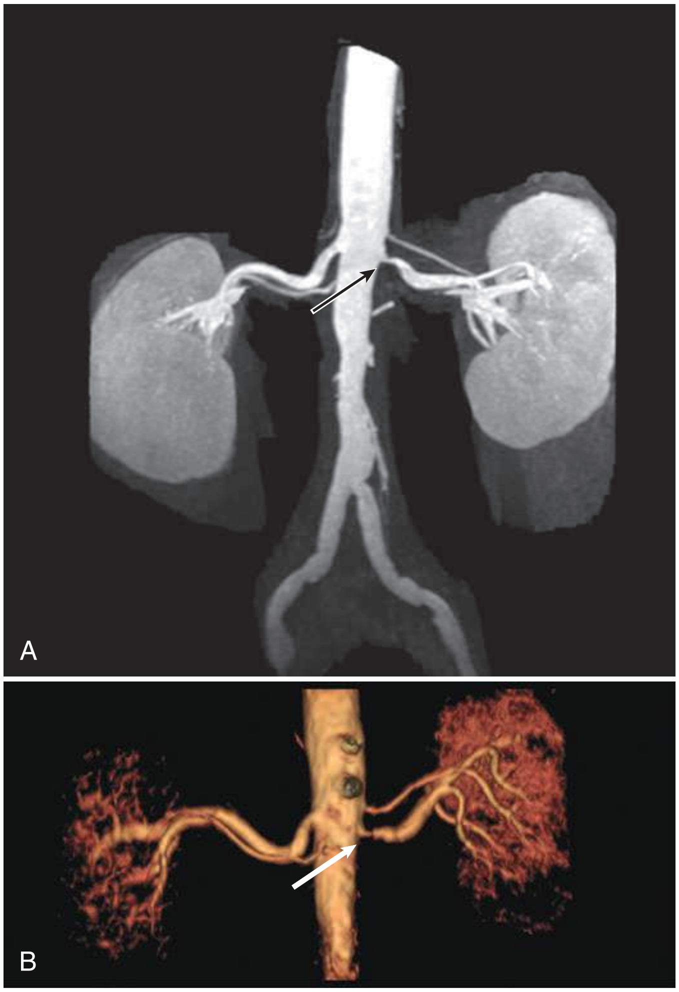

Fig. 41.6 Magnetic resonance angiogram with and without gadolinium contrast enhancement. (A) High-grade stenosis affecting the left inferior renal artery is evident, with functioning kidney tissue as reflected by gadolinium nephrogram *(arrow)*. Concerns about the role of gadolinium in the development of nephrogenic systemic fibrosis have greatly reduced the use of this contrast agent. (B) As a result, methods to image the vasculature without contrast material are being developed that produce excellent reconstructed images *(arrow)*.

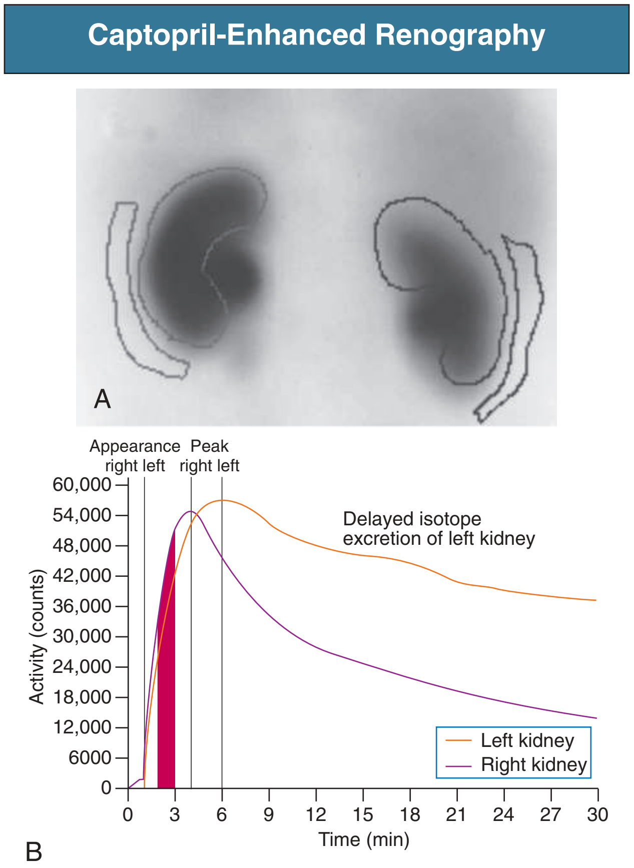

Fig. 41.7 **Captopril-enhanced renography.** (A) Scan in a patient with newly developing hypertension. (B) Renogram demonstrates delayed arrival and excretion of isotope (MAG3) in the affected left kidney.

TREATMENT OF ATHEROSCLEROTIC RENAL ARTERY STENOSIS AND FIBROMUSCULAR DYSPLASIA

Because RA FMD usually presents early in life and endovascular therapy has a high rate of cure of hypertension, FMD of hemodynamic significance should be treated with revascularization. The treatment of choice for FMD is percutaneous renal artery angioplasty (PTRA) usually without stenting. Successful PTRA results in disruption of the abnormal collagen bands in the lumen of the artery and the vascular wall leading to larger lumen diameter and less turbulent RA blood flow. Complete cure, defined as normalization of BP without the need for medications, occurs in 35% to 45% of cases. In over 85% of cases of FMD treated with PTRA, BP is improved with reduction in the number of antihypertensive medications.[51] Predictors of response to intervention include lower preintervention systolic BP, younger age at treatment, shorter duration of hypertension, and a positive pretreatment captopril renogram.[52] Primary technical success rates are high (>90%). Inadequate initial treatment or restenosis has been reported in up to 34% of treated cases. This is most common with the string of beads angiographic variant, which is multifocal and can require more than one procedure to adequately address all areas of stenosis. Some interventionalists recommend the use of intravascular ultrasound to guide adequate endovascular treatment of these lesions. The intimal and adventitial variants of FMD are associated with higher rates of PTRA failure and may require surgical revascularization for optimal management. When FMD is associated with aneurysmal dilatations exceeding 1.5 cm in diameter, surgical revascularization may be required. Endovascular management can sometimes be achieved by use of covered stents. Women of childbearing age with RA aneurysms should be treated before pursuing pregnancy because of the risk for rupture during pregnancy or delivery.

The optimal treatment of atherosclerotic RA stenosis presenting with RVH or other clinical syndromes has been the subject of much controversy. In the early 1990s, before the widespread use of RAAS blockade in the treatment of RVH, endovascular approaches to treating atherosclerotic RA stenosis emerged as an option for managing RA stenosis. Initially application of PTRA was associated with unacceptable rates of early restenosis. Subsequently, primary percutaneous renal artery stenting (PTRS) became standard treatment in many centers. Target vessel patency rates using PTRS regularly exceeds 95%. Between 1996 and 2005, enthusiastic application of PTRS in the treatment of atherosclerotic RA stenosis led to a marked rise in stent placement in these patients. Most case series and observational studies reported stabilization of BP and renal function in half of patients undergoing PTRS, improvement in up to 25%, and a decline in kidney function after PTRS in 25%.

The relative effectiveness of endovascular treatment of RA stenosis compared with medical therapy has now been studied in several randomized controlled trials. These are summarized in Table 41.2. The two largest trials, the Angioplasty and Stent for Renal Artery Lesions (ASTRAL) and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), comparing medical therapy and stenting to medical therapy alone demonstrated no differences in the primary end-points between groups.[43,44,53] The end-points were different for the two studies. In ASTRAL, 806 subjects with hypertension, many with CKD, were randomized to PTRS versus medical therapy and followed for a mean of 33.6 months. Of the enrolled patients, 53% had bilateral RA stenosis; the mean degree of luminal narrowing was 75.5%. ASTRAL reported no difference in the primary end-point of change in kidney function as measured by reciprocal creatinine. CORAL investigators enrolled 947 patients, all treated with well-defined medical therapy addressing all cardiovascular risk factors, used RAAS blockade as the cornerstone of antihypertensive therapy, and randomized half the group to medical therapy plus stent. CORAL had an imaging oversight laboratory and allowed enrollment based on angiographic as well as CTA, MRA, and duplex ultrasound definition of RA stenosis greater than 60%. At a median of 43 months of follow-up, there were no differences in the composite end-point of mortality, cardiovascular and renal events, or any of the individual components between the treatment groups.

Based on these data, the current consensus opinion is that the initial treatment of patients with RVH and CKD associated with atherosclerotic RA stenosis should be a focused medical management approach to addressing all cardiovascular and renal risk factors, including hypertension. Most patients with RVH secondary to RA stenosis can achieve BP control by applying antihypertensive algorithms that include the use of RAAS blockade. In CORAL, there was no difference in number of medications required to control BP between groups. For those patients with diabetes and CKD, attention to achieving hemoglobin A_{1c} as well as CKD mineral bone disease and anemia targets are important therapeutic goals associated with their general care. Statins are usually recommended in these patients both for cardiovascular risk reduction and with the goal of slowing progression of the RA lesion; there are also experimental data suggesting that statins attenuate renal parenchymal injury associated with atherosclerotic renovascular disease.[23,54]

Whether all patients with RA stenosis should be treated with RAAS blockade remains controversial.[55] RAAS blockers pose the risk for inducing AKI, and this risk is higher in patients with bilateral RA stenosis or stenosis to a single functioning kidney.[56] Although the unique properties of RAAS blockers allow more effective BP control in patients

TABLE 41.2 **Randomized Controlled Trials Comparing Medical Therapy to Medical Therapy With Renal Artery Stenting for Renal Artery Stenosis**

Year	**2009**	**2009**	**2014**
Study	**ASTRAL**[43]	**STAR**[44]	**CORAL**[53]
Cohort	Hypertension	Hypertension and CKD	Hypertension and/or CKD
Entry BP	No BP threshold required	BP <140/90 mm Hg and stable for 1 month and eGFR <80 mL/min	SBP >155 mm Hg on two or more medications or eGFR <60 mL/min
Stenosis	>50% by MRA, CTA, angiography	>50% by MRA, CTA, or angiography	>60% by MRA, CTA, angiography, DUS
Excluded	Clinician certain patient would benefit from stent or require stent within 6 months	Malignant hypertension Pulmonary edema with bilateral RAS Intolerance to ACEI/ARBs as evidenced by >20% drop in CrCl	Entry creatinine >4 mg/dl Kidney Length <7 cm
% Stenosis	75.5 mean %	NA	67.3%/66.2%
CKD	Mean creatinine 2.0 mg/dl	Mean creatinine 1.7 mg/dl	Mean eGFR 58 mL/min
% Bilateral	53.5%	47.9%	22%
Subjects per arm (N/N)	403/403	76/64	459/472
F/u	33.6 months	24 months	43 months
Treatment	Stent	Stent	Stent
Medical treatment	At discretion of sites BP control with or without ACEI or ARB No specified target BP	BP target <140/90 mm Hg ACEI/ARB last resort ASA Statin Smoking cessation counseling	BP target <140/90 mm Hg 130/80 mm Hg for DM and CKD ACE/ARB first-line ASA Statin goal LDL <70 mg/dl, HbA_{1c} <7.0% for DM Smoking cessation counseling
End-point	Rate of progression of CKD based on reciprocal creatinine over time	≥20% decrease in CrCl	Composite cardiovascular and renal events
Outcome	No significant difference	No significant difference	No significant difference

From references 43, 44, 53.

ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *ASA,* aspirin; *ASTRAL,* Angioplasty and Stenting for Renal Artery Lesions; *BP,* blood pressure; *CKD,* chronic kidney disease; *CORAL,* Cardiovascular Outcomes in Renal Atherosclerotic Lesions; *CrCl,* creatinine clearance; *CTA,* computed tomography angiography; *DM,* diabetes mellitus; *DUS,* Doppler ultrasound; *eGFR,* estimated glomerular filtration rate; *F/u,* follow-up; *GFR,* glomerular filtration rate; *HbA_{1c},* hemoglobin A_{1c}; *LDL,* low-density lipoprotein; *MRA,* magnetic resonance angiography; *N/N,* number of subjects in each arm; *RAS,* renal artery stenosis; *SBP,* systolic blood pressure; *STAR,* Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function.

with RVH, there is the potential for early loss of filtration pressure in patients with critical RA stenosis.

Clinical experience with RAAS blockers in the treatment of RVH is reassuring, however. Registry data and prospective follow-up studies in patients with atherosclerotic RA stenosis indicate that blockade of the RAAS is usually well-tolerated.[57,58] In the CORAL Trial, most patients received an ARB or ACE inhibitor. The lack of differences in renal end-points suggests that this was generally well tolerated. However, it is strongly advised that patients with atherosclerotic RA stenosis who are prescribed these agents have electrolytes and creatinine measured within 2 to 4 weeks after starting these agents and frequently (at least quarterly) over the course of follow-up.

Indications to Consider Renal Revascularization in Atherosclerotic Renal Artery Stenosis

Despite the lack of randomized controlled data and the risks, some patients may benefit from RA revascularization when medical therapy falls short. Indications to consider renal revascularization are listed in Box 41.6. First, uncontrolled hypertension despite all efforts to optimize pharmacologic and dietary interventions and to enhance adherence should prompt evaluation for all potential causes of resistance. Some patients will be intolerant of the very medications they need to control BP. Others may present with hypertensive urgency or emergency despite therapy. Some of these patients may respond to PTRS. Second, when RA stenosis critically reduces glomerular capillary pressure such that there is a rapid decline in GFR, renal revascularization may improve or retrieve renal function and avoid the need for dialysis. In these cases,

BOX 41.6 **Clinical Indications to Consider Renal Artery Revascularization**

- Worsening kidney function due to ischemic renal disease
- Uncontrolled hypertension failing medical therapy
- Intolerance to medical therapy
- Recurrent hospitalizations for pulmonary edema without other obvious cause
- while on optimal medical therapy
- Other unstable cardiac or renal trajectories
- Progressive renal atrophy (controversial)
- Potentially reversible dialysis dependence due to ischemic renal disease

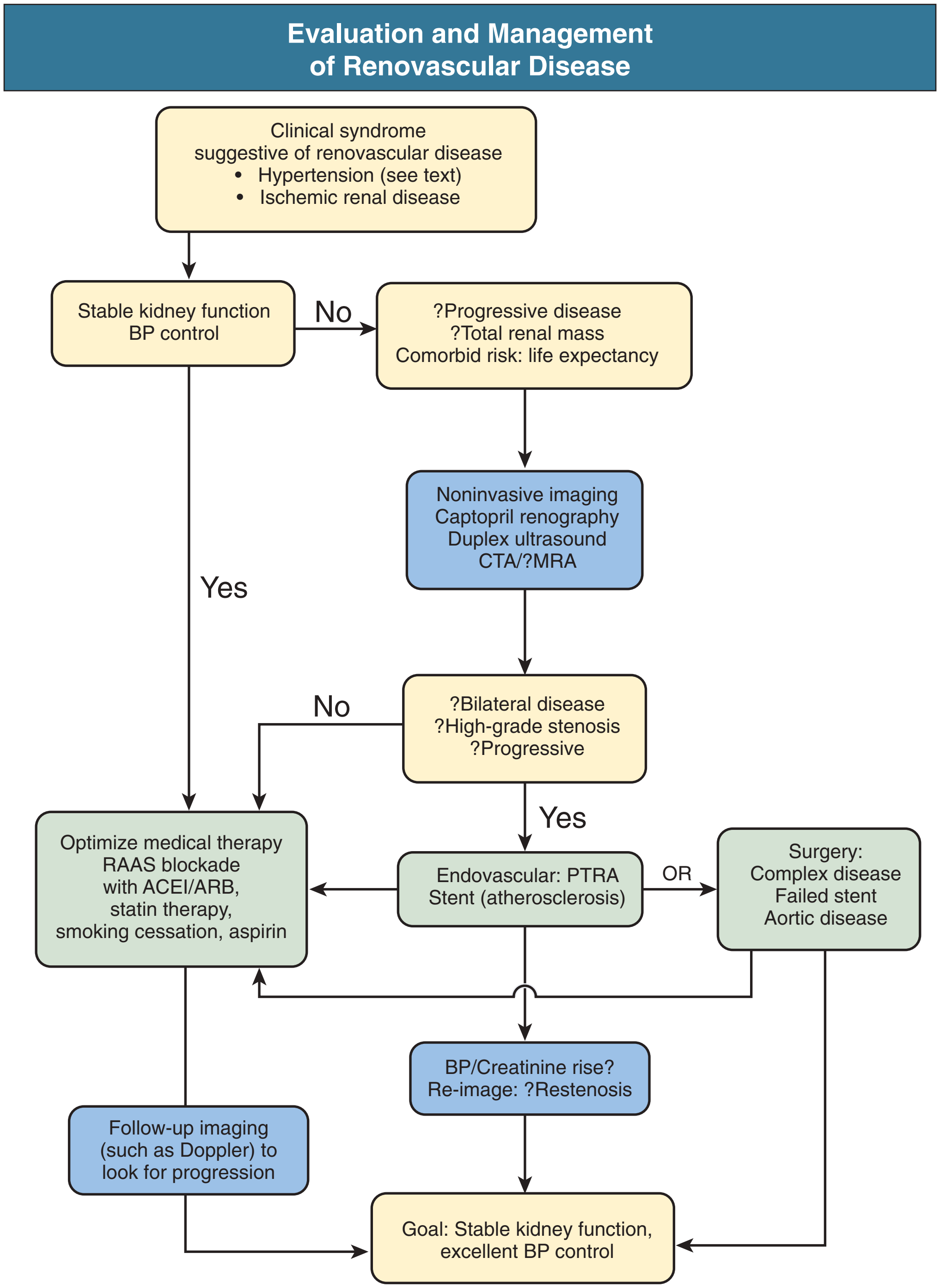
Evaluation and Management of Renovascular Disease
Clinical syndrome suggestive of renovascular disease
• Hypertension (see text)
• Ischemic renal disease
Stable kidney function BP control
No
?Progressive disease ?Total renal mass Comorbid risk: life expectancy
Noninvasive imaging Captopril renography Duplex ultrasound CTA/?MRA
Yes
No
?Bilateral disease ?High-grade stenosis ?Progressive
Yes
Optimize medical therapy RAAS blockade with ACEI/ARB, statin therapy, smoking cessation, aspirin
Endovascular: PTRA Stent (atherosclerosis)
OR
Surgery: Complex disease Failed stent Aortic disease
BP/Creatinine rise? Re-image: ?Restenosis
Follow-up imaging (such as Doppler) to look for progression
Goal: Stable kidney function, excellent BP control

Fig. 41.8 Evaluation and management of renovascular disease. The intensity of imaging and revascularization depends on both the level of kidney function and the blood pressure *(BP)*, in addition to the comorbid disease risks for the individual patient. The overall goal should focus on stable kidney function and BP levels. As with any other vascular disease, monitoring for disease progression and recurrence is an important element of long-term management. *ACEI*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *CTA*, computed tomographic angiography; *F/U*, follow-up; *MRA*, magnetic resonance angiography; *PTRA*, percutaneous transluminal renal angioplasty; *RAAS*, renin-angiotensin-aldosterone system.

there are often multiple other potential contributors to declining GFR that need to be considered. Given the risks for interventions in these patients, it is advised that a multidisciplinary group of clinicians with expertise in this area provide recommendations when interventions are considered. Finally, some patients with recurrent hospitalizations for flash pulmonary edema not resulting from other causes and attributed to medically resistant RA stenosis may benefit from RA revascularization.[59]

Fig. 41.8 outlines a proposed clinical algorithm for managing patients with atherosclerotic RA stenosis.

Surgical Renal Revascularization

Before the introduction of PTRA and PTRS, surgical revascularization was the standard treatment for patients with IRD and RVH. Such procedures carry considerable risk, cost, and morbidity. As a result, surgical intervention for renovascular disease is generally reserved for patients failing best medical therapy and in whom endovascular therapy is not feasible or who have associated aortic disease that is not amenable to endovascular therapy. Despite these caveats, successful surgical revascularization in well-selected cases provides durable restoration of kidney blood supply with good long-term patient survival.[60] Overall, the effects of surgical revascularization on BP and renal function response in patients with atherosclerotic RA stenosis mirror those for PTRS. Surgical revascularization in the modern era may provide more durable patency than PTRS with lower complication rates and risk for restenosis.[61]

Surgical revascularization should be considered in patients with total occlusion of the RA and abrupt loss of GFR for retrieval of kidney function. Some dialysis-dependent patients and some with advanced CKD with IRD experience recovery of kidney function after revascularization.[62] Treatment involves assessment of the risks versus potential benefits of heroic revascularization procedures. The status of the contralateral kidney and overall residual kidney function should be weighed against the potential retrievable function from the underperfused kidney, as well as the perioperative risk associated with surgical thrombectomy or bypass. Predictors of GFR recovery with revascularization in the setting of critical RA occlusion include preserved kidney size, evidence of a renal blush or nephrogram by imaging, recent decline in GFR, and recent baseline creatinine concentration below 3 mg/dl.[63]

When considerable renal atrophy with poor function and RVH refractory to optimal medical therapy are present, nephrectomy of the ischemic kidney may improve BP control with minimal impact on total GFR.

TRANSPLANT RENAL ARTERY STENOSIS

Transplant RA stenosis is a common post-transplantation complication occurring most often in the period between 3 months and 2 years after transplantation. The incidence ranges from 1.3% to 23% depending on the screening tests used.[64] In many cases, anastomotic stenoses are not hemodynamically significant. Renovascular complications, including RA stenosis, are more common in deceased donor than in living donor transplants and in allografts with multiple renal vessels.[65] The use of pediatric kidneys in adult recipients is associated with a higher rate of stenosis because of smaller donor vessel size, leading to greater turbulences and mismatch between donor and recipient vessels. As the transplant population ages, there has been increasing recognition of another subset of patients with pseudo–transplant RA stenosis, in which vascular disease proximal to the allograft artery, particularly involving the iliac vessel, results in reduced kidney perfusion.

The pathophysiologic basis for transplant RA stenosis may include atheromatous disease in the donor artery, intimal scarring, and hyperplasia in response to trauma to the vessel during harvesting, and anastomotic stenosis, which is most commonly associated with end-to-end anastomoses and may be related to suture technique. In end-to-side anastomoses, stenosis is typically postanastomotic, suggesting that turbulence or other hemodynamic factors play a role. Immunologic causes of transplant RA stenosis also have been proposed on the basis of histologic similarities with chronic vascular rejection and association with prior acute rejection. Other proposed pathogenic mechanisms include calcineurin inhibitor toxicity and cytomegalovirus infection. RA stenosis occurring many years after transplantation most often represents atherosclerotic disease.

Patients typically present with new-onset or worsening hypertension with or without decline in allograft function. Patients may present with IRD with rapid decline in GFR or episodes of AKI. When pseudo–transplant RA stenosis occurs, the patient often presents with ipsilateral lower extremity claudication associated with hypertension and worsening function in the allograft.[66] Risk factors for the development of transplant RA stenosis include male gender, diabetes mellitus, hyperlipidemia, smoking, and elevated serum creatinine at discharge from transplantation.

Renal duplex ultrasound is the screening test of choice for transplant RA stenosis because the vessel is superficial and easy to interrogate; the sensitivity and specificity range from 90% to 100% and 87% to 100%, respectively.[67] MRA provides excellent anatomic definition but is associated with clip artifact at the anastomosis and high false-positive rates. CTA is comparable to renal arteriography but requires a large amount of contrast material.

PTRA with or without stenting is the preferred initial approach to transplant RA stenosis.[68] Surgical renal revascularization of allografts is difficult and associated with high complication rates. Extensive fibrosis develops around the allograft and often involves the renal vessels, making surgical access to the renal vessels risky. Complications include graft loss (in 15% to 30% of cases), ureteral injury (14%), and death (5%).

RENAL INFARCTION

Abrupt interruption of blood flow to the kidney without adequate collateral blood supply can result in renal infarction. Small areas of the cortex or medulla or the entire kidney may be involved. Autopsy series suggest the incidence is between 0.5% and 1.5%. The most common presenting symptoms include loin, flank, or abdominal pain with nausea and/or vomiting. Urinalysis often demonstrates microhematuria and proteinuria. Transient or accelerated hypertension (i.e., RVH) may occur as a result of release of renin from the infarcted portion of the kidney. Transient elevations of the serum creatinine are not uncommon. Systemic signs of renal infarction may be present and include leukocytosis and fever. Up to one quarter of cases are asymptomatic, identified only by enhancement or functional defects on renal imaging. When bilateral occlusion of the renal arteries or infarction of a single functioning kidney occurs, the patient will present with oliguric or anuric AKI. Tissue injury results in elevations of serum enzymes, most commonly lactate dehydrogenase, however transaminases, creatine kinase, and alkaline phosphatase may also be elevated.[69-71]

A high clinical suspicion is required for the diagnosis of renal infarction because the presenting symptoms are common to those of a number of other disorders. CT with intravenous contrast administration is the imaging modality of choice for demonstrating areas of renal cortex that are not perfused. CT findings can include focal wedge-shaped areas of decreased attenuation or global infarction with or without a rim sign indicating intact collateral circulation to the renal cortex as demonstrated in Fig. 41.9. Perinephric stranding also may be seen. Simultaneous infarcts in the liver and spleen are not uncommon. Other potential imaging techniques include MRA with gadolinium or nuclear scintigraphy with dimercaptosuccinic acid (DMSA). When the entire kidney is not perfused well, it is often difficult to determine if there is any salvageable renal parenchyma. Studies in experimental animals with acute RA occlusion have shown that the collateral circulation can maintain renal viability for up to 3 hours after occlusion.[72] Patients with atherosclerotic RA disease may have developed collateral vessels, resulting in the maintenance of renal viability for days to weeks. In these patients, urgent arteriography to identify the location of the arterial thrombosis or embolus may allow renal salvage via percutaneous or surgical revascularization.

Causes of renal infarction are listed in Box 41.7. The most common are trauma, RA embolism from cardiac thrombus, dissection, and iatrogenic complications of endovascular procedures. Spontaneous RA thrombosis or dissection is most often associated with atherosclerotic disease of the aorta or RAs, but other inflammatory vascular disorders can lead to infarction.

Renal infarction secondary to traumatic RA injury occurs in 1% to 4% of all nonpenetrating abdominal trauma. Types of injuries

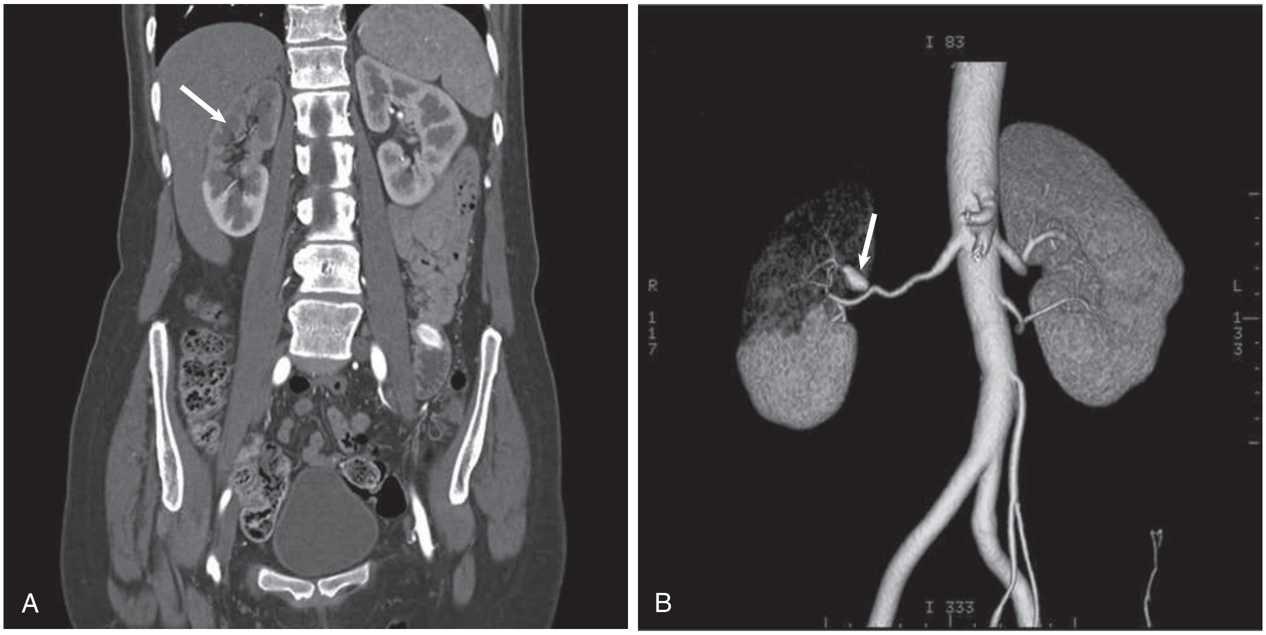

Fig. 41.9 **Computed tomography angiogram of renal artery aneurysm with area of renal infarction in right kidney.** (A) Coronal image demonstrates area of intact tissue with no blood perfusion within the kidney parenchyma *(white arrow)*. (B) Reconstructed view with vascular aneurysm *(arrow)* and minimal flow in the distribution beyond this segment, consistent with near-total occlusion. This patient presented with accelerated renovascular hypertension treated primarily with renin-angiotensin system (RAS) blockade.

BOX 41.7 Causes of Renal Infarction

Renal Artery Thrombosis

Spontaneous

- Renal artery atherosclerosis or fibromuscular dysplasia
- Renal artery or aortic dissection
- Renal or aortic aneurysms

Traumatic

- Postprocedure
- Endovascular stents
- Renal transplantation
- Hypercoagulable disorders
- Malignancy
- Antiphospholipid syndrome
- Renal artery vasculitis
- Vascular rejection
- Thrombotic microangiopathies
- Genetic
- Ehlers-Danlos vascular variant

Renal Embolism

- Atrial fibrillation
- Cardiac mural thrombi
- Valvular heart disease
- Paradoxical embolism
- Tumor or fat embolism
- Atheroemboli

Renal Vein Thrombosis

- Nephrotic syndrome
- Post–renal transplantation
- Traumatic

associated with RA or kidney injury include deceleration injury and direct blunt trauma to the loin or flank regions. Evidence of lumbar vertebral injury should raise suspicion in the emergency department for renovascular trauma. Traumatic renal vascular occlusion often leads to renal infarction within 3 to 6 hours. The success rate for revascularization of RA thrombosis after trauma remains low, even when diagnosed early.[73]

A common cause of renal infarction is RA embolism. The kidneys are frequently the target for emboli from thrombi originating in the heart. In one series, 1.4% of the general population had RA embolism at autopsy, of which only 2 of 205 cases (1%) were diagnosed clinically.[74] Emboli to the right and left RA occur with equal frequency, with 12% of cases being bilateral. Atrial fibrillation, cardiac thrombus after myocardial infarction, atrial myxoma or other cardiac tumors, endocarditis, paradoxical emboli, and aortic thrombus represent most of the conditions associated with renal embolism. Atrial fibrillation is the most common cause, with a rate of embolism four times higher than that of the general population; the highest risk is during the first year after the diagnosis of atrial fibrillation and when anticoagulation is subtherapeutic.[75] When echocardiography is performed, cardiac thrombus is only rarely detected. Other causes of renal emboli include fiber or foam related to cardiac bypass procedures, calcium from valve annuli, and even "bullet emboli" in the setting of trauma. Aortic endovascular stenting has been associated with a 10% incidence of new renal infarcts, presumably of embolic origin.[76] There is a 30-day mortality rate of 10% to 13% among patients experiencing renal embolism in the setting of atrial fibrillation. Up to 40% of cases of renal embolic events have at least transient reduction in kidney function.

Paradoxical RA embolism may occur in patients with right-to-left cardiac shunts most commonly due to atrial septal defects present in up to 9% to 35% of the general population. The diagnosis of paradoxical embolism requires clinical, angiographic, or pathologic evidence of systemic embolism, as well as the presence of a venous thrombus along with an abnormal communication between the right and left circulations with a favorable pressure gradient (typically diagnosed by "bubble" echocardiography) for the passage of clot from the right to the left side of the heart.

Less common causes of infarction include hypercoagulable states, inflammatory diseases of the retroperitoneum, and thrombotic microangiopathies. Antiphospholipid antibody syndrome is associated with both arterial and venous thrombotic events and is the most common cause of spontaneous arterial thrombosis.[77] Rare causes of renal infarction include autoimmune diseases and drug abuse, such as intravenous injection or nasal insufflation of cocaine or even marijuana smoking. The exact mechanism involved in the pathogenesis of renal infarction in some of these conditions is unclear.

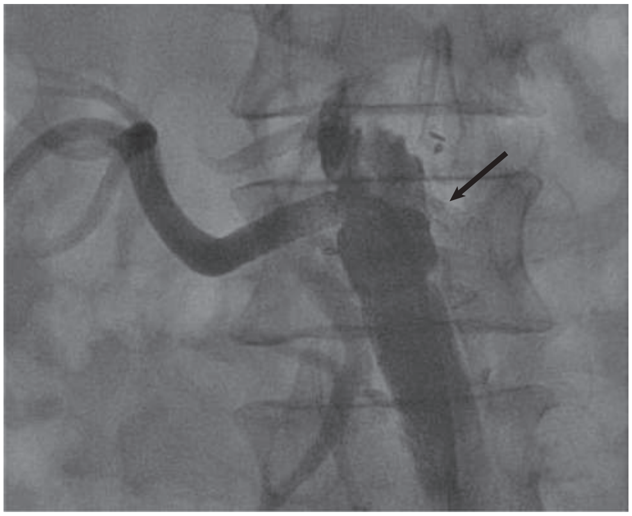

Fig. 41.10 **Thrombosis of renal artery complicating renal artery stenting.** Right and left renal artery stents. The left renal stent *(arrow)* is triangular, indicating crimping of the proximal portion, which in this patient was associated with thrombosis of the renal artery, seen here as no contrast entering the vessel. The right renal stent is patent.

Aortic dissection can lead to RA occlusion, reduced renal blood flow, or infarction. In this setting the predictors of renal salvage are the same as those for occlusion caused by atherosclerotic RA stenosis and include preserved renal size, collateral circulation permitting renal viability, and blush on imaging studies. Aortic dissection occurs most commonly in association with atheromatous aneurysmal vascular disease of the thoracic aorta, but it can occur in collagen disorders, such as Ehlers-Danlos type IV or Marfan syndrome, and with arteritis, such as TA.

RA thrombosis, dissection, laceration, or embolism can occur secondary to vascular interventions, especially those involving placement of endovascular stents. Endovascular aortic stents commonly used to treat infrarenal abdominal aortic aneurysms can cross the RA orifice, impair renal perfusion or cause RA thrombosis.[78,79] RA stent placement similarly may cause intimal dissection, atheroembolism, and thrombosis of the RA. Stent fracture also can be associated with thrombosis, as demonstrated in Fig. 41.10.

In-stent stenosis remains a significant complication occurring in up to 33% of post-PTRS cases and can occur at any time after stent placement, with the highest risk within the first year after PTRS. Whether duplex surveillance should be performed at various intervals after PTRS is unclear, but clinicians should be aware that RA stenosis and occlusion can occur within stents, sometimes without clinical clues. Clinicians need to inform patients with atherosclerotic RA stenosis regarding the risk and uncertain benefits of PTRS.[80]

Treatment of Acute Renal Infarction

Investigations should be done to determine whether the infarction is embolic or thrombotic. Treatment of the infarction itself is usually conservative and includes pain control and treatment of associated RVH, which can be labile. If RA occlusion is caused by thrombosis associated with a hypercoagulable state or an embolism from a central source, systemic anticoagulation is indicated. Salvage of the kidney by acute thrombolytic therapy also has been attempted, with limited success. There is no evidence that thrombolytic therapy can limit infarct size if it is administered in the acute setting.

When an embolism from a central source results in renal infarction or RA occlusion, a search for the source should be undertaken. An echocardiogram is usually indicated to evaluate for intracardiac or aortic arch thrombi and valvular abnormalities. Systemic anticoagulation is indicated to prevent recurrent embolic events, except when the source is septic emboli.

Thrombosis of atherosclerotic RAs (because of prior collateral development in most cases) often results in marked ischemia but not overt infarction of the kidney; in this setting surgical and, sometimes, percutaneous endovascular revascularization can restore kidney function.[81,82]

ATHEROEMBOLIC RENAL DISEASE

Atheroembolic renal disease is common and is estimated to account for up to 10% of unexplained renal failure in the elderly. It is typically associated with arterial manipulation that occurs during arteriography, vascular surgery, angioplasty, and stent placement. Spontaneous atheroemboli may occur in patients with extensive atherosclerosis and unstable plaques, especially after administration of oral or intravenous anticoagulants or thrombolytic agents. Atheroembolism may be expected to occur in up to 30% of patients with extensive aortic atherosclerosis after endovascular intervention. Careful studies using filters to capture embolic material confirm that PTRA and PTRS release thousands of atheromatous particles of various sizes in 70% to 100% of cases.[83] Preprocedure treatment with antiplatelet agents and intraprocedural use of embolic protection devices during PTRS is under investigation, with some positive results as means of reducing the frequency of this underdiagnosed cause of renal infarction and CKD.[84,85]

Ipsilateral RA stenosis may be present in up to 80% of patients with renal cholesterol embolization. Cholesterol embolization may contribute to the loss of renal function in patients with atherosclerotic IRD; cholesterol emboli were found in the kidneys of 36% of patients undergoing surgical revascularization.[86]

Most patients are older than 50 years with generalized atherosclerosis and have a history of recent endovascular procedures or signs and symptoms of atherosclerotic vascular disease. These signs and symptoms can include claudication or ischemic ulcers, abdominal pain, angina, myocardial infarction, transient ischemic attacks, amaurosis fugax, stroke, abdominal aortic aneurysm, RVH, or IRD. Most patients have atherosclerotic risk factors, including hypertension, hypercholesterolemia, diabetes, and smoking.

Clinical Presentation

Acute or subacute renal impairment caused by renal microinfarctions developing as long as 6 months after the atheroembolic insult is the most common presentation leading to the diagnosis of cholesterol embolization. The clinical picture is multisystemic and involves the kidneys in about 75% of patients.

If a large atheroembolic shower induces significant renal tubular damage, the resulting AKI may manifest with an oliguric phase characterized by a high fractional excretion of sodium. More often, the renal failure is nonoliguric. A slowly progressive, often stair-stepping subacute renal impairment is common. Some patients will have only moderate impairment in renal function, whereas others progress to ESRD. Urinalysis findings are nonspecific but may include mild proteinuria, microhematuria, pyuria, and eosinophiluria. Renin release by ischemic zones in areas of embolization can lead to labile hypertension early in the course, sometimes associated with transient marked proteinuria. Fever, often low grade, is characteristic.

Although the kidneys are the organs most commonly involved, extrarenal cholesterol embolization will provide clues to aid in the diagnosis. Cutaneous findings are seen in up to 60% of patients during initial presentation. These findings include blue or purple toes, mottled

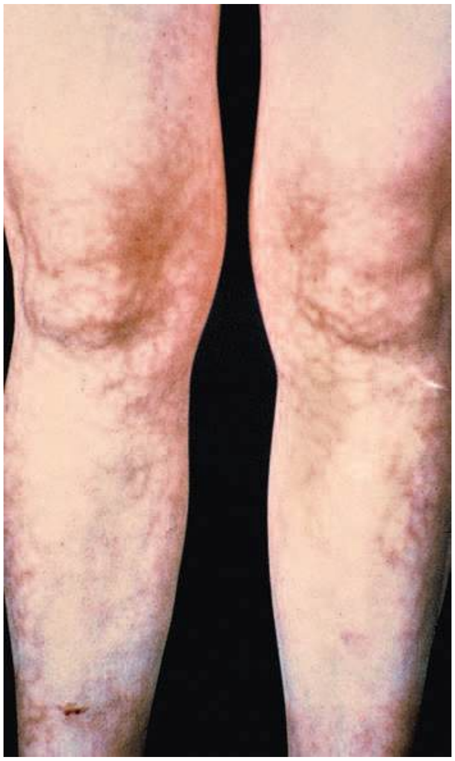

Fig. 41.11 **Livedo reticularis.** The mottled skin changes associated with peripheral cholesterol embolization may be seen over the legs, buttocks, back, or flank and may be transient.

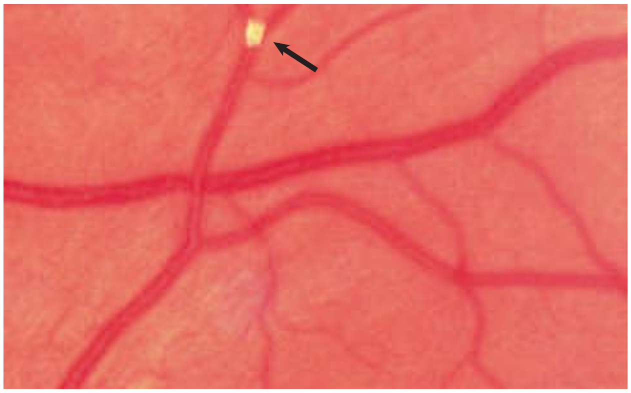

Fig. 41.12 **Hollenhorst bodies.** Cholesterol embolus of a retinal arteriole *(arrow)*. (Courtesy Richard Mills, University of Washington, Seattle, Wash.)

serpiginous rash (livedo reticularis; Fig. 41.11), petechiae, and purpura or necrotic ulceration in areas of skin embolization, such as the lower back, buttocks, lower abdomen, legs, feet, or digits.

Other organs often involved include the spleen (in 55% of cases), pancreas (52%), gastrointestinal tract (31%), liver (17%), and brain (14%). This involvement can result in a number of associated clinical symptoms, including abdominal or muscle pain, nausea, vomiting, ileus, gastrointestinal bleeding, ischemic bowel, hepatitis, angina, Hollenhorst plaques (Fig. 41.12), and visual and neurologic deficits.

Diagnosis

Atheroembolic renal disease should be suspected when renal failure develops after a vascular intervention in the presence of livedo reticularis. Many laboratory abnormalities indicative of tissue injury are associated with cholesterol embolization, including elevated erythrocyte sedimentation rate (in 97% of cases), elevated serum amylase (60%), leukocytosis (57%), anemia (46%), hypocomplementemia (especially low C3) (25% to 70%), and elevated lactate dehydrogenase and creatine kinase (38% to 60%). Peripheral eosinophilia, which may be transient, is seen in up to 57% of patients. The presence of eosinophilia should raise suspicion for atheroembolic renal disease in the appropriate clinical setting. Serum lactate elevation is usually seen only if concomitant ischemic bowel is present. In most circumstances, the diagnosis is made clinically. However, a definitive diagnosis can be made by biopsy of an involved organ or tissue. A skin or muscle biopsy in an involved area may preclude the need for kidney biopsy.

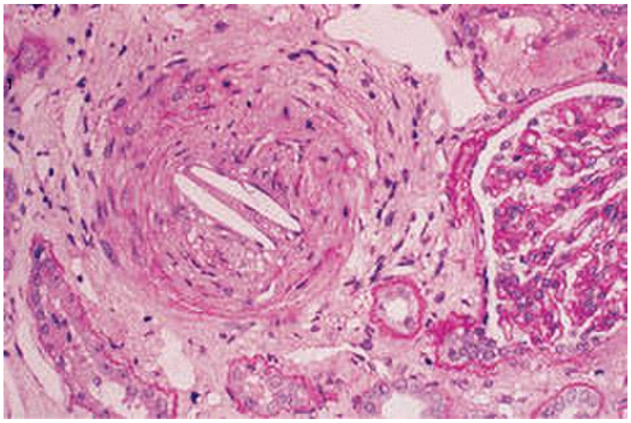

Fig. 41.13 **Cholesterol emboli in kidney biopsy specimen.** Biconvex cholesterol clefts with giant cell reaction and recanalization of the lumen of a medium-sized renal vessel. (Periodic acid–Schiff stain.) (Courtesy Dr. R. Horn, Vanderbilt University, Nashville, Tenn.)

Differential Diagnosis

In this setting, often after vascular interventions, other considerations include contrast nephropathy, acute tubular necrosis, renal infarction, or vascular occlusion. Peripheral eosinophilia and eosinophiluria, rash, fever, and renal dysfunction may also be misdiagnosed as acute interstitial nephritis. Acute cholesterol embolization syndrome may mimic vasculitis, occult infection, neoplasm, or thrombotic microangiopathy. Chronic cholesterol embolization syndrome may appear similar to hypertensive nephrosclerosis or IRD. In the kidney transplant recipient, renal atheroembolism may mimic acute rejection or chronic allograft nephropathy.

Pathology and Pathophysiology

If clinical or other pathologic evidence has not secured the diagnosis, kidney biopsy may be helpful. Diagnosis is based on the presence of birefringent, biconvex, elongated cholesterol crystals or biconcave clefts within the lumina of small vessels left behind in formalin-fixed tissue Fig. 41.13. Due to the patchy nature of this disorder, open wedge kidney biopsy has a higher likelihood of successful diagnosis relative to a percutaneous approach because it allows visualization and direct sampling of areas of ischemic infarction of the cortex. The pathologist should be alerted by the clinician that cholesterol embolization is in the differential diagnosis before the biopsy specimen is processed. In frozen sections of tissue, the cholesterol material can be identified with polarized light microscopy. The pathologic findings also may include intimal thickening and concentric fibrosis of vessels, giant cell reaction to the cholesterol particles, vascular recanalization, endothelial proliferation, tubulointerstitial fibrosis with both eosinophil and mononuclear cell infiltrates, glomerular ischemia, and even focal segmental glomerulosclerosis. In the kidney, the most commonly affected vessels are the arcuate and interlobular arterioles, leading to patchy ischemic changes distal to these vessels.

Natural History

The natural history is determined by the extent of organ involvement and the degree of the embolization. In one series of cases, renal function declined rapidly in 29%, with a more slowly progressive course seen in 61%.[87] Among the latter group, the decline in renal function was thought to result from a combination of cholesterol embolization and IRD. Patients also may manifest acute or subacute renal impairment followed by partial recovery of renal function. Conversely, the outcome can be dismal, particularly when cerebral embolization occurs or when there is a large unstable atheromatous burden. Some patients with cholesterol embolization may develop ESRD.

Treatment

There is no specific therapy for the cholesterol embolization syndrome. Therefore its risk should be considered before angiographic and vascular surgical procedures are undertaken in patients with diffuse, extensive atherosclerotic disease. Prevention is the most effective management strategy, so patients with extensive aortic atherosclerosis should be considered for alternative approaches to cardiac catheterization, such as through the brachial artery. When it is feasible, distal embolic protection devices should be used to trap embolic material for removal from the circulation to avoid end-organ damage by embolic debris.

Once the diagnosis of cholesterol embolization has been established, further endovascular interventions should be avoided. Poor outcomes have been reported in patients with cholesterol emboli who subsequently undergo coronary artery bypass surgery. When clinical factors dictate the need for aortic, renal, or peripheral arterial surgery, optimal timing and surgical approach are critical. Conversely, there is a growing surgical experience with segmental aortic replacement to remove the source of emboli, particularly when atheroembolic disease occurs spontaneously. Transesophageal echocardiography is often used to identify mobile ulcerative plaque in the aorta to guide intervention.

ACE inhibitors are effective in managing the labile hypertension seen early in the course of cholesterol embolization. Corticosteroids have been used with some success in patients with systemic cholesterol embolization and associated inflammatory symptoms.[88] There also have been several reports documenting improvement or stabilization of skin signs of cholesterol embolization after administration of statins,[89] which should be part of the treatment of the generalized atherosclerosis in these patients. Cholesterol embolization also has occurred after treatment with anticoagulants. Although direct causality between anticoagulants and cholesterol embolization has not been established, the proposed mechanism is that anticoagulants prevent thrombus organization over the ulcerative plaques. Therefore anticoagulation should be avoided in the acute setting of cholesterol embolization unless a critical life-threatening indication for anticoagulation is present. This has implications for the delivery of renal replacement therapy, if indicated.

RENAL VEIN THROMBOSIS

Renal veins begin in the subcapsular region of the kidney. These stellate veins communicate with perirenal and cortical venous channels and empty into interlobular and then arcuate veins. The venae rectae drain the pyramids and join the arcuate veins, which leave the renal parenchyma through interlobar vessels, converging into four to six trunks near the hilum of the kidney. Two or more renal veins have been described in up to 20% of people; this is more common on the right. The main renal veins empty into the IVC. The left renal vein is three times longer than the right (7.5 vs. 2.5 cm) and traverses behind the splenic vein and body of the pancreas before it crosses in front of the aorta near its termination at the IVC. About 25% of people have retro-aortic or circumaortic renal veins.

Renal vein thrombosis is rare and primarily observed in children with severe dehydration (with an incidence in neonates of 0.26% to 0.7%) or in adults with nephrotic syndrome, renal tumors, or hypercoagulable states and after surgery or trauma to the renal vessels.[90] When it occurs in adults, the diagnosis is often never considered.

Thrombosis of the longer left renal vein also may involve the ureteral, gonadal, adrenal, and phrenic branches that drain into the left vein, whereas on the right side, the adrenal and gonadal veins drain directly into the IVC. The renal veins also communicate with perirenal veins outside of the Gerota fascia as part of the retroperitoneal collateral venous network: tributaries of the portal system, lumbar, azygos, and hemiazygos. Because of this network of venous complexes, occlusion of the left renal vein results in enlargement of the systemic collateral vessels and provides some protection against infarction (Fig. 41.14).

Acute Versus Chronic Renal Vein Thrombosis

Experimentally, acute RVT is associated with immediate enlargement of the kidney, with a marked increase in renal vein pressure, leading to a significant decrease in renal arterial flow. Complications include hemorrhagic infarction, kidney rupture, and retroperitoneal hemorrhage. In the dog, the kidney enlarges over the course of a week, then proceeds to atrophy as a result of progressive fibrosis. In contrast, slow, progressive (chronic) thrombosis may allow collateral formation, resulting in minimal symptoms.

Clinical Presentation

Acute RVT is usually symptomatic and associated with loin, testicular, or flank pain and even the development of scrotal swelling or hydrocele. The patient may present with fever, leukocytosis, and, in the setting of a single kidney or renal transplant, oliguric AKI. Acute RVT is associated with renal edema and swelling. Nausea and vomiting often accompany acute RVT, and symptoms might be confused with those of acute pyelonephritis. Hematuria is nearly universal and most often is microscopic. The high venous pressures result in a marked increase in proteinuria. Urinalysis sometimes reveals evidence of proximal tubule dysfunction, such as glycosuria. In some patients, RVT is diagnosed only after the patient has developed an acute pulmonary embolus and the source of the embolus is investigated or with worsening of renal function in the setting of proteinuric CKD.

Chronic RVT may be asymptomatic. Extensive venous collaterals may allow for minimal impairment of kidney function and structure. Often, however, microhematuria, proteinuria, and evidence of reduced GFR or tubular dysfunction are present, particularly when indices of differential renal function are sought, such as with nuclear studies.

When RVT causes renal infarction, the distribution of the hypoperfused region tends to be medullary or subcortical. The renal impairment tends to be patchy and subtotal. These patients can develop severe hypertension acutely. The swollen kidney can rupture the capsule and result in massive retroperitoneal hemorrhage.

Etiology

The causes of RVT are listed in Box 41.8. Renal vein thrombosis occurs in neonates in situations of dehydration and thrombophilia. The classic presentation triad includes a palpable abdominal mass, hematuria, and thrombocytopenia. Proteinuria, tubular dysfunction, reduced GFR, and hypertension may be associated. There is a greater predilection for development of RVT in male infants, with 67% of the reported cases

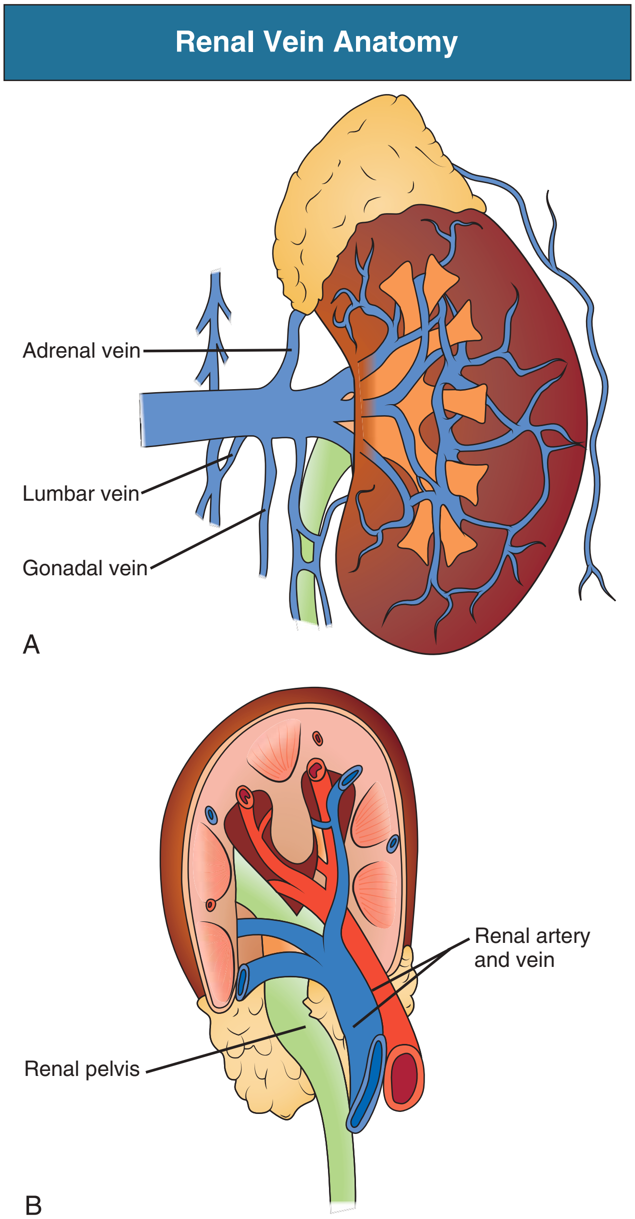

Fig. 41.14 Renal vein anatomy. (A) There is extensive communication between the renal venous plexus and lumbar, gonadal, and adrenal veins, which provide alternative outflow in the setting of renal vein thrombosis, particularly on the left. (B) Transverse section of the kidney showing relative position of vascular structures in the renal pelvis. (Redrawn from Graham SD, Keane TE, Glenn JF, eds. Glenn's Urologic Surgery. 7th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2010.)

occurring in boys.[91] Most cases are unilateral, with the left renal vein more commonly affected. In neonates, the diagnosis is made by renal ultrasound and Doppler study of the renal veins. The strongest predictor of poor renal outcome is marked decrease in perfusion detected on initial Doppler ultrasound.[92] The optimal treatment approach to neonatal RVT is controversial. Fibrinolytic therapy may be associated with bleeding complications, including adrenal hemorrhage, and is usually not successful in restoring renal function unless it is undertaken within 24 hours of the thrombotic event.[93]

BOX 41.8 Causes of Renal Vein Thrombosis

- **Malignant neoplasia**
  - Direct invasion of tumor into the renal vein
  - Retroperitoneal adenopathy, fibrosis, or tumor compressing the renal vein
  - Extension of inferior vena cava (IVC) obstruction by tumor invasion
  - Hypercoagulable state associated with malignant disease
- **Complication of IVC filters**
- **Complication of PICC lines**
- **Nephrotic Syndrome**
  - Membranous nephropathy
  - Lupus Nephritis
- **Acute pyelonephritis**
- **Complicating inflammatory bowel disease**
- **Acute Pancreatitis**
- **Inflammatory aortic aneurysm**
- **Neonatal**
  - Congenital
  - Dehydration
  - Thrombophilia
  - Complication of umbilical vein catheterization
  - Transmission of maternal procoagulant factors
- **Hypercoagulable states**
  - Antiphospholipid antibody syndrome
  - Factor V Leiden mutation
  - Antithrombin III deficiency
  - Protein S and C abnormalities
  - Hyperhomocysteinemia
  - Elevated levels of clotting factors VIII, IX, and XI
  - Heparin-induced thrombocytopenia
  - Birth control pill
- **Thrombophilia**
- **Chuvash polycythemia**
- **Post Renal Transplantation**
  - Acute rejection, OKT3
  - Vascular rejection
  - Compression or kinking of renal vein
  - Hypercoagulable disorders
  - Sticky platelet syndrome
  - Calcineurin inhibitors
  - Viral infection of the allograft
- **Complication of surgical compression**
  - After aortic aneurysm surgery
  - After pyeloplasty
  - After partial nephrectomy
- **Traumatic renal vein thrombosis**
- **Pregnancy**
  - Compression
  - Preeclampsia, eclampsia
- **Complication of embolization of gastric varices**
- **Budd-Chiari syndrome**
- **Behcet's disease**

PICC, peripherally inserted central catheter

Patients with nephrotic syndrome have increased risk for venous thromboembolism. The prevalence of RVT in nephrotic syndrome is unclear because it is largely undiagnosed; studies report frequencies from 5% to 62%.[94] Numerous abnormalities promoting a prothrombotic state occur secondary to heavy proteinuria. It is interesting to note that RVT appears to be more common in membranous nephropathy and lupus nephritis, but RVT can complicate any cause of proteinuric renal

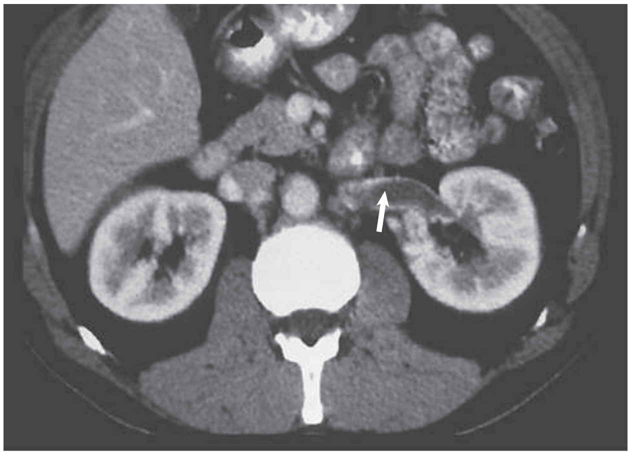

Fig. 41.15 Computed tomography venogram demonstrating left renal vein thrombosis *(arrow).* (Courtesy Dr. S. Rankin, Guy's Hospital, London.)

disease. In this setting, RVT can lead to an increase in baseline proteinuria and present with AKI superimposed on CKD.

RVT after transplantation is rare and occurs in less than 0.5% to 4% of transplants, usually within the first week after transplantation.[95] It usually leads to graft infarction, but rupture of the allograft also can occur. Causes include technical issues related to the anastomosis, compression of the renal vein by fluid collections, volume depletion, acute rejection, and hemostatic and hypercoagulable states. Factor V Leiden mutation, which occurs in 2% to 5% of the population, is a risk factor for transplant RVT and should be sought when it occurs. Another prothrombotic syndrome known as *sticky platelet syndrome* can result in post-transplant RVT. There are some data supporting the protective effects of low-dose aspirin in this population. Renal salvage is possible with early diagnosis, surgical exploration, and thrombectomy.

Pregnancy and the postpartum state are hypercoagulable states. There have been reports of spontaneous RVT in the postpartum period associated with renal infarction. RVT complicating pregnancy should be suspected when clinical clues such as flank pain, proteinuria, and hematuria are present.

Malignancy accounts for the greatest number of cases of RVT.[96] RVT can result from invasion of tumor of renal origin into the renal vein. About half of renal cell carcinomas are associated with RVT at autopsy. In addition, neoplasia originating in the renal vein or IVC, such as leiomyosarcoma or cavernous hemangioma, can cause RVT. Extrinsic compression of the renal vein by a tumor or retroperitoneal fibrosis also may cause this syndrome.

Diagnosis

Diagnosis of RVT requires imaging. Conventional ultrasound may demonstrate alterations in size and echogenicity. Sonographic findings in neonatal RVT include renal enlargement, loss of corticomedullary differentiation, and linear echogenicities radiating from the renal hilum as a result of interlobular and interlobar venous clot. Later scans may show linear, punctuate, or lace-like calcifications in these regions, representing calcified thrombi. Renal duplex ultrasound may show increases in resistive indices and can directly visualize the filling defect. In patients with renal transplant RVT, the duplex waveform pattern demonstrates reversal of diastolic flow, which is not pathognomonic or specific for RVT. Imaging of the renal vein by MRI or CT venography is needed to confirm transplant RVT. In adults, these modalities have much greater sensitivity than renal vein duplex studies for the diagnosis of RVT. Fig. 41.15 is a CT venogram demonstrating unilateral RVT.

Treatment

Treatment is controversial and depends on the setting, acuteness, and renal consequences. If there is no contraindication, most patients are treated acutely with systemic anticoagulation. In adults with acute RVT that is compromising renal function, catheter-directed thrombolytic therapy with urokinase or tissue plasminogen activator with or without percutaneous mechanical thrombectomy can restore vessel patency.[97] The long-term benefit of this approach is unclear, and it is less successful when the thrombotic process begins in the small intrarenal venules rather than in the major veins, as is often the case when primary renal disease or a hypercoagulable state initiates the process. In neonatal RVT, which often results in renal nonfunction, thrombolytic therapy and anticoagulation have been used with variable results.

Surgical interventions include nephrectomy, thrombectomy, and retroperitoneal surgery for non–renal-associated abnormalities, such as tumor, retroperitoneal fibrosis, aortic aneurysm, and acute pancreatitis. Surgery tends to be reserved for situations in which the RVT results in hemorrhage from renal capsular rupture or for long-term consequences of RVT, such as hypertension or infection of a nonfunctioning kidney.

A conservative approach may be favored when left RVT occurs because of the extensive collateral venous supply on that side, ultimately allowing venous drainage and delayed improvement in renal function. Systemic anticoagulation is indicated acutely to prevent extension of thrombus into the IVC and prevent pulmonary emboli. Anticoagulation should be continued indefinitely in patients with a persistent hypercoagulable state after RVT.

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SELF-ASSESSMENT QUESTIONS

1. A 24-year-old woman presents with hypertension and bruits over her carotid arteries. She does not know the onset of her hypertension, which was discovered during a regular gynecologic check-up. In evaluating her, you discover the presence of a heart murmur heard loudest over the posterior thorax. She has no abdominal bruits. There is no difference between blood pressure (BP) measurements taken in each arm. She has a radial-femoral delay, and otherwise her pulses are equal and present. Which of the following is the most likely cause of her hypertension?
   - **A.** Takayasu arteritis
   - **B.** Fibromuscular dysplasia of the renal artery
   - **C.** Coarctation of the aorta
   - **D.** Vasculitis
   - **E.** Atherosclerotic renal artery (RA) stenosis
2. A 76-year-old woman comes to see you because her primary care doctor has had difficulty getting her BP controlled. She tells you she never had hypertension until about 4 or 5 years ago. She has a history of smoking one pack per day of cigarettes for 40 years. She had coronary artery bypass grafting 8 years ago and has been well without chest pain or dyspnea since then. Examination is notable for systolic BP of 180. She has a left carotid bruit audible and diminished dorsalis pedis pulses. Her creatinine is 1.3 mg/dl and potassium is 3.4 mg/dl. A renal duplex shows normal velocities in the left RA but a peak systolic volume of 350 cm/sec in the proximal portion of the right RA. She is on the following antihypertensive medications: metoprolol 50 mg twice daily, amlodipine 5 mg/day, hydrochlorothiazide 25 mg/day, and atorvastatin 80 mg/day and is taking aspirin. What is the most appropriate next action?
   - **A.** Refer right for RA stent
   - **B.** Start angiotensin-converting enzyme (ACE) inhibitor and follow BP response and potassium and creatinine closely
   - **C.** Refer to vascular surgery for RA bypass
   - **D.** Stop aspirin and atorvastatin
   - **E.** Add doxazocin
3. A 32-year-old woman with lupus nephritis class V is currently being treated with induction therapy with mycophenolate mofetil 1500 mg twice daily and oral steroids. She continues to have proteinuria, and her last 24-hour quantitative protein concentration was 6 g. Fortunately, her creatinine has remained normal at 0.8 mg/dl. She presents to the emergency department with pleuritic chest pain. A ventilation/perfusion ($\dot{V}/\dot{Q}$) scan shows high probability for pulmonary embolism. When you see her, you note that her creatinine is 1.8 and urine protein/creatinine is 30 g/g. She is started on anticoagulation therapy and admitted. As the renal consult, which of the following tests would you recommend the team order?
   - **A.** Antiphospholipid antibody
   - **B.** Renal vein Doppler study and renal ultrasound
   - **C.** Computed tomographic angiography (CTA) of pulmonary arteries
   - **D.** Both a and b
   - **E.** None of the above
4. An 83-year-old woman presents with congestive heart failure and hypertension. She has a history of peripheral vascular disease and chronic kidney disease with a baseline creatinine of 1.5 mg/dl and a single kidney because she donated one to her son with diabetic nephropathy 30 years earlier. She is admitted and treated with diuretics and achieves a net negative fluid balance of 6 liters over 3 days. Her BP, which was 180/90 on admission, is now 120/80. An echo shows left ventricular hypertrophy with diastolic dysfunction, preserved ejection faction, and no valvular abnormalities. Over the past 24 hours her creatinine has risen to 3.8 and she has produced almost no urine. She has no flank pain. Despite stopping her diuretics, her creatinine does not improve over the next 72 hours and she is oliguric. She appears euvolemic and does not respond to empiric intravenous fluids for 24 hours. Her medications are reviewed, and she is receiving no nephrotoxic agents and all diuretics and antihypertensives are on hold. An ultrasound and Doppler examination show a blunted waveform concerning for possible critical renal artery stenosis. What test would be best to rule out critical RA stenosis?
   - **A.** MRA of renal arteries
   - **B.** CTA of RAs
   - **C.** Captopril renography
   - **D.** Direct renal angiography with carbon dioxide
   - **E.** Peripheral renin level
5. A 62-year-old man with a history of hypertension presents with acute left flank pain with no dysuria. Urinalysis shows hematuria without pyuria. He has a temperature of 99.8° F and a white blood cell count of 12,000. He is in new-onset atrial fibrillation. His creatinine is noted to be 1.3, above his recent normal level of 0.9 mg/dl 1 month previously. An abdominal ultrasound is done, and the kidneys appear normal. Which of the following tests would help sort out the cause of his flank pain?
   - **A.** Echocardiogram
   - **B.** CT without contrast
   - **C.** CT with and without contrast and serum lactate dehydrogenase (LDH)
   - **D.** Urine culture
   - **E.** Brain natriuretic peptide
6. A 60-year-old White man with a history of hypertension and diabetes undergoes cardiac angiography with stent placement after presenting to the emergency department with symptoms consistent with unstable angina. Three days later he is noted to have a rise in serum creatinine from a baseline of 0.8 to 1.9. Along with this rise he is noted to have a slight increase in eosinophils on his complete blood count. On examination the patient is noted to have a serpiginous rash on the bilateral lower extremities to the level of the ankles. Which of the following is the likely cause for the AKI?
   - **A.** Cardiorenal syndrome
   - **B.** Cholesterol emboli
   - **C.** Contrast-induced nephropathy
   - **D.** Acute interstitial nephritis
   - **E.** Renal infarction

42

Renal Physiology and Complications in Normal Pregnancy

Shikha Aggarwal, Mark A. Brown

RENAL PHYSIOLOGY IN NORMAL PREGNANCY

Renal physiology changes significantly in normal pregnancy. Marked volume expansion and vasodilation result in alterations in systemic and renal hemodynamics, renal size, and volume, with physiologic hydronephrosis being common. Renal plasma flow (RPF) increases by approximately 80% and glomerular filtration rate (GFR) by 50%.[1] Renal tubular function responds to these changes with alterations in water and electrolyte handling, with the predominant findings being lower serum osmolality, mild hyponatremia, and increased urinary glucose and protein (Fig. 42.1).

ANATOMY

Renal size increases by 1 to 1.5 cm bilaterally during pregnancy,[1] and there is progressive dilatation of the renal pelvis, calyces, and ureter, more prominent on the right (Fig. 42.2). These changes are thought to be due to ureteral compression by iliac vessels and/or impaired peristalsis from increased progesterone production. The dilated collecting system can hold 200 to 300 ml of urine, promoting urinary stasis and increasing the risk for pyelonephritis in women with asymptomatic bacteriuria. Renal volume increases by up to 30%, thought to be secondary to increased vascular volume rather than nephron size.[2]

HEMODYNAMIC CHANGES

Systemic

Plasma volume increases until 32 to 34 weeks of gestation, by as much as 1.25 liters. Despite an increase in red blood cells (RBCs) there is a disproportional increase in plasma causing physiologic anemia of normal pregnancy.[3] Cardiac output increases by 40% to 50% secondary to increased heart rate, stroke volume, and venous return.[4] Despite this, systemic blood pressure decreases as a result of reductions in systemic vascular resistance (SVR) thought to be due to vasodilatory factors, including prostacyclin, nitric oxide (NO), relaxin, and progesterone.

Renal

Systemic vasodilation, increased arterial compliance, and decreased vascular resistance result in increased renal perfusion and increased GFR as early as 4 weeks of gestation that peaks at 40% to 50% above baseline by the second trimester, after which there is a mild decline until term.[1] These changes result in decreased serum creatinine concentrations to a normal range of 0.4 to 0.8 mg/dl (35 to 70 µmol/l). Although a value above 0.8 mg/dl (70 µmol/l) may be normal in the nonpregnant state, in pregnancy this indicates renal dysfunction. Most clinicians view a serum creatinine value greater than 1.0 mg/dl (>90 µmol/l) as being abnormal in pregnancy. RPF increases by approximately 80% above the increment in GFR, thereby resulting in a decreased filtration fraction. Despite increased RPF, there is no change in glomerular pressure because of equal dilation of the preglomerular and postglomerular resistance vessels.

Mechanisms of Increased Glomerular Filtration Rate

The exact mechanisms behind increased GFR are not completely understood.

$$GFR = (\Delta P - \pi_{GC}) x Kf$$

where ΔP is the net hydraulic pressure in the glomerulus, π_{GC} is the oncotic pressure in the glomerulus, and Kf is the glomerular ultrafiltration coefficient. As a result of plasma volume expansion, π_{GC} is decreased in pregnancy, contributing to the rise in GFR. Changes in hydraulic permeability and the surface area for filtration may cause minor changes in Kf, and it is unclear whether ΔP changes in pregnancy.

Measuring Glomerular Filtration Rate

Estimation of GFR in pregnancy can be challenging because the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) formulas significantly underestimate true GFR.[5] The true GFR can be measured in pregnancy only by using inulin or creatinine clearance. More recent biomarkers such as cystatin C cannot yet be recommended for clinical use. However, change in GFR for an individual woman as pregnancy advances is more useful for measuring renal function than an absolute value.

Renin-Angiotensin-Aldosterone System

In early gestation, vasodilation and decreased SVR activate the renin-angiotensin-aldosterone system (RAAS) to increase renin, angiotensin II (Ang II), and aldosterone. This allows for an aldosterone-dependent increase in plasma volume, which is essential to maintain adequate uteroplacental blood flow. Maternal blood pressure (BP), however, does not increase, perhaps because of reduced responsiveness to the pressor effect of Ang II through reduced sensitivity of arterial smooth muscle and downregulation of AT1 receptors. Angiotensin (1-7) is elevated in pregnancy and may contribute to vasodilation through activation of

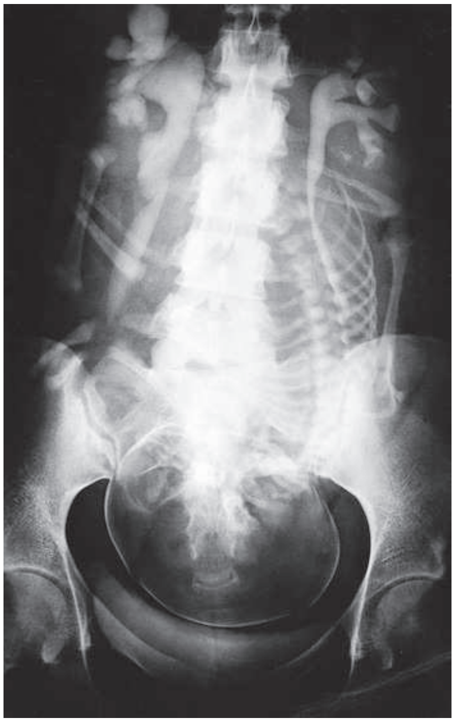

Fig. 42.1 Hydronephrosis in normal pregnancy. Intravenous urogram at 36 weeks of gestation. Note bilateral hydronephrosis, more marked on the right side.

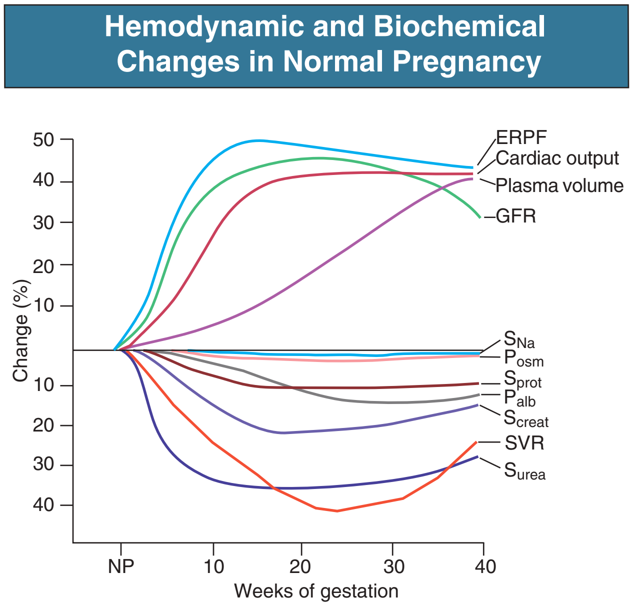

Fig. 42.2 Hemodynamic alterations induced by normal pregnancy. Increments and decrements in hemodynamic and biochemical parameters shown as percentage of change from nonpregnant baseline. *ERPF,* Effective renal plasma flow; *GFR,* glomerular filtration rate; *NP,* nonpregnant state; *S,* serum; *SVR,* systemic vascular resistance.

the Mas receptor. The ovarian hormone and vasodilator relaxin is a key mediator for enhanced NO signaling in pregnancy[6] and probably contributes to the vasodilated state of normal pregnancy. Relaxin is produced in the corpus luteum and in pregnancy is secreted in large amounts by the placenta in early gestation, peaking at 6 weeks and then returning to normal by 6 weeks postpartum.

TABLE 42.1 Changes in Some Common Indices During Pregnancy

	Nonpregnant	Pregnant
Hematocrit (%)	41	33
Serum protein (g/dl)	7.0	6.0
Plasma osmolality (mOsm/kg)	285	275
Serum sodium (mmol/l)	140	135
Serum creatinine (mg/dl, μmol/l)	0.8 (73)	0.5 (45)
Blood urea nitrogen (mg/dl)	12.7	9.3
Serum urea (mmol/l)	4.5	3.3
pH	7.40	7.44
Arterial P_{CO_2} (mm Hg)	40	30
Serum bicarbonate (mmol/l)	25	20
Serum uric acid (mg/dl, μmol/l)	4.0 (240)	3.2 (190) early 4.3 (260) late
Systolic BP (mm Hg)	115	105
Diastolic BP (mm Hg)	70	60

Mean values compiled from reference 56.
BP, Blood pressure, *P_{CO_2}, carbon dioxide partial pressure.*

RENAL TUBULAR CHANGES

The elevated GFR means that the filtered solute load is increased, though tubular reabsorption is proportionally increased. The renal handling of common solutes is discussed later (Table 42.1).

Sodium Handling and Osmoregulation

In early gestation, serum osmolality decreases by approximately 10 mOsm/kg to a new set point of about 270 mOsm/kg, with a reduction in serum sodium concentration by 4 to 5 mmol/l below nonpregnant states.[1] In pregnancy the physiologic vasopressin (AVP) release response mechanisms of thirst and are reset to recognize this new set point in osmolality; β-human chorionic gonadotrophin (β-hCG) and relaxin may play a role in this resetting. The decrease in serum sodium is thought to be secondary to systemic vasodilation, arterial underfilling, and subsequent release of AVP.[7] In addition, the natriuretic effects of increased GFR and elevated progesterone promote sodium excretion, which is balanced by increased aldosterone and Ang II directly increasing sodium reabsorption, increased deoxycorticosterone promoting sodium retention, and upregulation of the epithelial sodium channel (ENaC) sodium channel.[8] Although there is a gradual gain in total body sodium during pregnancy of about 900 to 1000 mmol, there is greater water gain (Table 42.2).

Potassium

Despite increased aldosterone and mild alkalosis in pregnancy, hypokalemia does not occur, although typical pregnancy serum K^+ concentration is at the lower limit of normal. This may be partly due to the anti-mineralocorticoid effect of progesterone and the capacity of progesterone to inhibit K^+ excretion independent of anti-mineralocorticoid effects.

Calcium

There is increased urinary excretion of calcium but also of magnesium, citrate, acidic glycoproteins, and nephrocalcin that help prevent calcium oxalate stone formation associated with calcium super-saturation.

TABLE 42.2 **Antinatriuretic and Natriuretic Factors Influencing Sodium Excretion During Pregnancy**

Antinatriuretic	Natriuretic
Aldosterone	Increased glomerular filtration rate
Angiotensin II	Progesterone
Estrogen	Atrial natriuretic peptide
Deoxycorticosterone	Nitric oxide
Epithelial sodium channel	Prostaglandins
Supine posture	
Upright posture	
Decreased blood pressure	
Increased urethral pressure	
Placental shunting	

Uric Acid

Serum uric acid falls early in pregnancy to 2.0 to 3.0 mg/dl (119 to 178 μmol/l). After 22 to 24 weeks, uric acid levels start to rise as uric acid production increases secondary to trophoblast breakdown, ischemia, and the release of cytokines. Renal tubular absorption of urate also increases.[9] By 37 weeks of gestation, serum uric acid can reach nonpregnant levels.

Acid-Base

In pregnancy there is typically chronic mild respiratory alkalosis secondary to hyperventilation that lowers arterial carbon dioxide tension. Increased minute ventilation probably results from direct stimulation of the respiratory centers by progesterone.

Urine Protein

There is a rise in urine protein excretion in normal pregnancy. The mechanisms and clinical implications of proteinuria in pregnancy are discussed later.

Glucose

Glycosuria in pregnancy occurs secondary to increased glucose filtration coupled with decreased tubular reabsorption, thought to be secondary to increased plasma volume. Once the filtered load of glucose has reached the maximum reabsorptive capacity of the proximal tubule, there is physiologic glycosuria, although serum glucose concentrations typically remain normal.

RENAL COMPLICATIONS IN NORMAL PREGNANCY

The most common renal tract problem in pregnancy in an otherwise well woman is urinary tract infection (UTI), and the most common *de novo* "renal disease" in the second half of pregnancy is preeclampsia.

URINALYSIS AND MICROSCOPY

Many young women have urinalysis and urine microscopy performed for the first time during pregnancy, leading to the detection of hematuria, proteinuria, and pyuria, either related to or coincidental to the pregnancy.

Hematuria

Definition and Epidemiology

Microhematuria is detected at some time during pregnancy in about 20% of women.[10] Clinically significant *microhematuria* is defined as three or more RBCs per high-power field on microscopic evaluation of urinary sediment from two of three properly collected (clean-catch, midstream) urine specimens,[11] or greater than 2500 RBCs/ml. Microhematuria disappears in about 75% of women after delivery, but if secondary to glomerulonephritis (GN), it persists after the pregnancy and can be further investigated postpartum.

Etiology and Outcome

Dysmorphic microhematuria (defined by phase contrast microscopy, see Chapter 4) during pregnancy is most frequently caused by primary GN or lupus nephritis but is occasionally associated with preeclampsia. *Isomorphic* hematuria is more likely to be caused by bladder infection or bladder compression by the fetal head. Isolated microhematuria has no adverse effects on pregnancy; there is similar gestational age at delivery and no difference in birth weight, gestational hypertension, or preeclampsia.[12]

Macrohematuria (gross hematuria) in pregnancy is most often the result of vaginal bleeding or hemorrhagic bacterial cystitis. Other, less common causes include renal calculi, renal arteriovenous malformations, renal vein thrombosis, polycystic kidneys, and, rarely, bladder or kidney neoplasms.

Differential Diagnosis

When microhematuria is found, a urine culture is required to exclude infection. If there is no proteinuria, and BP and serum creatinine values are normal, further investigations can be delayed until 3 months postpartum, when microscopy to determine RBC morphology, serologic tests including antinuclear antibody (ANA) testing, and renal ultrasound can be performed. When there are significant numbers of dysmorphic urinary RBCs in pregnancy and BP is normal, the most likely cause is GN, for example, thin basement membrane nephropathy, IgA nephropathy, or lupus nephritis. As in nonpregnant women, ultrasound will exclude the presence of stones in only two thirds of pregnant women with calculi but may demonstrate other abnormalities such as polycystic kidneys and in rare cases neoplasms. For persistent isomorphic microhematuria, we do not recommend cystoscopy during pregnancy. This microhematuria often disappears spontaneously after pregnancy, and the likelihood of urothelial tumors is very low in this age group.

Treatment

The treatment of associated UTI and calculi is discussed later. There is no specific treatment for GN during pregnancy, provided renal function is normal and nephrotic syndrome and lupus are absent.

Proteinuria

Proteinuria during pregnancy warrants investigation and will most often be associated with preeclampsia, but renal disease secondary to GN or systemic conditions such as diabetes or essential hypertension may be detected first in pregnancy and present with proteinuria. *Gestational proteinuria* (isolated *de novo* proteinuria with no features of preeclampsia) also may develop, and this has no adverse effects for fetus or mother.

Definition

There is a rise in urine protein excretion in normal pregnancy that may continue into the postpartum period and may take 5 to 6 months to resolve.[13] The increase is greater in twin pregnancy. Some studies suggest this results from a combination of increased GFR and increased permeability of the glomerular basement membrane, whereas other studies implicate increased tubular proteinuria.

Abnormal urine protein excretion is defined as greater than 150 mg/day in nonpregnant women, and proteinuria in pregnancy is generally defined as total urine protein greater than 300 mg/day, though more than 95% of pregnant women excrete less than 200 mg/day.[14]

Proteinuria is most frequently detected in pregnancy by dipstick urinalysis, but this method is notoriously unreliable, with a significant proportion of false-positive and false-negative results.[15] These false results are usually secondary to the variable osmolality of a random urine specimen. Other causes of false-positive results include macrohematuria, alkaline urine (pH >7.0), and the presence of radiocontrast agents or additives in the urine collection container. False-negative results may occur with acidic urine, low specific gravity (<1.001) or high salt concentration. A negative dipstick result is generally reliable, although not perfect, for confirming the absence of proteinuria or true proteinuria when dipstick readings are 3+ (>3 g/l) or 4+ (>20 g/l). At intermediate levels, false-positive rates are as high as 50%. Detection may be improved using an automated urinalysis device, thereby reducing observer error.

The 24-hour urine collection remains the gold standard for quantitation but is impractical when a quick assessment of proteinuria is required, as in preeclampsia. A reliable alternative is the ratio of urine protein to creatinine (uPCR); a ratio greater than 30 mg protein/mmol creatinine (~0.3 mg/mg) correlates reasonably well for urine protein greater than 300 mg/24 h.[16]

The albumin-to-creatinine ratio correlates with the uPCR but offers no greater clinical advantage, and clinicians should continue to use the protein-to-creatinine ratio until further data are available.[16]

Differential Diagnosis

Proteinuria arising *de novo* in pregnancy should be quantitated and further investigated according to the clinical situation. The course of pregnancy in women with proteinuria present before pregnancy is discussed in Chapter 43.

Persistent proteinuria associated with preeclampsia usually arises in the second half of pregnancy (>20 weeks) and generally but not always after the development of hypertension. The severity of the proteinuria is not indicative of the severity of preeclampsia and should not be used to guide management. Furthermore, proteinuria may be absent in up to 25% of women with other clinical manifestations of preeclampsia and is no longer mandatory for a diagnosis of preeclampsia. In the absence of preeclampsia, isolated proteinuria in an otherwise asymptomatic pregnant woman usually reflects gestational proteinuria or new-onset renal disease such as primary GN. Alternatively, proteinuria may appear because pregnancy has unmasked renal disease secondary to systemic disorders such as diabetes mellitus, systemic lupus, or chronic hypertension.

We limit investigation of *de novo* non-preeclamptic, non-nephrotic proteinuria during pregnancy to a renal ultrasound and the measurement of serum creatinine concentration, electrolyte concentrations, albumin, and ANA titers. A renal biopsy is not indicated. When underlying renal disease has been unmasked by pregnancy, appropriate investigations usually can be delayed until the postpartum period. The exceptions to this are women with nephrotic syndrome or renal impairment in whom prompt delivery is not desired (i.e., <24 weeks of gestation). In these patients, full investigation should be undertaken quickly, often including a renal biopsy, to determine whether specific treatment (e.g., corticosteroids) may be of benefit.

Natural History

Proteinuria occurring as a complication of preeclampsia invariably resolves in the postpartum period. Gestational proteinuria (i.e., new-onset proteinuria without features of preeclampsia) also resolves postpartum. Tradition holds that in both cases, proteinuria disappears within 3 months postpartum, but many cases take longer. In the absence of impaired renal function, we do not investigate non-nephrotic proteinuria unless it persists after 12 months postpartum.

Treatment

For women with nephrotic syndrome, an inverse correlation exists between serum albumin and birth weight, although no studies have examined whether reducing proteinuria can reverse reduced fetal growth. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated in pregnancy because of their unwanted effects on the fetus.

Intravenous albumin has little role in managing nephrotic syndrome during pregnancy unless there is progressive deterioration in renal function. We recommend intravenous albumin infusion when serum creatinine rises above 100 µmol/l (1.2 mg/dl) with no other explanation, acknowledging that this may provide only a temporary benefit. Diuretics and sodium restriction should be avoided unless the woman has severe, intractable edema; the concern is that diuretics will lead to a further reduction in plasma volume and reduced uteroplacental perfusion. The pregnant woman with nephrotic syndrome is at high risk for venous thromboembolism and should receive prophylactic anticoagulation therapy during pregnancy and until the nephrotic syndrome has resolved postpartum.

Pyuria

Isolated pyuria without UTI is common in normal pregnancy, usually from contamination by vaginal secretions. There is also an increased white blood cell excretion rate in normal pregnancy. It requires no further follow-up other than ensuring it disappears, usually by 3 months postpartum.

URINARY TRACT INFECTION

Definitions

In asymptomatic bacteriuria (ASB), the urinary tract is colonized by a single species of bacteria in the absence of specific symptoms. Outside of pregnancy, ASB usually should not be treated with antibiotics. The traditional view is that ASB can lead to serious complications in pregnancy (e.g., pyelonephritis), and there is a cost benefit from its screening and treatment.[17] This view has recently been challenged,[18] but for now we recommend it is safest to continue to adopt concern about the risks for ASB in pregnancy until further trials examine this issue. Although the gold standard for diagnosis is detection of more than 10^5 organisms per milliliter, without epithelial cells, in a midstream urine specimen on two or more occasions, in practice, bacteriuria is usually detected by a single routine bacterial culture early in pregnancy. As many as 1% to 2% of pregnancies are complicated by *acute bacterial cystitis,* defined as an acute bacterial UTI accompanied by symptoms such as frequency, dysuria, or strangury. Although more than 10^5 organisms per milliliter defines ASB, as few as 10^2 organisms per milliliter is sufficient to diagnose cystitis if accompanied by pyuria and characteristic symptoms. In *acute pyelonephritis* there are generally more than 10^5 organisms per milliliter in the urine, in association with parenchymal bacterial infiltration. This is usually diagnosed clinically by fever, loin pain, and sometimes systemic sepsis.

Epidemiology

ASB affects 2% to 10% of all pregnant women. The prevalence is higher in women from lower socioeconomic groups and increases with age, parity, coexistent genital tract infection, and sickle cell trait. ASB is

BOX 42.1 Organisms Typically Causing Urinary Tract Infection in Pregnancy

- *Escherichia coli* (>70% of infections)
- *Klebsiella* spp.
- *Proteus* spp. (particularly in diabetic women or urinary tract obstruction)
- Enterococci
- Staphylococci, especially *Staphylococcus saprophyticus*
- *Pseudomonas*

more common in women with urinary tract abnormalities such as reflux nephropathy and neurogenic bladder, in diabetic patients, and in women with previous UTIs.

The overall incidence of acute pyelonephritis in pregnancy is approximately 1%, but it may occur in up to 30% of women with ASB. It is thought that about 70% of women who develop acute pyelonephritis have preceding covert bacteriuria, but this is difficult to prove. With treatment of ASB, it has been estimated that the incidence of pyelonephritis would be reduced by more than 80%. When possible, urethral catheters should be avoided, even in women having cesarean section, because the incidence of UTI in these women is twice that of those not catheterized.

Pathogenesis

Certain host characteristics may increase the risk for UTI or pyelonephritis (see Chapter 51). Women, such as those who do not express the antibody to the O antigen of *Escherichia coli,* may have ASB that predates pregnancy (i.e., are chronically colonized). Pregnancy is a state of relative urinary tract stasis; the calyces, pelves, and ureters dilate, particularly on the right, and this contributes to ASB developing into ascending acute pyelonephritis. The most common mechanism of infection is through the urethra from perineal bacteria. Box 42.1 lists common organisms causing UTI in pregnancy. Some strains of *E. coli* are particularly virulent and are associated with both ASB and pyelonephritis. They possess fimbriae, which enable the bacteria to attach themselves to the uroepithelial cells with pili, allowing them to ascend the urinary tract from the perineum. Unfortunately, infection with multi-resistant organisms is becoming more common.

Clinical Manifestations

Asymptomatic Bacteriuria

A Cochrane systematic review has indicated that treatment of ASB during pregnancy reduces the incidence of pyelonephritis, low birth weight, and preterm delivery.[19] More recent evidence challenges this. The mechanism by which UTI may cause premature labor is not fully understood, but proinflammatory cytokines secreted in response to bacterial endotoxins likely initiate labor in these women.

Most maternity units operate a policy of screening all pregnant women at least once, whether by dipstick urinalysis for leukocytes or nitrites or by urine culture. Both dipstick and urine culture appear cost-effective compared with no screening when the prevalence of ASB is 2% to 6%. Because isolated pyuria on dipstick testing is very common in normal pregnancy, we recommend screening by primary urine culture rather than the dipstick method.

Pyelonephritis

Pyelonephritis most often presents between 20 and 28 weeks of gestation. Not all women will have had lower urinary tract symptoms, and pyelonephritis also can manifest in pregnancy as acute abdominal pain or may be detected only after presentation with premature labor. Pyelonephritis is more common in pregnant women with urologic abnormalities or diabetes and more often affects the right kidney, probably because the ureter is generally more dilated on that side.

The diagnosis of pyelonephritis is usually made on clinical grounds. Definitive diagnosis requires positive urine culture, but this may take about 2 days, and treatment should not be delayed. *E. coli* is the most common infecting organism (>85% of cultures).

Bacteremia is a common and usually transient complication of pyelonephritis. Occasionally, however, women become septicemic and may develop endotoxemia with shock, with sequelae including respiratory failure, disseminated intravascular coagulation (DIC), and acute kidney injury (AKI). Pyelonephrosis and perinephric abscess are rare complications but should be suspected when treatment fails.

Without treatment, the complications of acute pyelonephritis during pregnancy can be severe, probably more so than in nonpregnant women. In the preantibiotic era, maternal mortality was 3% to 4%; death from pyelonephritis is now rare in developed countries.

Treatment

Asymptomatic Bacteriuria

For now we agree that antibiotic treatment of ASB significantly reduces the incidence of pyelonephritis in pregnancy and thereby reduces the risk for preterm delivery.[19]

In choosing treatment, the clinician must consider the safety of the antibiotic in pregnancy. In most women, treatment with cephalexin, amoxicillin–clavulanic acid, or nitrofurantoin is first-line therapy. Overall, trials demonstrate that longer duration of treatment is likely to be more effective than single-dose therapy, although data are limited.[20] Until evidence from new trials is available, a 3- to 7-day treatment regimen is recommended.

Without treatment, ASB will persist in 80% of women, and even with treatment 20% will still have ASB. Those with persistent colonization are difficult to treat, with eradication achieved in only 40% after a second course of antibiotics. Where eradication is not achieved, we recommend prophylactic antibiotics, usually cephalexin 250 mg at night, throughout pregnancy to prevent pyelonephritis and its consequences; however, no studies specifically address this situation. The incidence of pyelonephritis after effective treatment of ASB is reduced from about 30% to 3%, comparing favorably with a 1% prevalence of pyelonephritis for the overall pregnant population.

Cystitis

Treatment of cystitis at the first presentation should be for 5 days with an appropriate antibiotic. As for ASB, it is important to obtain a follow-up urine culture to be certain infection has been eradicated.

Pyelonephritis

It is usual practice to admit pregnant women with pyelonephritis to hospital, although a trial has reported successful outpatient management for milder cases.[20] Treatment may occasionally require resuscitation with intravenous (IV) fluids, but usually a short course of IV antibiotics followed by oral antibiotics, once the woman is afebrile, is adequate therapy.

A cephalosporin is usual first-line treatment with addition of an aminoglycoside in more severe cases, used for 24 to 48 hours while awaiting urine cultures, provided maternal renal function is satisfactory. The risk for irreversible fetal ototoxicity precludes prolonged use, and aminoglycosides are not recommended in the first trimester. The full duration of treatment is generally 2 weeks, and it is imperative to repeat urine culture 1 week after treatment to ensure eradication. We then recommend prophylactic antibiotics such as cephalexin 250 mg at night until delivery, to prevent further episodes and preterm labor. Periodic urine culture is also recommended to monitor the risk for antibiotic

TABLE 42.3 Antibiotic Regimens for Treatment for Urinary Tract Infections in Pregnancy*

Antibiotic	Dose	Duration
Acute Cystitis		
Amoxicillin	500 mg three times daily	3-5 days
Nitrofurantoin	100 mg four times daily	3-5 days
Cephalexin	500 mg three times daily	3-5 days
Asymptomatic Bacteriuria		
Cephalexin	500 mg three times daily	3 days
Amoxicillin	500 mg three times daily	3 days
Amoxicillin–clavulanic acid	500 mg three times daily	3 days
Nitrofurantoin	50 mg four times daily	3 days
Fosfomycin	3 g single dose	
Recurrent Bacteriuria or Cystitis		
Cephalexin	250 mg nighttime (or postcoital)	
Nitrofurantoin	50 mg nighttime (or postcoital)	
Amoxicillin	250 mg nighttime (or postcoital)	
Pyelonephritis (Initial Intravenous Therapy)		
Ceftriaxone	1 g daily	
Cephazolin	1g every 8 hours	
Ampicillin (with gentamicin)	1 g every 6 hours	
Gentamicin	3 mg/kg daily	
Ticarcillin	3.2 g every 8 hours	
Piperacillin	4 g every 8 hours	

*Avoid tetracyclines at all stages and sulfamethoxazole (in the third trimester) and use aminoglycosides only when other drugs are not suitable.

resistance and to decrease the risk for prematurity resulting from recurrent infection.

Renal ultrasound is generally not indicated during an initial infection, because urinary tract dilation is common, and cannot be distinguished from urinary tract obstruction. However, if infection persists, ultrasound is indicated to help exclude pyelonephritis, perinephric abscess, and renal calculi. If pyelonephritis persists despite adequate antibiotic therapy and urinary tract dilation is confirmed, percutaneous nephrostomy should be performed under ultrasound guidance. In our experience, this is rarely necessary, but nephrostomy is the only way to be certain that urinary tract obstruction and pyelonephritis have been properly treated.

Clinicians also should remain alert for premature labor in the presence of pyelonephritis and institute appropriate treatment while aggressively treating the infection. When more than two UTIs have occurred in pregnancy, prophylaxis is indicated until delivery with either nitrofurantoin 50 mg or cephalexin 250 mg at night. Table 42.3 outlines some antibiotic regimens suitable for use in pregnancy.

RENAL CALCULI

Epidemiology

Despite normal pregnancy being an ideal environment for renal stone formation, the incidence of renal calculi remains similar in pregnant and nonpregnant women, in the range of 0.03% to 1%.

Pathogenesis

The majority of stones are formed from calcium oxalate and calcium phosphate. Struvite stones are the next most common, usually when the urinary tract is infected with organisms such as *Proteus* spp. Small proportions of renal stones are formed from uric acid or cystine. Although pregnancy is a physiologic state of relative urinary stasis and increased calcium and uric acid excretion, this is balanced against enhanced excretion of inhibitors of stone formation, such as magnesium, citrate, and the glycoprotein nephrocalcin.

Clinical Manifestations

Symptomatic stones during pregnancy are rare, usually presenting in the second or third trimester with acute flank pain radiating to the groin or lower abdomen and hematuria. However, clinical features of renal calculi may be more difficult to interpret in pregnancy because frequent episodes of diffuse, poorly localized abdominal pain and lower urinary tract symptoms are relatively common in normal pregnancy.

Approximately 75% to 85% of stones will pass spontaneously during pregnancy, and some women with calculi will have a concomitant UTI. Pregnant women with renal calculi are at greater risk for superimposed pyelonephritis and complications including preterm labor, hypertensive disorders, gestational diabetes, and cesarean deliveries.[21]

The diagnosis of renal calculi in pregnancy is difficult because of the risk for radiation to the fetus if investigating the urinary tract with computed tomography (CT). Ultrasound will detect hydronephrosis (usually as part of normal pregnancy) and will often detect calculi within the kidney, but ultrasound rarely finds ureteral stones and is less accurate than CT for this purpose. If pain persists, transvaginal ultrasound should be performed when transabdominal ultrasound is uninformative, to detect distal ureteral stones. If symptoms persist and further diagnosis is required, magnetic resonance (MR) urography or low-dose CT (in second or third trimester) can be used, although in our experience, this is rarely needed.

Treatment

Initial management of renal calculi is conservative, with appropriate hydration, antiemetics, and analgesia. The woman should lie on her side, with the symptomatic side up, enabling relief of pressure on the ureter from the gravid uterus. Calcium intake should not be limited, but women in whom calcium oxalate stones form persistently can limit foods high in oxalate, such as spinach, rhubarb, and chocolate. Urine should always be cultured and appropriate antibiotics administered when a UTI is suspected.

Quantitation of urine calcium, uric acid, or other mineral excretion is not necessary in pregnancy, because specific pharmacologic agents to modify excretion (including thiazides and allopurinol) are contraindicated. Investigations can be completed postpartum.

Surgical intervention is considered only when stones cause persistent obstruction, deteriorating renal function, intractable pain or infection, or premature labor unresponsive to other treatment. This is a rare situation. Both cystoscopy with ureteral stenting and ureteroscopic removal of stones have been reported.[22] Lithotripsy is generally contraindicated during pregnancy because of the presumed adverse effect of the shock waves on the fetus; however, some centers have used ureteroscopic laser lithotripsy in pregnant women.[22] Although not recommended for routine use, extracorporeal shock wave lithotripsy has been reported as an inadvertent procedure in six women in the first month of pregnancy, all of whom subsequently delivered normal infants.[22]

Postpartum follow-up is important. In the absence of ongoing symptoms, we perform a CT scan of kidney, ureters, and bladder 3 months later. This delay is necessary because calyceal and ureteral dilation may persist well after delivery and may cause confusion. Women planning a further pregnancy should be assessed for idiopathic hypercalciuria or other causes of renal calculi after a minimum of 3 months postpartum.

HYPERTENSION IN PREGNANCY

Definitions

There are four major hypertensive disorders related to pregnancy (Fig. 42.3).

Hypertension in pregnancy is defined as BP of 140 mm Hg or greater systolic or 90 mm Hg diastolic. Normal pregnancy is characterized by a decrease in BP, beginning in the first trimester and reaching a nadir in the second trimester. BP rises toward preconception levels near the end of the third trimester. A BP increment of 30 mm Hg or greater systolic and/or 15 mm Hg diastolic but still below 140/90 mm Hg warrants increased frequency of follow-up. By itself, this BP increase does not diagnose gestational hypertension or preeclampsia, but in the presence of proteinuria, this may signify preeclampsia in some women.

The development of newly elevated BP after 20 weeks of gestation without evidence of maternal organ dysfunction is known as *gestational hypertension*. This should usually resolve by 12 weeks postpartum. If hypertension persists beyond that, the diagnosis is likely chronic/preexisting hypertension that has been masked by the physiologic decrease in BP that occurs in early pregnancy. However, some women with preeclampsia or gestational hypertension may take longer for their high BP to resolve.

Preeclampsia is hypertension developing in the second half of pregnancy, but this more serious disorder includes accompanying evidence of maternal renal, cerebral, hepatic, cardiac dysfunction, or clotting abnormalities and fetal growth restriction. Neither proteinuria nor edema are now considered necessary for a diagnosis of preeclampsia. The International Society for the Study of Hypertension in Pregnancy (ISSHP)[23] defines preeclampsia as *de novo* hypertension manifesting after 20 weeks of gestation combined with one or more of the following:

1. Proteinuria (spot urine protein/creatinine >30 mg/mmol [0.3 mg/mg] or >300 mg/day or at least 1 g/l [2+] on dipstick testing)
2. Other maternal organ dysfunction: Renal impairment (serum creatinine ≥90 μmol/l [1 mg/dl]), liver involvement (elevated transaminases—at least twice the upper limit of normal ± right upper quadrant or epigastric abdominal pain), neurologic complications (e.g., eclampsia, altered mental status, blindness, stroke, or, more commonly, hyperreflexia with clonus, severe headaches with hyperreflexia, persistent visual scotomata), hematologic complications (thrombocytopenia—platelet count below 150×10^9/l, DIC, hemolysis)
3. Uteroplacental dysfunction: Fetal growth restriction

Chronic/preexisting hypertension is BP greater than 140/90 mm Hg that antedates pregnancy or is present before the 20th week of pregnancy

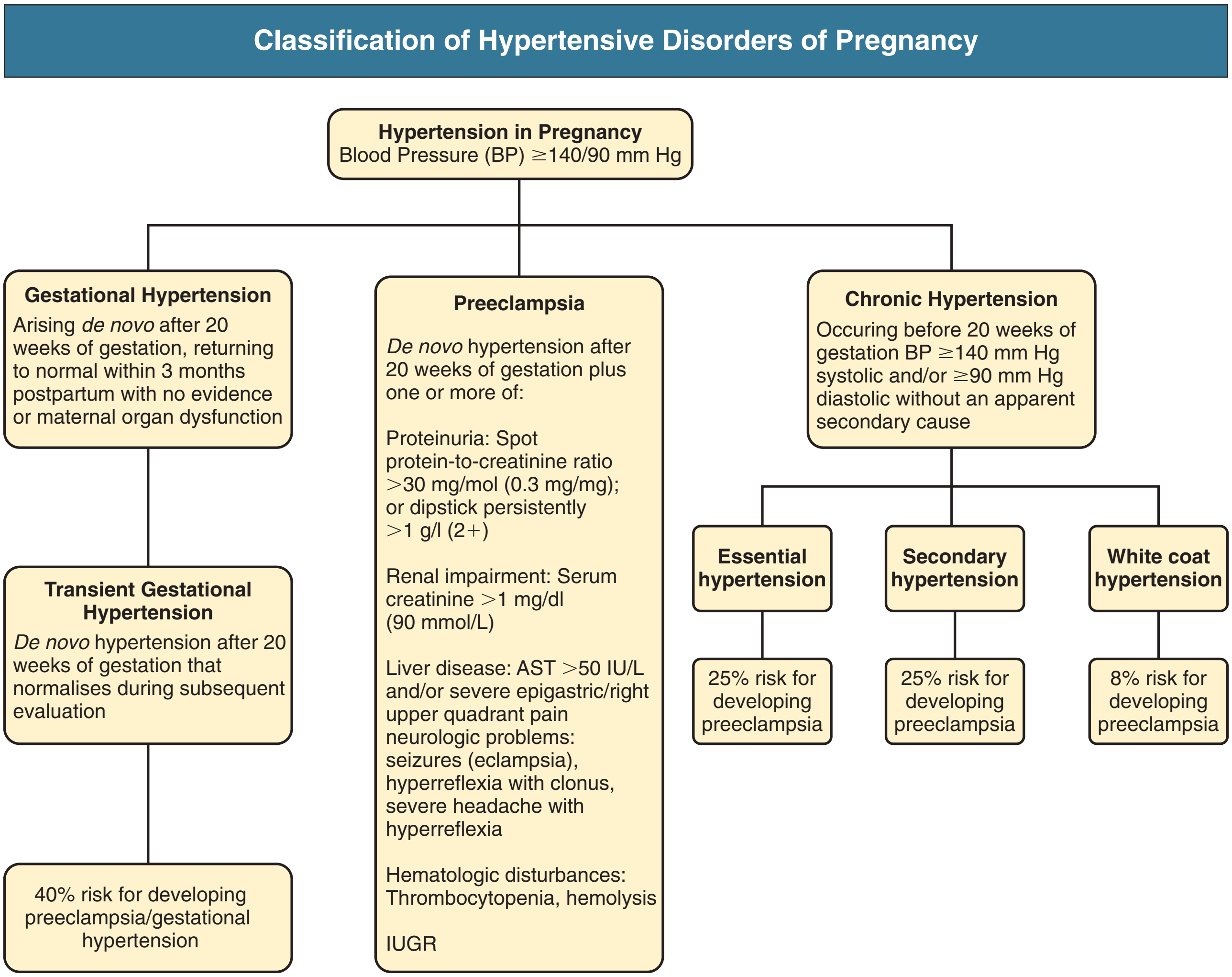
Classification of Hypertensive Disorders of Pregnancy
Hypertension in Pregnancy
Blood Pressure (BP) ≥140/90 mm Hg
Gestational Hypertension
Arising de novo after 20 weeks of gestation, returning to normal within 3 months postpartum with no evidence or maternal organ dysfunction
Transient Gestational Hypertension
De novo hypertension after 20 weeks of gestation that normalises during subsequent evaluation
40% risk for developing preeclampsia/gestational hypertension
Preeclampsia
De novo hypertension after 20 weeks of gestation plus one or more of:
Proteinuria: Spot protein-to-creatinine ratio >30 mg/mol (0.3 mg/mg); or dipstick persistently >1 g/l (2+)
Renal impairment: Serum creatinine >1 mg/dl (90 mmol/L)
Liver disease: AST >50 IU/L and/or severe epigastric/right upper quadrant pain neurologic problems: seizures (eclampsia), hyperreflexia with clonus, severe headache with hyperreflexia
Hematologic disturbances: Thrombocytopenia, hemolysis
IUGR
Chronic Hypertension
Occuring before 20 weeks of gestation BP ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic without an apparent secondary cause
Essential hypertension
Secondary hypertension
White coat hypertension
25% risk for developing preeclampsia
25% risk for developing preeclampsia
8% risk for developing preeclampsia

Fig. 42.3 Classification of hypertensive disorders of pregnancy. *AST,* Aspartate aminotransferase; *BP,* blood pressure; *IUGR,* intrauterine growth restriction.

(on at least two occasions) or persists beyond 12 weeks postpartum. This should be confirmed by 24-hour ambulatory BP monitoring or home self-monitoring, to exclude *white coat hypertension,* which is common in pregnancy.[24] Superimposed preeclampsia is the development of new proteinuria or new renal dysfunction, thrombocytopenia, neurologic features, or abnormal liver function after 20 weeks of gestation in a woman with chronic/preexisting hypertension.

Eclampsia (seizures) is now uncommon in developed countries, with a prevalence of about 0.3% of hypertensive pregnancies. In developing countries, eclampsia is much more common, with greater risks for maternal mortality and morbidity, as well as perinatal mortality.

Epidemiology

Hypertensive disorders of pregnancy are the second most common cause for maternal death worldwide, after hemorrhage.[24] Hypertension affects 10% to 12% of all pregnancies, and tertiary referral units tend to have a higher proportion of severe preeclamptic cases. In general, primary chronic hypertension accounts for about 20% and preeclampsia and gestational hypertension each about 40% of cases. About one in four women with apparent primary hypertension early in pregnancy have white coat hypertension, and their outcomes are better than those with true chronic hypertension. Women with white coat hypertension may be managed without medication through regular home BP monitoring. A small proportion will go on to develop preeclampsia.[24]

PREECLAMPSIA

Epidemiology

Preeclampsia follows no recognized racial patterns, and no specific genotype-phenotype relation has been associated with this disorder.[25] It remains a major contributor to maternal, fetal, and neonatal mortality worldwide.[26] Box 42.2 lists risk factors for preeclampsia. The risk is highest in those with a history of preeclampsia, with rates ranging from 15% to 65% depending on the gestation at onset of the preeclampsia and in women with assisted reproduction, antiphospholipid syndrome, diabetes, obesity, and chronic hypertension.[27] Risk for preeclampsia is usually higher in a first pregnancy. The reduced risk for preeclampsia in subsequent pregnancies is intriguing. However, the risk returns to that of a first pregnancy in women who have a new partner. This observation, combined with an increased likelihood of preeclampsia in women who have used barrier methods of contraception, raised the possibility of an impaired immunologic response to paternal antigens in such pregnancies. However, this may be explained simply by a longer interpregnancy interval rather than a change of partners, with the incidence increasing after about 7 years between pregnancies.

Smoking reduces the risk for preeclampsia by a third, but increases the risk for preterm labor, intrauterine growth restriction (IUGR), and placental abruption.[28]

Pathogenesis

The pathogenesis of preeclampsia is complex. The placenta likely causes preeclampsia, with other maternal organs (e.g., kidney) amplifying the disease process (Fig. 42.4). This is supported by the observation that preeclampsia can occur in hydatidiform mole, where the fetus is absent, with the condition resolving when the placenta is removed. Preeclampsia is considered a maternal endothelial disorder made up of two stages: (1) placental ischemia and/or hypoxia secondary to abnormal placental implantation or a placental oxygen demand mismatch and (2) ischemia-reperfusion injury resulting in a maternal inflammatory syndrome. The following key mechanisms are involved in the progression to the clinical preeclamptic syndrome:

BOX 42.2 Risk Factors for Preeclampsia

Maternal Obstetric Factors
- Nulliparity
- Multiple-gestation pregnancy
- History of previous preeclampsia
- Prior intrauterine growth restriction
- Prior placental abruption
- Artificial reproductive technology
- Molar pregnancy
- Trisomy 13 or fetal hydrops
- Gestational diabetes

Obstetric Paternal Factors
- Father born from preeclamptic pregnancy
- Family history of preeclampsia

Maternal Comorbid Conditions
- Chronic hypertension
- Chronic kidney disease
- Pregestational diabetes
- Obesity (body mass index >30 kg/m^2)
- Antiphospholipid antibody
- Systemic lupus erythematosus
- Polycystic ovarian syndrome

Maternal Genetic Factor
- Thrombophilia
- Preeclampsia in pregnancy of first-degree relative

Other Maternal Factors
- Age older than 40 years
- Having been born small for gestational age
- Pregnancy interval greater than 10 years

Maternal risk factors determined at 16 weeks of gestation
Modified from reference 27.

- *The immune response at the placental-maternal interface.* The fetal-maternal immunologic interaction at placentation involves maternal natural killer (NK) cells, immunoglobulin-like receptors, and fetal human leukocyte antigen (HLA-C and HLA-G) molecules. This interaction fails in preeclampsia, leading to an abnormal interaction among uterine NK cells, trophoblastic cells, and macrophage-derived tumor necrosis factor α (TNF-α).
- *Superficial placentation with insufficient remodeling of spiral arteries.* In normal pregnancy, invasive cytotrophoblasts penetrate the walls of the spiral arteries, where they replace maternal endothelium, converting them to capacitance vessels capable of carrying greater blood flow through the placenta and reducing their capacity for vasoconstriction. In preeclampsia the spiral arteries often fail to undergo this transformation resulting in uteroplacental ischemia and making them more prone to the lesion of acute atherosis and inflammation. There is also a hypoxic microenvironment, indicated by the finding of hypoxia-inducible factor 1 α (HIF-1α), a marker of cellular oxygen deprivation, in placentas of women with preeclampsia.[29] It remains unclear how commonly this is due to structural changes in the spiral arteries or an oxygen demand-supply mismatch in the placenta.
- Imbalance of angiogenic factors and Ang II type 1 receptor autoantibodies.

  Angiogenic and anti-angiogenic factors implicated in the pathogenesis of preeclampsia include placental growth factor (PlGF), vascular

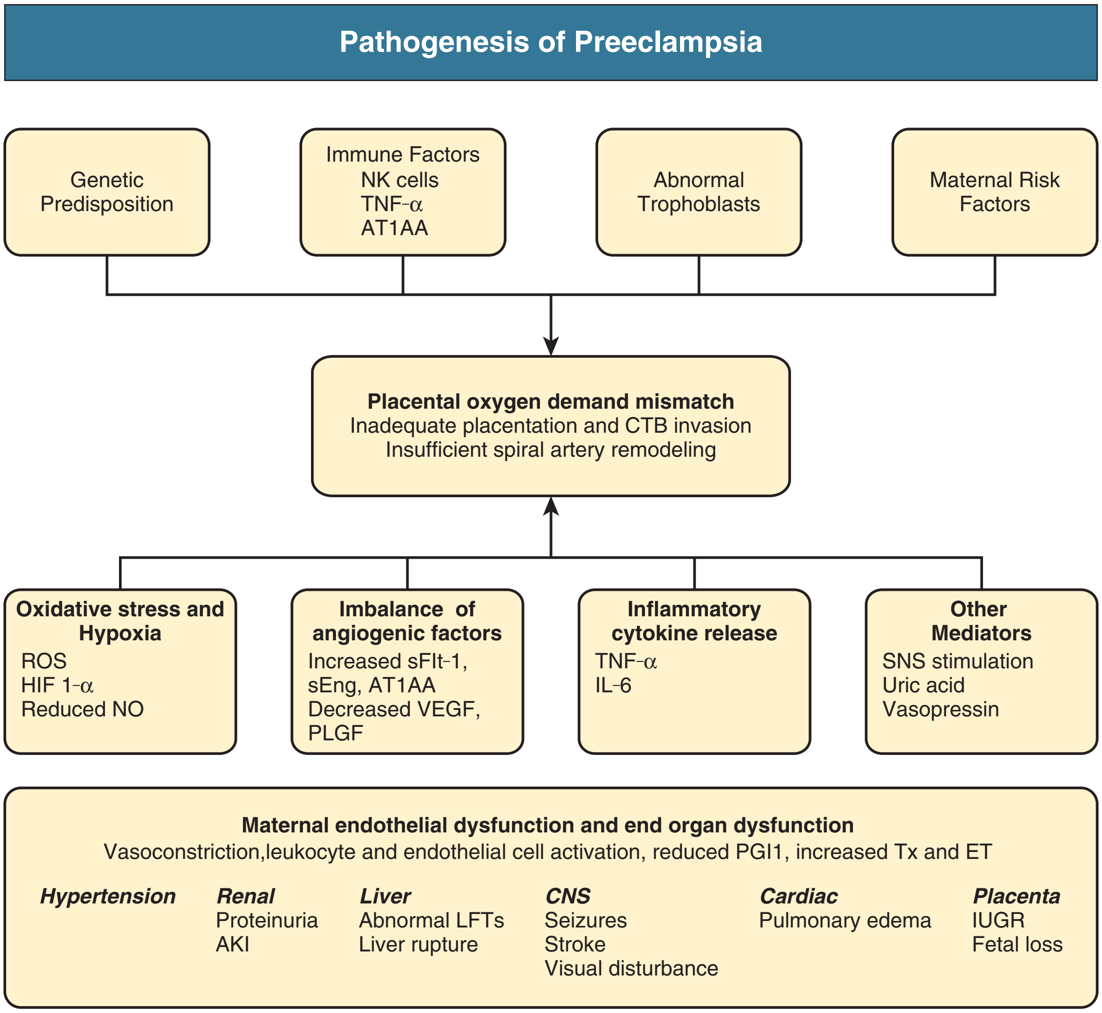
Pathogenesis of Preeclampsia
Genetic Predisposition
Immune Factors
NK cells
TNF-α
AT1AA
Abnormal Trophoblasts
Maternal Risk Factors
Placental oxygen demand mismatch
Inadequate placentation and CTB invasion
Insufficient spiral artery remodeling
Oxidative stress and Hypoxia
ROS
HIF 1-α
Reduced NO
Imbalance of angiogenic factors
Increased sFlt-1, sEng, AT1AA
Decreased VEGF, PLGF
Inflammatory cytokine release
TNF-α
IL-6
Other Mediators
SNS stimulation
Uric acid
Vasopressin
Maternal endothelial dysfunction and end organ dysfunction
Vasoconstriction,leukocyte and endothelial cell activation, reduced PGI1, increased Tx and ET
Hypertension
Renal
Proteinuria
AKI
Liver
Abnormal LFTs
Liver rupture
CNS
Seizures
Stroke
Visual disturbance
Cardiac
Pulmonary edema
Placenta
IUGR
Fetal loss

Fig. 42.4 Pathogenesis of preeclampsia. *AT1AA,* Angiotensin-II type 1 receptor autoantibodies; *CNS,* central nervous system; *CTB,* cytotrophoblast; *ET,* endothelin; *HIF-1,* hypoxia inducible factor 1; *IL-6,* interleukin 6; *IUGR,* intrauterine growth restriction; *NK cells,* natural killer cells 1; *NO,* nitric oxide; *PlGF,* placental growth factor; *PGI2,* prostacyclin; *ROS,* reactive oxygen species; *sEng,* soluble endogolin; *sFlt-1,* soluble fms-like tyrosine kinase 1; *SNS,* sympathetic nervous system; *TNF,* tumor necrosis factor; *Tx,* thromboxane; *VEGF,* vascular endothelial growth factor. (Modified from reference 29.)

endothelial growth factor (VEGF-A), the VEGF receptor soluble fms-like tyrosine kinase 1 (sFlt-1), transforming growth factor-β (TGF-β), and soluble endoglin (sEng).[30] There is an excess of syncytiotrophoblast-derived anti-angiogenic factors, such as sEng and sFlt-1, thought to be triggered by placental ischemia or hypoxia. In the serum, sFlt-1 binds to VEGF and PlGF, preventing their interaction with endothelial receptors on the cell surface, inducing endothelial dysfunction and increasing sensitivity to pro-inflammatory factors such as TNF-α (Fig. 42.5). In addition, sEng, a cell surface coreceptor of TGF-β induces proliferation and migration of endothelial cells. High concentrations as seen in preeclampsia result in interference with NO signaling, vasoconstriction, and increased vascular permeability. Ang II type 1 receptor autoantibodies (AT1AA), often present in preeclampsia, may contribute to the hypertension, increased production of reactive oxygen species (ROS), increased thrombin generation, impaired fibrinolysis, endothelial cell damage, and impaired trophoblast invasiveness seen in preeclampsia.[29] However, further study is required to identify the exact role of AT1AA in preeclampsia pathogenesis.

- *Oxidative stress that triggers inflammation.* Maternal blood enters the intervillous space at higher pressure and faster rate when there is impaired arterial remodeling of the spiral arteries. This exposes the placental villi to fluctuating oxygen concentrations, leading to oxidative stress and activation of nuclear factor-κB, a transcription factor central to the inflammatory response. Increase in necrotic trophoblast shedding occurs and may be important in the pathogenesis of preeclampsia through systemic endothelial cell activation by secretion of interleukin-6 (IL-6). Microparticles derived from placental syncytiotrophoblasts in maternal plasma interact with leukocytes and monocytes and stimulate production of proinflammatory cytokines.

Thus abnormal placentation leads to an imbalance in angiogenic factors and oxidative stress that triggers inflammation. The resulting insufficient placental function, release of placental factors into the

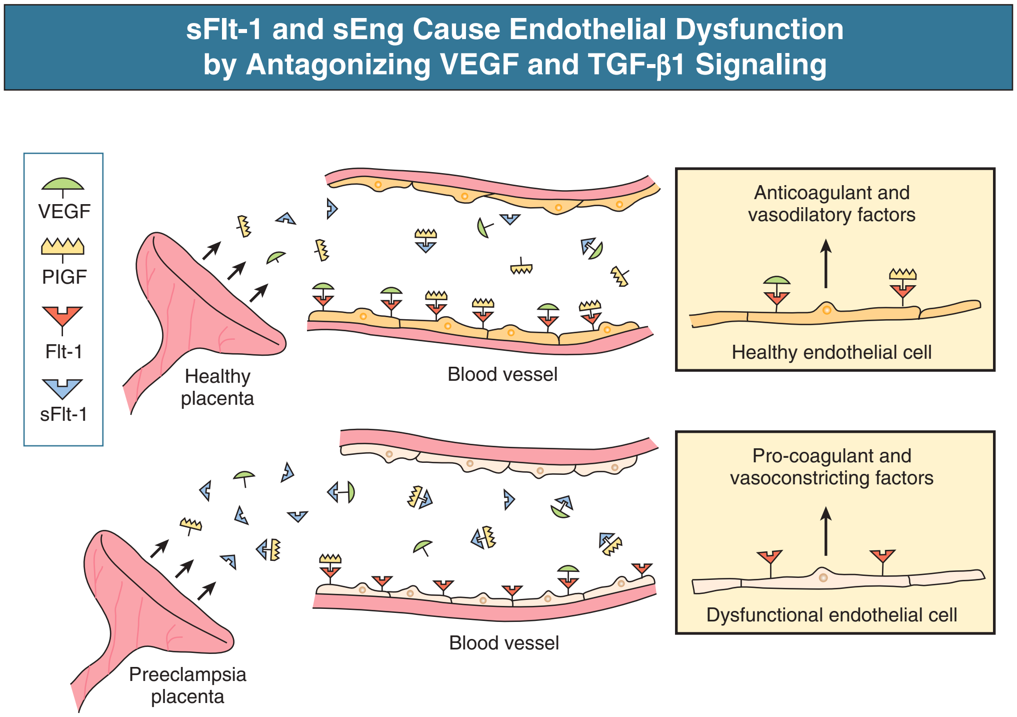
sFlt-1 and sEng Cause Endothelial Dysfunction by Antagonizing VEGF and TGF-β1 Signaling
VEGF
PIGF
Flt-1
sFlt-1
Healthy placenta
Blood vessel
Anticoagulant and vasodilatory factors
Healthy endothelial cell
Pro-coagulant and vasoconstricting factors
Dysfunctional endothelial cell
Blood vessel
Preeclampsia placenta

Fig. 42.5 Proteins sFlt-1 and sEng cause endothelial dysfunction by antagonizing vascular endothelial growth factor (*V*EGF) and transforming growth factor β1 (TGF-β) signaling. There is mounting evidence that VEGF and TG-**β**1 are required to maintain endothelial health in several tissues, including the kidney and perhaps the placenta. During normal pregnancy, vascular homeostasis is maintained by physiologic levels of VEGF and TGF-**β**1 signaling in the vasculature. In preeclampsia, excess placental secretion of sFlt-1 and sEng (two endogenous circulating antiangiogenic proteins) inhibits VEGF and TGF-**β**1 signaling, respectively, in the vasculature. This results in endothelial cell dysfunction, including decreased prostacyclin, nitric oxide production, and release of pro-coagulant proteins. *PIGF,* Placental growth factor; *sEng,* soluble endoglin; *sFlt-1,* soluble fms-like tyrosine kinase 1. (Modified from reference 54.)

maternal circulation, and exaggerated maternal inflammatory response cause a generalized endothelial dysfunction with leukocyte and clotting activation.

Regardless of cause, preeclampsia is characterized by vasoconstriction, platelet activation with intravascular coagulation (usually local but occasionally disseminated), and maternal plasma volume contraction associated with capillary leak.

These abnormalities lead to further impairment of blood flow through the placenta as well as through the maternal kidneys, liver, and brain. It is unknown why these organs are most often affected in preeclampsia or why other vascular beds (e.g., gut) are unaffected, even in severe cases.

The clinical presentation of preeclampsia will depend on the extent to which maternal organ systems and the placenta have been affected by this process, but once begun, preeclampsia runs a progressive course until delivery, the only definitive cure.

Renal Abnormalities in Preeclampsia

Several abnormalities of renal function and structure occur in preeclampsia (Fig. 42.6). Characteristic pathologic changes in preeclampsia include diffuse *glomerular endotheliosis,* characterized by swelling and vacuolization of endothelial cells, capillary lumen occlusion, and glomerular enlargement. The swollen endothelial cytoplasm encroaches on glomerular capillary lumina, contributing to the tuft ischemia (Fig. 42.7). Immunofluorescence may reveal fibrin deposits. These changes are infrequently seen in clinical practice because renal biopsy is rarely performed in preeclamptic women.

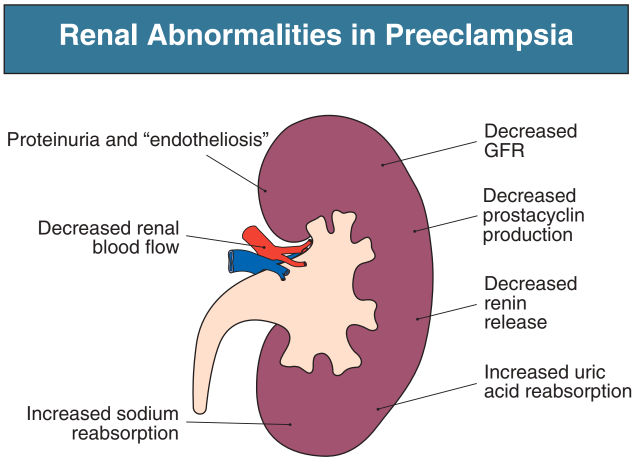
Renal Abnormalities in Preeclampsia
Proteinuria and "endotheliosis"
Decreased renal blood flow
Increased sodium reabsorption
Decreased GFR
Decreased prostacyclin production
Decreased renin release
Increased uric acid reabsorption

Fig. 42.6 Renal abnormalities in preeclampsia. *GFR,* Glomerular filtration rate.

Proteinuria

The urine sediment is usually bland. Both tubular and glomerular patterns of proteinuria have been reported in preeclampsia. Glomerular proteinuria is nonselective and may vary from a few hundred milligrams per day up to the nephrotic range. Levels of proteinuria in women with preeclampsia do not seem to correlate with maternal and fetal outcomes,[31] and women with mild or no proteinuria should be managed with the same caution as those with nephrotic-range proteinuria.

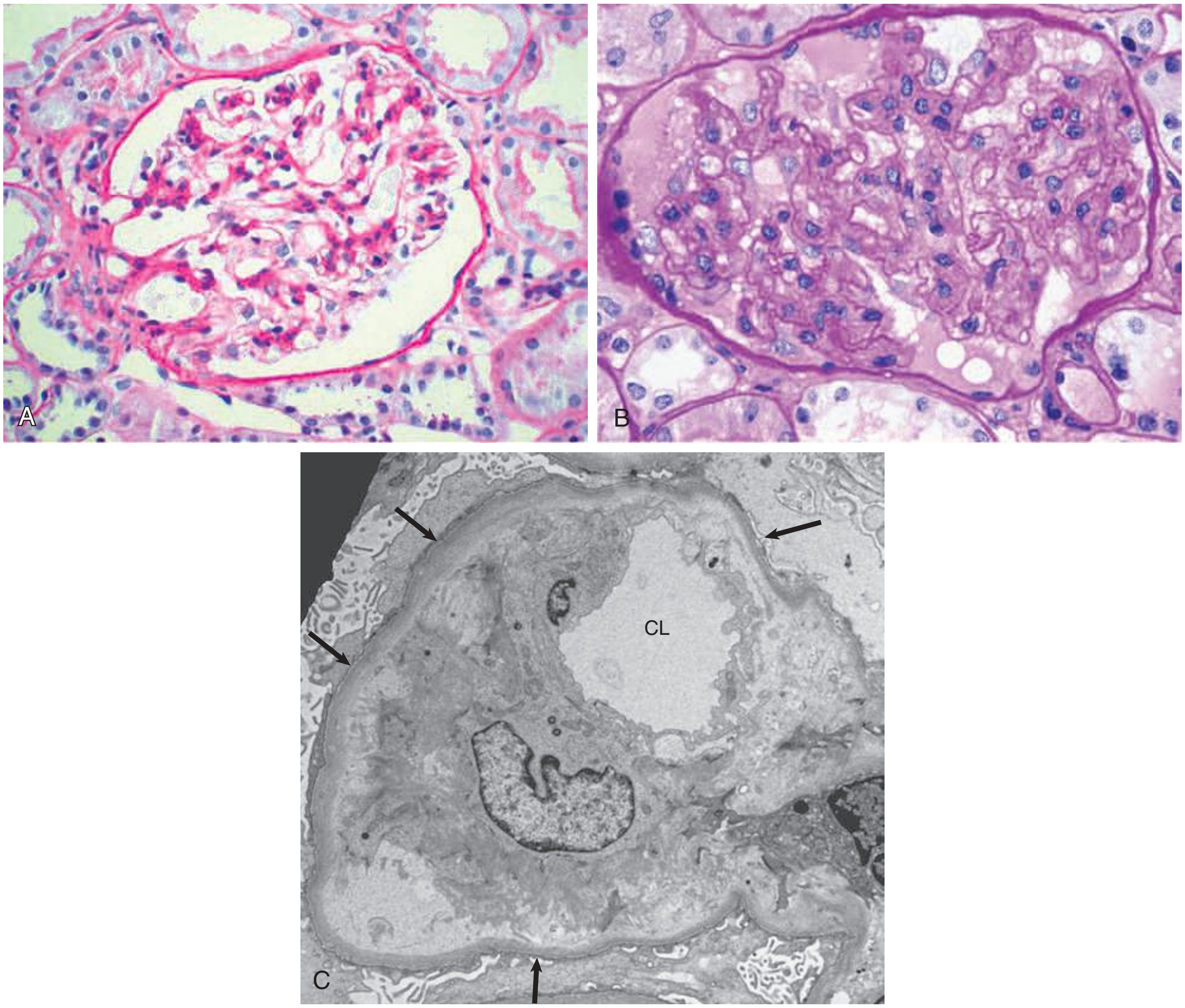

Fig. 42.7 Glomerular endotheliosis. (A) Normal glomerulus on light microscopy. (B) Glomerulus from a patient with preeclampsia on light microscopy. Note occlusion of capillary lumina by swollen endothelial cells. (C) On electron microscopy, note glomerular basement membrane *(arrows)* and marked reduction of capillary lumen *(CL)* caused by swollen endothelial cell cytoplasm. (*A* and *B,* Periodic acid–Schiff reaction; magnification ×40; *C,* original magnification ×7500.) (Courtesy Prof. P. Furness, University of Leicester, UK.)

Proteinuria may be part of the general capillary leak of preeclampsia or may be, in part, a consequence of glomerular endotheliosis.

Decreased Glomerular Filtration Rate

A fall in the GFR may be partly caused by the decrease in renal blood flow (in turn caused by vasoconstriction, plasma volume loss, and decreased cardiac output). Other factors may be involved, including impaired placental production of the vasodilator relaxin, impaired renal prostacyclin or NO production, or the glomerular morphologic changes themselves.

Acute Tubular Necrosis

Acute tubular necrosis (ATN) is the most common cause of AKI in preeclampsia. Impaired GFR (serum creatinine ≥90 μmol/l [1.2 mg/dl]) is only sometimes corrected by BP control and plasma volume restoration, and delivery is indicated if renal function continues to deteriorate.

Sodium Retention

Avid sodium retention occurs in preeclampsia, as a renal tubular response to perceived reduction in renal perfusion and perhaps also to increased sympathetic nervous system activity or alterations in expression of epithelial sodium channels. This is a normal renal response to the hemodynamic changes and may lead to oliguria; in the absence of an elevated serum creatinine, oliguria should not itself be an indication for delivery.

Renin-Angiotensin-Aldosterone System

Plasma renin and aldosterone concentrations are reduced in preeclampsia, compared with their elevation in normal pregnancy, and their levels correlate inversely with the severity of the disorder. This has little direct clinical relevance; however, it may be explained by a mineralocorticoid receptor mutation, *MRL810,* which allows factors normally antagonistic to aldosterone, such as progesterone, to bind and activate this receptor leading to inappropriate sodium retention, hypertension, and subsequent

TABLE 42.4 Gestation-Corrected Serum Uric Acid During Pregnancy

Gestational Age	Serum Uric Acid (μmol/l)	Serum Uric Acid (mg/dl)
<32 wk	>240	>4.0
32-35 wk	>270	>4.5
36-37 wk	>290	>4.9
≥38 wk	>330	>5.6

Concentrations above these levels should prompt review for associated adverse pregnancy outcomes, even in patients with gestational hypertension alone. Data are from 1610 hypertensive pregnant women.
From reference 34.

suppression of renin and aldosterone release.[32] There is a general upregulation of the systemic and placental RAAS systems in normal pregnancy. However, it seems that in preeclampsia, placental RAAS is upregulated, possibly because of agonistic AT1AA, whereas systemic RAAS components are lower, possibly as a result of increased epithelial sodium channel activation.[33]

Increased Uric Acid Reabsorption

Uric acid may be involved in the pathogenesis of preeclampsia. Hyperuricemia in preeclampsia results largely from renal uric acid retention, although there is probably also a component of increased uric acid production, perhaps by the placenta.[9] Serum uric acid is a not a useful test in the diagnosis of hypertensive pregnant women, but the degree of hyperuricemia correlates with fetal risk, even in women with gestational hypertension alone, and should alert clinicians to seek evidence of fetal growth restriction (Table 42.4).[34]

Clinical Manifestations

Preeclampsia is initially detected in most women by the onset of hypertension, typically after the 20th week of pregnancy (Box 42.3). Symptoms are not always present, but may include severe headaches, seizures, stroke, repeated visual scotomata (all manifestations of cerebral involvement), severe epigastric or right upper quadrant pain (reflecting hepatic ischemia), oliguria, bleeding caused by DIC, lower abdominal pain caused by placental abruption, or reduced fetal movements. Neurologic complications include eclampsia (see later discussion), stroke/reversible ischemic deficit, retinal detachment, cortical blindness, and posterior reversible encephalopathy. Hepatic complications include subcapsular hematoma and in rare cases liver rupture. Renal involvement can result in AKI requiring dialysis, and cardiorespiratory complications include myocardial ischemia and pulmonary edema.

Routine evaluation should include assessment of fetal growth, fetal heart rate patterns measured by cardiotocography (CTG), and assessment of the maternal reflexes because clonus can be a warning sign of impending eclampsia. The following investigations should be performed in all patients:

- Urine dipstick testing for proteinuria, with quantitation by measuring the uPCR if the dipstick is 1+ (30 mg/dl) or higher
- Hemoglobin, platelet count
- Serum creatinine, electrolytes, uric acid
- Serum transaminases
- Ultrasound assessment of fetal growth, amniotic fluid volume, and umbilical artery flow

BOX 42.3 Clinical Features of Preeclampsia

Primary Manifestation
- Hypertension

Renal Involvement
- Significant proteinuria: Dipstick positive confirmed by spot ratio of urine protein to creatinine >30 mg/mmol (about >300 mg/g creatinine)
- Acute kidney injury: Serum or plasma creatinine >90 mmol/l
- Oliguria

Hematologic Involvement
- Thrombocytopenia
- Hemolysis
- Disseminated intravascular coagulation

Liver Involvement
- Raised serum transaminases
- Severe epigastric or right upper quadrant pain

Neurologic Involvement
- Seizures (eclampsia)
- Hyperreflexia with sustained clonus
- Severe headache with hyperreflexia
- Persistent visual disturbances (photopsia, scotomata, cortical blindness, retinal vasospasm)
- Cerebrovascular accident (stroke)

Other Major Features
- Pulmonary edema
- Fetal growth restriction
- Placental abruption

Eclampsia

Eclampsia is the occurrence of tonic-clonic seizures in a woman who is pregnant or has recently delivered that cannot be attributed to other causes. Of these women, the majority, but not all, have premonitory signs and symptoms present during the week before the first eclamptic seizure: headache (56%), visual disturbances (23%), epigastric pain (17%), hypertension (48%), proteinuria (46%), or concurrent hypertension and proteinuria (38%).[35] Risk for eclampsia is not directly related to BP level. Although some view this as a form of hypertensive posterior reversible encephalopathy syndrome eclampsia may occur with relatively low BP and can occur in the absence of proteinuria. Importantly, about half the cases of eclampsia occur after delivery, usually within the first 5 days postpartum.

HELLP Syndrome

The HELLP syndrome—hemolysis, elevated liver enzymes, and low platelet count—is a variant of preeclampsia. Although sometimes regarded as a separate entity, HELLP simply refers to a severe form of preeclampsia in which the hepatic and platelet abnormalities dominate, with thrombotic microangiopathy. The diagnosis of HELLP syndrome is based on the following laboratory criteria:

- Microangiopathic hemolytic anemia: schistocytes in a blood film, elevated serum bilirubin or lactate dehydrogenase, low haptoglobin
- Increased liver transaminases: aspartate transaminase (AST) >70 U/l
- Platelet count: Less than 100 × 10^9/l

Maternal mortality from severe HELLP syndrome is about 1% and perinatal mortality between 7% and 34%, largely depending on gestational age.[36] It is best to consider this as a variant of preeclampsia and

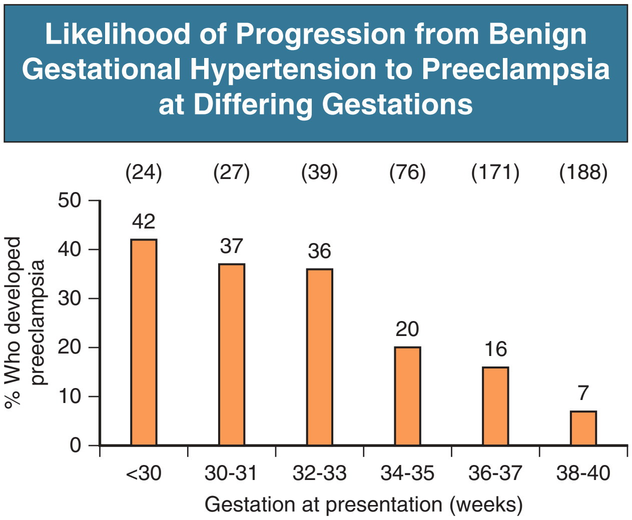

Fig. 42.8 Likelihood of hypertension progressing to preeclampsia at various weeks of gestation. The earlier the presentation with gestational hypertension, the greater is the likelihood of progression to preeclampsia. (Modified from reference 55.)

continue to seek and manage all the features of preeclampsia as these arise.

Natural History

Women with gestational hypertension have a 10% risk for developing preeclampsia if they present after 36 weeks of gestation, but a greater than one third risk if they present before 32 weeks (Fig. 42.8).

In general, the prognosis is favorable for women with preeclampsia but complications include abnormal liver function or thrombocytopenia (10% to 20%), pulmonary edema (<0.5%), AKI (1% to 5%), placental abruption (1% to 4%), fetal growth restriction (10% to 25%), neurologic damage (<1%), preterm birth, and perinatal death.[37] After delivery, all clinical and laboratory derangements of preeclampsia resolve but may be delayed by several days; thus it is critical to remain vigilant until the patient's clinical picture improves. Some patients require antihypertensives for the first time in the postnatal period, which we recommend is commenced when BP exceeds 140/90 mm Hg. Hypertension may persist for days, weeks, or months but will eventually resolve if preeclampsia is responsible for the elevated BP.

Prediction and Prevention

Despite numerous studies, including measurement of circulating angiogenic factors, no test has been found that can reliably predict the development of preeclampsia. Recently copeptin, a glycopeptide component of prepro–arginine vassopressin (prepro-AVP) that is the precursor protein of vasopressin (AVP), also has been suggested as a new biomarker,[38] but this requires further confirmation. Combination screening with maternal risk factors, late first-trimester uterine artery Doppler ultrasound, and various biomarkers has been shown in some studies to predict early-onset preeclampsia with high sensitivity and specificity[39,40]; but these models require further validation before adoption into routine clinical practice. Once preeclampsia has developed, or is suspected clinically, measuring the sFlt-1/PlGF ratio may be predictive of women needing delivery in the next 2 weeks, or, conversely, if the ratio is low, of women not needing intervention in the next week. However, it is too early to recommend this become part of standard practice.

The observation that preeclampsia is associated with increased platelet turnover and increased platelet-derived thromboxane levels led to several trials investigating the effect of aspirin in prevention of preeclampsia. It has subsequently been found that aspirin has other effects, perhaps on angiogenic factor production. Regardless, aspirin reduces the risk for developing early preeclampsia, particularly in high-risk women has been shown many times, most recently in the large Aspirin Vs Placebo in pregnancies at high risk for preterm preeclampsia (ASPRE) trial.[40a] We advocate starting aspirin at 12 to 14 weeks of gestation because the pathophysiologic features of preeclampsia develop at this time, and we typically recommend cessation at 37 weeks.[41] Bleeding is not significantly increased, even for women in labor while taking aspirin. Women who have already developed preeclampsia do not benefit from aspirin in preventing progression to more severe disease.

Oral calcium supplementation appears to halve the risk for preeclampsia in women at high risk and in communities with low dietary calcium intake.[42] The World Health Organization recommends calcium supplementation (1.5 to 2 g/day) after 20 weeks of gestation only in women with low dietary calcium intake. Nutritional supplements, including magnesium, folic acid, fish oils, antioxidants, and garlic, have been extensively studied and do not seem to be effective in preventing preeclampsia.[41] In particular, combined use of vitamins C and E has been associated with worse maternal and fetal outcomes. L-Arginine (a precursor of NO) has been shown to reduce the risk for preeclampsia when given in combination with antioxidants in high-risk populations[41]; however, its role in low-risk women is still being evaluated. Currently, anti-coagulation is not recommended for reducing the risk for preeclampsia except in rare cases related to lupus/antiphospholipid syndrome. Maternal obesity is associated with an increased risk for preeclampsia, and weight loss has been shown to reduce that risk.

Antihypertensive drugs do not reduce the risk for preeclampsia, but do reduce the incidence of severe hypertension with its associated maternal risks, particularly stroke.

Treatment

The only definitive treatment for preeclampsia is delivery of the placenta. The disorder may occur in the absence of the fetus (e.g., hydatidiform mole), and thus it is removal of the placenta that is important. Therefore preeclampsia that continues to worsen several days postpartum should prompt evaluation for retained placental products.

Indications for delivery are:

- Progressive evidence of maternal organ dysfunction: Worsening renal or hepatic function, worsening thrombocytopenia, and development of neurologic symptoms or signs
- Inability to control BP
- Failure of fetal growth or concern about fetal status
- Gestational age beyond 37 weeks

Timing of delivery should be based on optimizing perinatal outcomes while avoiding maternal risks. This requires assessment of fetal well-being with ultrasound and CTG, as well as assessment of the likely benefit of further intrauterine time. Antenatal corticosteroids for fetal lung maturation should be given to all women at risk for delivery at less than 34 weeks of gestation; many obstetricians also give steroids at later gestation if cesarean birth is likely.

There is consensus after the hypertension and preeclampsia intervention trial at near term (HYPITAT) trials that women with preeclampsia at later than 37 weeks of gestation should be delivered and that below 37 weeks such women can be managed expectantly to hope for further fetal growth and maturation, with delivery if any of the previously listed indications arise.[43,44]

General Management

All women with preeclampsia should be admitted at the initial diagnosis. If the condition then appears stable, outpatient care is reasonable provided appropriate resources and expertise are available. Reviews should include once- or twice-weekly laboratory evaluation of platelet count, serum creatinine, and AST, as well as CTG. Repeated quantification of proteinuria is not required once the protein-to-creatinine ratio has risen to 30 mg/mmol, because the amount or rate of increase of proteinuria is not associated with maternal or perinatal outcome. Ultrasound estimation of fetal weight, looking for growth restriction, and oligohydramnios, along with umbilical artery Doppler flow should be done at diagnosis and every 2 to 3 weeks if initially normal.

Blood Pressure Management

The major indication for antihypertensive therapy in preeclampsia is prevention of maternal cerebrovascular accident (stroke) and other sequelae of severe hypertension, such as placental abruption. Treatment does not affect the course of preeclampsia because the primary pathogenic process is related to the maternal response to abnormal placental function. However, lowering BP removes one maternal indication for delivery and therefore allows pregnancy to be prolonged, with further fetal maturation.

Antihypertensive medications are always recommended for systolic BP 160 mm Hg or greater and/or diastolic BP 100 mm Hg or greater, although it is controversial whether treatment is required at lower BP. Treatment of hypertension in the range 140 to 160 mm Hg systolic and 90 to 100 mm Hg diastolic is a reasonable approach and will reflect local practice. For such chronic treatment, the first-line agents are oxprenolol, labetalol, and methyldopa (Table 42.5). When additional treatment is required, hydralazine, nifedipine, or prazosin may be added. ACE inhibitors and ARBs should be avoided, because they cause fetal renal abnormalities in the latter half of pregnancy and possibly fetal cardiac or other abnormalities with first-trimester exposure. Diuretics should be avoided because they reduce an already-impaired maternal blood volume, although there are no convincing data about harm of diuretics in pregnancy.

Target BP is controversial; the control of hypertension in pregnancy (CHIPS) trial found better maternal outcomes without adverse fetal consequences at a target diastolic BP of 85 mm Hg in women with chronic hypertension or new-onset hypertension in pregnancy.[45] Our practice is to target BP between 110 to 140/80 to 85 mm Hg, trying to reduce the risk for maternal stroke while ensuring placental perfusion.

BP of 160/110 mm Hg or higher always requires acute treatment to prevent maternal stroke and eclampsia. In such a patient, oral short-acting nifedipine 10 mg tablets, IV hydralazine bolus 5 mg every 20-30 minutes to a maximum dose of 20 mg followed by an IV infusion at 5-10 mg/h, or labetalol 50 mg every 20 minutes to a maximum dose of 300 mg is typically used.

Magnesium sulfate 4 g over 10 to 15 minutes, followed by an infusion (1 to 2 g/h) is used as seizure prophylaxis and after a seizure; it should be continued for at least 24 hours. Magnesium sulfate is renally excreted, so caution is required in women with oliguria or renal failure. It is not usually necessary to monitor serum magnesium, but all women should be monitored with electrocardiogram, respiratory rate, oxygen saturation, and examination of the reflexes. The recurrence rate of seizures despite appropriate magnesium therapy is 10% to 15%.[46] In our view, seizure prophylaxis should usually be reserved for preeclamptic women who either have severe disease or already have clinical evidence of cerebral involvement, such as hyperreflexia with clonus, severe headaches, and visual scotomata. Withholding seizure prophylaxis in the remainder is associated with an extremely low likelihood of fits and avoids the potential for drug toxicity in a large number of pregnant women.[47] However, in low- and middle-income countries, we recommend routine magnesium prophylaxis because the rate of eclampsia is higher and the cost benefit much greater.

Although preeclampsia is a volume-contracted state, the increased capillary permeability makes intravenous volume expansion a potentially harmful procedure, with the ever-present risk for pulmonary edema. Therefore volume expansion should be used only in select patients, such as before parenteral treatment of acute severe hypertension (when rapid vasodilation may occur) and as initial treatment in the persistently oliguric woman. No more than 1 liter of crystalloid or colloid should be given in such women, usually over 4 to 6 hours. This will restore the average plasma volume deficit in most preeclamptic women, but careful clinical observation is required for the possibility of pulmonary edema, particularly if oliguria persists.

Platelet transfusion is generally given for platelet counts less than 20×10^9/l, but in some cases at higher levels (e.g., 20 to 40 × 10^9/l) if hypertension is difficult to control and the risk for intracerebral hemorrhage is therefore high. Fresh-frozen plasma is indicated only if there is accompanying microangiopathy and thrombocytopenia, when it may be difficult to differentiate preeclampsia from hemolytic uremic syndrome (HUS), or when hepatic disease leads to impaired coagulation in preeclamptic women. We do not recommend plasma exchange or corticosteroids for HELLP syndrome. Adsorption of sFlt-1 by dextran column apheresis is the subject of ongoing study but is not part of standard practice at present.[48] Fig. 42.9 summarizes management of preeclampsia.

Postpartum Management

Recovery should be anticipated over 5 to 7 days in most women after delivery. In many women, the condition may worsen in the first 3 days after delivery, and they should be monitored and treated as vigorously as antepartum. Some women may require up to 3 months for all the features to resolve, and a few will have proteinuria that takes up to 1 year to disappear completely.

TABLE 42.5 Medications Typically Used in the Treatment of Hypertension in Women With Preeclampsia

Drug	Treatment Regimen
Acute Hypertension	
Hydralazine	5-mg IV bolus every 20-30 min, to maximum of 20 mg, then infusion at 5-10 mg/h
Labetalol	50 mg IV every 20 min, to maximum 300 mg
Nifedipine	10 mg oral (tablets, not capsules)
Chronic Hypertension	
First-Line Choice	
Methyldopa	500-2000 mg/day PO
Clonidine	0.2-0.8 mg/day PO
Oxprenolol	80-480 mg/day PO
Labetalol	200-1200 mg/day PO
Second-Line Choice	
Hydralazine	25-200 mg/day PO
Prazosin	1-15 mg/day PO
Nifedipine SR	40-120 mg/day PO

Diuretics and propranolol are not recommended. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated.

IV, Intravenously; *PO,* orally; *SR,* sustained release. All medications for chronic hypertension are given as divided doses.

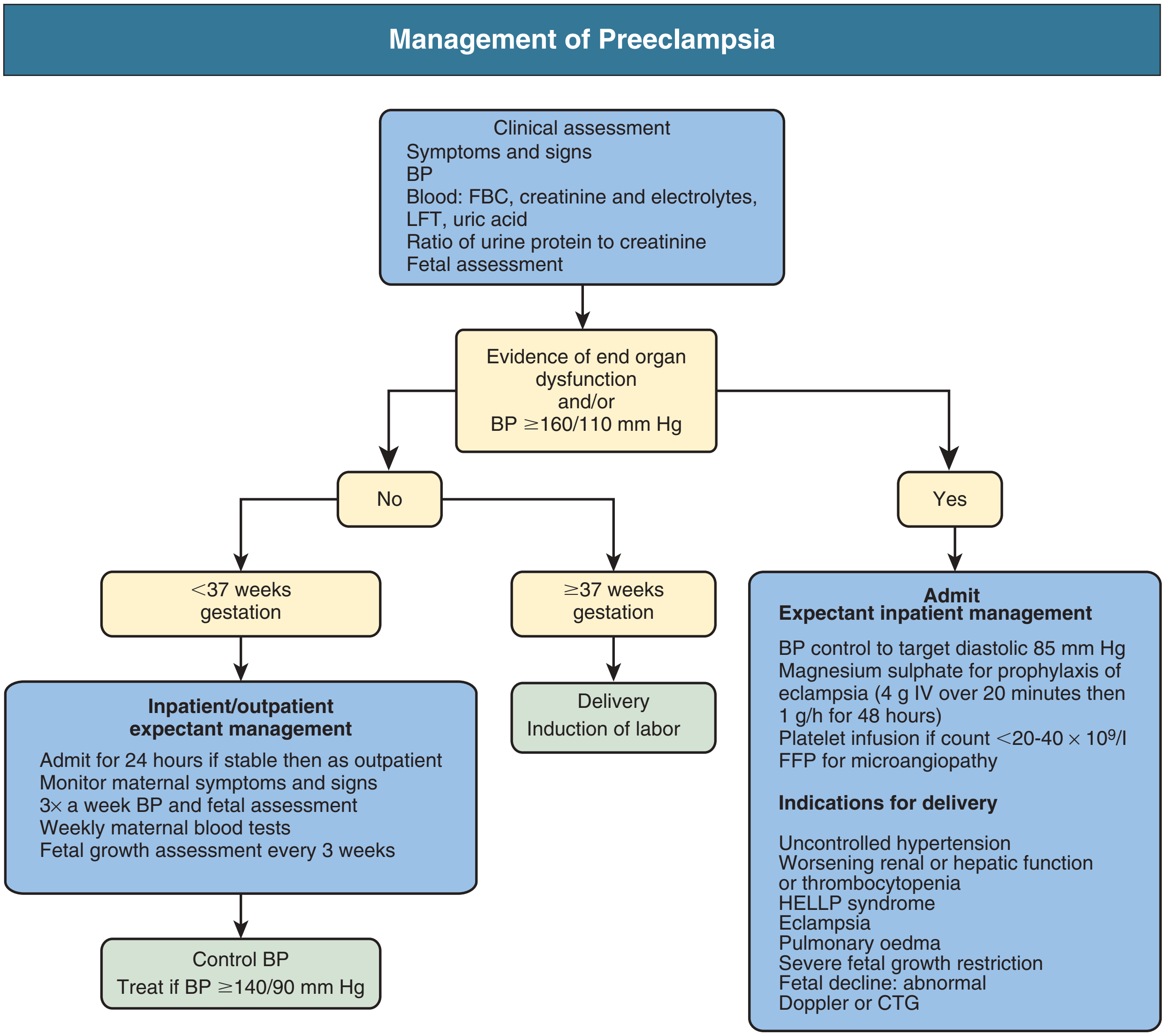
Management of Preeclampsia
Clinical assessment
Symptoms and signs
BP
Blood: FBC, creatinine and electrolytes, LFT, uric acid
Ratio of urine protein to creatinine
Fetal assessment
Evidence of end organ dysfunction and/or BP ≥160/110 mm Hg
No
Yes
<37 weeks gestation
≥37 weeks gestation
Inpatient/outpatient expectant management
Admit for 24 hours if stable then as outpatient
Monitor maternal symptoms and signs
3× a week BP and fetal assessment
Weekly maternal blood tests
Fetal growth assessment every 3 weeks
Control BP
Treat if BP ≥140/90 mm Hg
Delivery
Induction of labor
Admit
Expectant inpatient management
BP control to target diastolic 85 mm Hg
Magnesium sulphate for prophylaxis of eclampsia (4 g IV over 20 minutes then 1 g/h for 48 hours)
Platelet infusion if count <20-40 × 10⁹/l
FFP for microangiopathy
Indications for delivery
Uncontrolled hypertension
Worsening renal or hepatic function or thrombocytopenia
HELLP syndrome
Eclampsia
Pulmonary oedma
Severe fetal growth restriction
Fetal decline: abnormal Doppler or CTG

Fig. 42.9 **Management of preeclampsia.** Management depends on disease severity and gestational age of diagnosis. Prompt and adequate treatment can reduce the risk for adverse maternal and fetal outcomes. *BP,* blood pressure; *CTG,* cardiotocography; *FBC,* full blood count; *FFP,* fresh frozen plasma; *HELLP,* hemolysis, elevated liver enzymes, and low platelet count; *LFTs,* liver function tests. (Modified from reference 41.)

Assessment of the preeclamptic woman several months postpartum is mandatory. The BP should have returned to normal within 3 months in most women, and, if not, this should prompt a search for underlying primary or secondary hypertension. Urinalysis and urine microscopy should be normal by 12 months postpartum, and, if not, a primary underlying renal disease should be sought.

Women with recurrent preeclampsia, or severe early-onset preeclampsia (in whom recurrence is more likely) should be tested for underlying connective tissue, renal, thrombophilic and antiphospholipid or autoimmune disorders.

Preeclampsia and the more benign gestational hypertension will recur in only about 15% of women in a subsequent pregnancy. However, women who have presented at or before 28 weeks of gestation have at least a 25% risk for recurrence.

Especially if it occurs before 37 weeks of gestation, preeclampsia has well-recognized long-term implications, including an increased risk for primary hypertension, coronary heart disease, stroke, venous thromboembolism, and end-stage renal disease (Box 42.4). The mechanism for these increased risks appears to be a tendency to metabolic syndrome.[49] It is appropriate to counsel women who develop hypertension in pregnancy on cardiovascular risk factor lifestyle modifications, along with periodic BP, serum lipid, and blood glucose checks. All such women should also receive counseling before embarking on another pregnancy.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) presents in the third trimester and has an incidence of 1 per 7000 to 20,000 pregnancies,[50] but many milder cases may go undiagnosed. The incidence is higher in primigravid women, multiple gestations, and pregnancies with male fetuses. AKI is a common complication of AFLP, although the exact incidence is unclear.

BOX 42.4 Long-Term Consequences of Preeclampsia

After preeclampsia, there is long-term increased likelihood of:
- Fatal and nonfatal coronary heart disease
- Cerebrovascular accident (stroke)
- Hypertension
- Thromboembolism
- End-stage renal disease
- Diabetes
- Cognitive dysfunction and white matter lesions on cerebral computed tomography scan
- Death from any cause

Pathogenesis and Pathology

The disease is frequently associated with an autosomal recessive genetic error that causes a functional defect in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), an enzyme involved in mitochondrial fatty acid β-oxidation. This causes excessive fetal fatty acid accumulation, which is released into the maternal circulation, deposits in liver tissue, and leads to maternal hepatic dysfunction. The hallmark of the hepatic pathologic process is lipid microvesicle infiltration of the hepatocytes without inflammation or necrosis.

The renal involvement in AFLP is nonspecific, and the pathophysiology is unclear. It may be caused by hemodynamic changes similar to those seen in the hepatorenal syndrome or by a thrombotic microangiopathy. Coexisting preeclampsia may also contribute to the renal injury. Renal biopsy and autopsy studies have shown mild glomerular hypercellularity with thick, narrow capillary loops and tubular free fatty acid accumulation, suggesting that abnormal fatty acid oxidation also may contribute to renal dysfunction.

Clinical Manifestations

Patients with AFLP present with any combination of fever, malaise, epigastric pain, nausea, vomiting, and jaundice and 50% present with symptoms and signs of preeclampsia. The severity of liver involvement in women with AFLP is highly variable, ranging from a moderate isolated increase in transaminases to fulminant hepatic failure with encephalopathy and coagulopathy. Characteristic laboratory abnormalities include hyperbilirubinemia, increased transaminases, hypoglycemia, leukocytosis, and evidence of coagulopathy (hypofibrinogenemia, prolonged prothrombin time, depressed antithrombin III levels).

Differential Diagnosis

Viral hepatitis and biliary obstruction should be excluded before confirming the diagnosis of AFLP. Distinguishing AFLP from severe preeclampsia can be challenging because the two disorders share many pathophysiologic and clinical features. Indeed, some suspect that these are part of the same spectrum of disease. Nevertheless, distinguishing between preeclampsia and AFLP is important to guide whether offspring should be assessed for the LCHAD mutation.

Treatment and Outcome

Early diagnosis, supportive care (reversal of coagulopathy, correction of hypoglycemia, and fluid status management), and prompt delivery are critical in the management of AFLP. In most women, there is complete liver and kidney recovery after delivery. However, AFLP is associated with maternal and perinatal mortality of up to 18% and 55%, respectively.[51] Renal recovery typically follows delivery, but dialysis may be needed.

THROMBOTIC MICROANGIOPATHY

Pregnancy-associated thrombotic microangiopathy (TMA) is defined by the presence of fibrin and platelet thrombi in the microcirculation of multiple organs, microangiopathic hemolysis, and thrombocytopenia. Manifestations of pregnancy-associated TMA include the HELLP syndrome, HUS, and thrombotic thrombocytopenic purpura (TTP). Pregnancy-associated TMA is further discussed in Chapter 29.

Clinical Manifestations and Differential Diagnosis

Women with HUS typically present with AKI (often with hypertension) in the postpartum period, although this can occur at any time during pregnancy, even as early as the first trimester. TTP often presents antepartum, usually before 28 weeks of gestation. Coagulation studies and liver function tests are usually normal in HUS and TTP, unlike cases of severe preeclampsia or AFLP. One study suggests that a high ratio of lactate dehydrogenase to AST (25:1) indicates that HUS is a more likely diagnosis than preeclampsia/HELLP in the third trimester.

In practice, it is difficult to distinguish HUS and TTP from preeclampsia without renal biopsy, which often must be delayed until thrombocytopenia is resolving. If renal injury is progressive, biopsy becomes more important to guide ongoing therapy, including plasma exchange or eculizumab.

Natural History

The maternal mortality in pregnancy-associated TMA has declined in recent years and is now between 10% and 20%. However, perinatal mortality is high (30% to 80%), mainly from growth restriction and placental infarction caused by thrombosis of decidua arterioles.[52]

Treatment

The mainstay of treatment of TTP in pregnancy is plasma exchange/infusions. Delivery is indicated in cases of fetal distress or progressive maternal clinical features. Treatment for HUS is supportive, and the use of eculizumab (monoclonal C5 inhibitor) in pregnancy has been described in a few case reports.

ACUTE KIDNEY INJURY

Definition

The diagnosis of AKI in pregnancy is based on the serum creatinine increase. The usual formulas for estimating GFR are not validated in pregnancy, nor are systems for defining AKI (e.g., Acute Kidney Injury Network [AKIN]; Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease [RIFLE]; Kidney Disease: Improving Global Outcomes [KDIGO]; see Chapter 68). Unfortunately, there is still no agreed definition of AKI in pregnancy, but we suggest investigating women with a serum creatinine of 90 µmol/l (>1 mg/dl) or greater or an increase within 48 hours of 44 µmol/l (0.5 mg/dl) above baseline.

Epidemiology

AKI necessitating dialysis in developed countries occurs in about 1 of 20,000 pregnancies, so a typical obstetric unit (with 2000 to 3000 unselected deliveries per year) will only see one case every 6 to 10 years; the incidence will be greater in tertiary referral centers but is still very low. The development of AKI in pregnancy follows a bimodal distribution with two incidence peaks: the first and third trimesters. Prerenal causes are more common in the first trimester because of hyperemesis gravidarum, ATN in the context of septic abortion, or AKI associated with viral or bacterial infections or sepsis. Common causes in the later stages of pregnancy are preeclampsia, AFLP, TMA, or ATN/acute cortical

TABLE 42.6 Common Causes of Acute Kidney Injury in Pregnancy

Category	Specific Causes
Prerenal	Antepartum or postpartum hemorrhage Hyperemesis gravidarum Sepsis Congestive heart failure (rare)
Renal	Acute tubular necrosis Pyelonephritis Renal cortical necrosis Thrombotic microangiopathy Preeclampsia/HELLP syndrome Acute fatty liver of pregnancy Glomerulonephritis Medication toxicity
Post-renal	Urinary tract obstruction Gravid uterus (rare) Calculi

HELLP, Hemolysis, elevated liver enzymes, and low platelet count.

necrosis secondary to hemorrhage. Obstructive uropathy is an uncommon cause of AKI in pregnancy.

Etiology and Pathogenesis

The causes of AKI in pregnancy are best classified as prerenal, renal, and postrenal (Table 42.6).

Prerenal AKI in pregnancy is associated with volume contraction and vasoconstriction as well as intravascular coagulation, each of which reduce renal perfusion, leading to renal ischemia. It is generally believed that a pregnant woman is more likely to develop AKI than a nonpregnant woman exposed to the same set of conditions that threaten renal perfusion, although there are no confirmatory data for this view. The best explanation for this would be that many of the renal "protective" mechanisms (e.g., increased prostacyclin production to enhance renal blood flow) are already activated maximally in normal pregnancy and may not be augmented in the setting of prerenal AKI.

It is also a common view that subsequent bilateral renal cortical necrosis is more likely than if AKI had developed outside of pregnancy. The risk for cortical necrosis is estimated at 20% when AKI follows septic abortion. This contrasts with a lower incidence of cortical necrosis (~2%) after other causes of AKI in pregnancy. Irreversible renal damage follows 10% to 25% of such cases of cortical necrosis, mostly after preeclampsia or antepartum hemorrhage. Septic abortion is now an uncommon problem in developed countries; hence cortical necrosis is a less common cause of AKI than in the past, although this risk remains higher in developing countries where opportunities to prevent AKI are fewer.

Antepartum Hemorrhage, Prolonged Intrauterine Fetal Death, or Amniotic Fluid Embolism

In these conditions, DIC and severe renal ischemia (leading to endothelial damage and secondary fibrin deposition) are the initiating events. Local release of NO normally minimizes the degree of thrombus formation by diminishing platelet aggregation, but if endothelial injury is too great, NO release is impaired, accelerating the tendency to thrombosis. Renal cortical necrosis or ATN (in less severe cases) may then occur, manifesting as abrupt-onset oliguria or anuria with gross hematuria, flank pain, and often hypotension caused by the initiating disorder.

Sepsis

In septic conditions in pregnancy, AKI is probably the result of cytokine-induced changes in vascular permeability and a loss of effective RPF, sometimes with accompanying hemolysis or DIC. Common causes of sepsis in pregnancy include pyelonephritis, chorioamnionitis, and pneumonia.

Preeclampsia, Acute Fatty Liver of Pregnancy, and Thrombotic Microangiography

Preeclampsia and HELLP syndrome accounts for 40% of AKI, usually later in pregnancy. The pathogenesis of renal impairment in these conditions is a combination of volume depletion, vasoconstriction, and activation of the inflammatory and coagulation cascades.

Clinical Manifestations and Differential Diagnosis

Most cases of AKI in pregnancy are associated with oliguria, and the clinical manifestations in the mother are the same as for AKI in general (see Chapter 68). However, there is the added concern of fetal death because the fetus does not survive in an environment of prolonged uremia.

Preeclampsia

Oliguria in the context of preeclampsia is a worrying sign but of itself may represent a normal renal response to volume contraction. The rise in serum creatinine can sometimes be prevented by good BP control and judicious volume expansion in these women. AKI is more likely to develop in the HELLP syndrome. Table 42.7 outlines the differential clinical features of preeclampsia/HELLP syndrome, HUS, and AFLP.

Obstructive Uropathy

Although compression of the renal system resulting in urinary stasis is common in pregnancy, obstruction as a cause of AKI in pregnancy is rare. Usually, there are no specific clinical features; renal failure is discovered when serum creatinine is measured because a pregnant woman is progressively unwell or is oliguric. Ureteral dilation in normal pregnancy makes the use of ultrasound to diagnose obstructive uropathy difficult. In cases of obstructive uropathy with progressive renal failure and delay in initiating delivery, percutaneous nephrostomy may rarely be required. The diagnosis is then confirmed if serum creatinine falls.

Natural History

Maternal mortality after AKI in pregnancy is reported as 6% and 30%.[53] Fetal mortality rates are much higher but vary enormously depending on the availability of perinatal care.

Treatment

The mainstay of treatment for AKI in pregnancy is restoration of fluid volume deficits and in later gestations, delivery of the baby and placenta, because this is likely to remove the stimulus for AKI. Treatment is easier to initiate when AKI develops late in pregnancy, but if fetal viability is uncertain and the maternal condition stable, dialysis and specific treatment of the underlying condition are commenced. Albumin infusions have not been shown to improve renal function. Pharmacotherapies specific for cause such as antihypertensives in preeclampsia and antibiotics in sepsis should be administered promptly.

Dialysis

The absolute indications for dialysis are the same as for the general population with severe AKI: uremic symptoms (encephalopathy or pericarditis), volume overload, hyperkalemia, and metabolic acidosis unresponsive to medical treatment. However, it is generally recommended

TABLE 42.7 Differential Clinical and Laboratory Features of Syndromes That Cause Acute Kidney Injury in Pregnancy

Clinical Features	PE	HUS/TTP	HELLP	AFLP
Hemolytic anemia	+/–	+++	++	+/–
Thrombocytopenia	+/–	+++	++	+/–
Coagulopathy	+/–	–	+/–	+
CNS symptoms	+/–	+/– (HUS) ++ (TTP)	+/–	+/–
Renal failure	+/–	+++	+	++
Hypertension	++	+/–	+++	+/–
Proteinuria	+/–	+/–	++	+/–
Elevated AST	+/–	+/–	++	+++
Elevated ALT	+/–	–	++	+++
Elevated bilirubin	+/–	++	+	+++
Anemia	+/–	++	+	+/–
Blood ammonia	Normal	Normal	Normal	High
ADAMTS13	–	– (HUS) + (TTP)	–	–
Effect of delivery on disease	Recovery	None	Recovery	Recovery
Management	Supportive care/delivery	Plasma exchange/eculizumab	Supportive care/delivery	Supportive care/delivery

AFLP, Acute fatty liver of pregnancy; *ALT,* alanine aminotransferase; *AST* aspartate aminotransferase; *CNS*, central nervous system; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *HUS,* hemolytic uremic syndrome; *PE*, preeclampsia; *TTP*, thrombotic thrombocytopenic purpura.

to start dialysis earlier than in nonpregnant patients (i.e. blood urea nitrogen (BUN) >42 mg/dl (serum urea >15 mmol/l) despite volume restoration, because the uremic environment has a negative effect on fetal survival. Both peritoneal dialysis and hemodialysis have been used in pregnancy with success. Peritoneal dialysis requires dialysis catheter insertion under direct vision and has the potential advantage of maintaining fairly constant maternal hemodynamics without threatening uteroplacental blood flow, but carries the risk for peritonitis. Hemodialysis is required more frequently than in nonpregnant patients and has the risk for impairing uteroplacental perfusion if sudden fluid shifts occur. Neither peritoneal dialysis nor hemodialysis has been proven superior, and there is only limited experience with continuous renal replacement therapy in pregnancy. Dialysis in pregnancy is discussed in more detail in Chapter 43.

OVARIAN HYPERSTIMULATION SYNDROME

Definition and Epidemiology

Ovarian hyperstimulation syndrome (OHSS) is an exaggerated response to ovulation induction associated with *in vitro* fertilization therapy. OHSS manifests as increased capillary permeability and fluid retention, with inflammatory mediators.

Pathogenesis

After treatment with gonadotropin-releasing hormone analogues, massive follicular luteinization occurs, which can lead to excessive release of factors, including VEGF, cytokines, prostaglandins, histamine, and Ang. These factors increase vascular permeability, causing loss of fluid into the third space, resulting in ascites, pleural and pericardial effusions, and edema. The hemoconcentration, hypovolemia, and elevated estrogen increase susceptibility to thromboembolic events, oliguric AKI, hyperkalemia, hyponatremia, and acidosis. The majority of patients with severe OHSS will have at least one febrile episode over 24 hours.

Clinical Manifestations and Investigations

Early-onset OHSS occurs 3 to 7 days typically after the administration of the ovulatory dose of human chorionic gonadotropin (hCG), and late-onset OHSS is defined as occurring more than 1 week after hCG administration. Pregnancy-related OHSS is usually clinically severe and more prolonged than OHSS that occurs before embryo implantation. Patients should be investigated with full blood count and hematocrit, serum creatinine, electrolytes, liver function tests (albumin), β-hCG, and coagulation studies. An abdominal ultrasound will help confirm the diagnosis. Abdominal pain must be investigated thoroughly because the enlarged, fragile ovaries are prone to torsion and rupture. Intra-abdominal infection and ectopic pregnancy also must be considered.

Management

OHSS is self-limiting, with an average duration of 7 days in nonpregnant patients and 10 to 20 days in pregnant patients. Treatment is mainly supportive. In the woman with moderate to severe OHSS, hospital admission is required for correcting volume depletion, monitoring and correcting electrolyte abnormalities (particularly hyperkalemia), providing analgesia, offering nutrition and psychological support, preventing deep vein thrombosis, and supporting respiratory function. The ideal fluid replacement is not clear. Our practice is to give only 2 liters of crystalloid over 24 hours to correct intravascular volume depletion, recognizing that some of this will be lost into third-space fluid. Paracentesis may be necessary to improve symptoms and respiratory function in the short term. Simultaneous albumin infusion should be given to avoid protein depletion, hypotension, and rapid reaccumulation of fluid within the pleural and peritoneal spaces. Diuretics are contraindicated because they will not reduce third-space fluid and may worsen hypovolemia and hemoconcentration and precipitate AKI. Prophylactic anticoagulation with heparin is required due to the risk for thromboembolism.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following does not occur in normal pregnancy?
   - **A.** Lower serum osmolality
   - **B.** Hypernatremia
   - **C.** Elevated glomerular filtration rate
   - **D.** Glycosuria
2. Which of the following antibiotics should be avoided for use in treatment of urinary tract infections in pregnancy?
   - **A.** Cephalexin
   - **B.** Nitrofurantoin
   - **C.** Amoxicillin–clavulanic acid
   - **D.** Trimethoprim
3. Which of the following factors have been implicated in the pathogenesis of preeclampsia?
   - **A.** Soluble fms-like tyrosine kinase 1
   - **B.** Angiotensin II type 1 receptor antibodies
   - **C.** Tumor necrosis factor α
   - **D.** Reactive oxygen species
   - **E.** All of the above
4. Which of the following is not an indication for delivery in preeclampsia?
   - **A.** Proteinuria 2 g/day
   - **B.** Gestation ≥ 37 weeks
   - **C.** Pulmonary edema
   - **D.** Worsening renal function
5. Which of the following syndromes causing acute kidney injury are least likely to recover after delivery?
   - **A.** Preeclampsia
   - **B.** HELLP syndrome
   - **C.** Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
   - **D.** Acute fatty liver of pregnancy

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Pregnancy With Preexisting Kidney Disease

Kate Bramham, Mark A. Brown

Historically, renal disease was considered a contraindication to pregnancy but now many pregnant women with chronic kidney disease (CKD) have successful outcomes. However, adverse pregnancy outcomes remain more frequent in women with CKD than healthy controls; thus nephrologists and obstetricians need to be skilled in disease optimization before pregnancy, counseling regarding possible pregnancy outcomes, and antenatal and postpartum management of such women. In this chapter we will consider the current evidence for maternal and fetal complications for women with CKD, including management of those with normal renal function, those with renal transplants, and women with end-stage renal disease (ESRD) requiring dialysis.

THE ADVERSE EFFECTS OF CHRONIC KIDNEY DISEASE ON PREGNANCY

CKD affects up to 6% and 9% of women of child-bearing age in high- and low-income countries, respectively, approximately a third of whom have stages 3 to 5 CKD.[1] Available data on pregnancy outcomes in women with CKD are mainly from studies published 10 to 20 years ago and probably overestimate risk compared with modern practice, particularly with improvements in neonatal intensive care. The following key prepregnancy factors are the main predictors of pregnancy outcome:

- Degree of renal impairment
- Severity of hypertension
- Degree of proteinuria

In most circumstances, these features are more important in predicting outcome than the mother's specific renal disease.

The traditional view was that most women with mild renal impairment (serum creatinine <1.5 mg/dl [130 µmol/l]) and controlled hypertension have a successful pregnancy outcome, with preexisting hypertension being the main predictor of pregnancy outcome in women with mild renal impairment. However, even CKD stages 1 and 2 are associated with a higher rate of preeclampsia and perinatal mortality, preterm delivery, and small for gestation age rates; the development of superimposed preeclampsia appears higher in women with a preconception creatinine value of 1.4 mg/dl (125 µmol/l) but greater than 0.9 mg/dl (100 µmol/l) in early pregnancy and indeed even in women with normal glomerular filtration rate (GFR) but dipstick-positive proteinuria and one or more other risk factors for preeclampsia.[2] Those with moderate (serum creatinine 1.5 to 2.5 mg/dl [130 to 220 µmol/l]) to severe (>2.5 mg/dl [220 µmol/l]) renal impairment, particularly when accompanied by hypertension and heavy proteinuria, have a lower chance of having a live baby and a greater risk for maternal complications, including progression of their renal disease. Outcomes according to severity of renal function are presented in Boxes 43.1 and 43.2.

Severity of Hypertension

Preexisting hypertension is associated with significantly higher risk for adverse pregnancy outcomes than the general population,[3] and in pregnant women with CKD, the presence of secondary hypertension is an important predictor of adverse events. For example, a retrospective analysis of 358 pregnant women with CKD found an association between diastolic BP greater than 90 mm Hg (treated or untreated) and neonatal death, which compounded the risk for preterm birth that arises because of renal impairment alone.[4] Preexisting hypertension conferred an approximate doubling of risk for severe neonatal outcome (early preterm delivery, requirement for neonatal intensive care and/or small for gestational age infant) in a recent large prospective Italian cohort study.[5]

Proteinuria

Preexisting proteinuria as a risk factor for poor pregnancy outcome is variably reported, with some studies reporting no influence and others have identified an association among preterm delivery, cesarean section rates, and need for neonatal intensive care, particularly if baseline proteinuria was more than 1 g/day.[6]

MANAGEMENT COMMON TO ALL PREGNANCY WITH PREEXISTING KIDNEY DISEASE

The general principles of management of pregnancy in women with CKD are summarized in Box 43.3.

Prepregnancy Counseling

It has long been known that any woman with stage 3 to 5 CKD should receive prepregnancy counseling. Studies from Italy have found that preterm delivery, cesarean section rates, and need for neonatal intensive care were higher than in the general population, even in women with stage 1 CKD without systemic disease, hypertension, or proteinuria.[5] Another meta-analysis included older studies but also many women with stage 1 CKD; the presence of any form of CKD was associated with worse maternal and fetal outcomes,[7] and thus prepregnancy counseling should be provided for all women with CKD. Issues that should be covered in counseling are shown in Box 43.4. This counseling should include the relevant information on pregnancy outcomes in CKD shown in Boxes 43.1 and 43.2.

Pregnancy may be unplanned in women with CKD, and detailed discussion regarding maternal and fetal outcomes should be provided in early pregnancy. Furthermore, pregnancy may be the first opportunity for identification of CKD; for example, in a prospective cohort study 16% of women with CKD were diagnosed in pregnancy,[8] and similarly these women should be informed of potential pregnancy-related risks.

BOX 43.1 Maternal Renal Outcomes According to Prepregnancy Serum Creatinine*

Creatinine <1.5 mg/dl (130 µmol/l)

- Permanent loss of GFR in <10% of women
- Greatest risk if GFR is <40 ml/min and proteinuria is >1 g/day
- Major determinant of ESRD progression is hypertension
- 40% risk for preeclampsia if baseline proteinuria is >500 mg/day

Creatinine 1.5 to 2.5 mg/dl (130-220 µmol/l)

- Decline or permanent loss of GFR in 30% of women
- Increased to 50% if uncontrolled hypertension
- 10% ESRD soon after pregnancy

Creatinine >2.5 mg/dl (220 µmol/l)

- Progression to ESRD highly likely during or soon after pregnancy

*Note that Modification of Diet in Renal Disease or Chronic Kidney Disease–Epidemiology Collaboration or CKD-EPI formula for estimation of GFR are not valid for pregnancy.
ESRD, End-stage renal disease; *GFR,* glomerular filtration rate.

BOX 43.2 Fetal Outcomes According to Maternal Prepregnancy Serum Creatinine*

Outcomes after accounting for first-trimester miscarriage:

Creatinine <1.5 mg/dl (130 µmol/l)

- Live births in >90% of women
- Up to 50% preterm delivery, 60% small for gestational age if baseline proteinuria >500 mg/day

Creatinine 1.5 to 2.5 mg/dl (130 to 220 µmol/l)

- Live births in about 85% of women unless uncontrolled hypertension (mean arterial pressure >105) at conception
- 60% prematurity, mainly iatrogenic (preeclampsia/fetal growth restriction)

Creatinine >2.5 mg/dl (220 µmol/l)

- Fetal loss high; estimates uncertain

*Note that Modification of Diet in Renal Disease (MDRD) formula and Chronic Kidney Disease-Epidemiology (CKD-Epi) formula for estimation of GFR are not valid for pregnancy.

BOX 43.3 Principles of Antenatal Care With Preexisting Chronic Kidney Disease

- Management of hypertension aiming for BP 110 to 140/80 to 85 mm Hg*
- Aspirin (75-150 mg daily) for all women with CKD
- Regular medication review: Discontinue statins, ACE inhibitors, ARBs
- Correct interpretation of changes in serum creatinine
- Clinical assessment and maintenance of volume homeostasis
- Interpretation and management of proteinuria, including nephrotic syndrome
- Identification of superimposed preeclampsia
- Identification and management of urinary tract infection
- Consideration of the primary renal disease
- Assessment for fetal well-being and consider if delivery is indicated (see Box 43.5)

*See text for further discussion.
ACE, Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *BP,* blood pressure.

BOX 43.4 Prepregnancy Counseling for Women With Chronic Kidney Disease

Maternal Risks

- Accelerated decline in glomerular filtration rate, sometimes precipitating dialysis during pregnancy or soon after
- Severe maternal hypertension with risk for stroke
- Superimposed preeclampsia with renal, hepatic, thrombotic, or bleeding and neurologic risks
- Nephrotic syndrome with risks for thrombosis or sepsis and iron or vitamin D deficiency

Fetal Risks

- Fetal growth restriction or intrauterine fetal death from placental insufficiency
- Prematurity, with both short-term and long-term consequences
- Complications of drug therapy for renal disease during pregnancy
- Inheritance of a renal disorder

Fertility Assessment

Fertility is reported to be reduced in women with moderate to severe CKD, but there is limited study of underlying mechanisms; however, raised prolactin and luteinizing hormone concentrations are reported.[9] With the advent of assisted conception overcoming natural fertility barriers to conception in women with CKD, nephrologists may be approached for advice regarding hormone stimulation therapies and embryo transfer. There is no evidence so far to suggest that hormonal manipulation has additional adverse consequences in women with CKD unless they develop ovarian hyperstimulation syndrome (see Chapter 42), which may further compromise kidney function. Single embryo transfer is recommended because of the additional maternal and neonatal risk for multiple fetal pregnancies.

Contraception should be offered to women with CKD of childbearing age who do not wish to conceive, including those on dialysis. For the majority of patients with CKD, estrogen-containing preparations are contraindicated because of exacerbation of hypertension or thrombotic risk and progesterone methods are preferred. Women taking immunosuppression have historically been advised against intrauterine devices because of concerns related to failure and pelvic inflammatory disease, although there is no robust evidence to support this recommendation, and case series of women with renal transplants suggest that contraceptive performance is comparable to that in the general population.[10]

Volume Homeostasis

Adequate intravascular volume is essential to preservation of GFR and good pregnancy outcome for mother and baby. Peripheral edema is a common finding even in healthy pregnancy; thus it is not a useful tool for assessing volume status in pregnant women with CKD. Hematocrit should be measured in women with underlying CKD at the initial first-trimester visit, along with serum albumin. A rise in either value strongly suggests intravascular volume contraction, though there is no absolute discriminant value. Conversely, a significant fall in either value does not by itself diagnose excessive volume expansion because both hematocrit and albumin are influenced by other factors (e.g., estimated GFR [eGFR], albuminuria).

When there is concern about fetal growth or deteriorating GFR in women with CKD and reduced intravascular volume is suggested by the change in hematocrit and albumin from baseline, a trial of intravenous normal saline (no more than 1 L) under observation in hospital is a reasonable clinical approach.

Urinalysis: Proteinuria

Any woman with 1+ (0.3 g/l) proteinuria or above should have protein excretion quantified with a spot ratio of urine protein creatinine (uPCR) or 24-hour urine collection. The upper limit of normal protein excretion during pregnancy is defined as 300 mg/day. In a mid-stream specimen of urine, uPCR greater than 30 mg/mmol (0.27 mg/mg) correlates with more than 300 mg/day proteinuria. Although the spot uPCR in pregnancy is a reasonably reliable method of determining whether protein excretion is abnormal, it is not recommended that serial measurements of uPCR be used to reliably predict *changes* in proteinuria. When there is a true increase in protein excretion during pregnancy in women with underlying renal disease there are few therapeutic options apart from ensuring BP control (see later discussion).

Isolated non-nephrotic proteinuria may develop *de novo* during pregnancy, which usually indicates one of the following scenarios and usually does *not* require antenatal renal biopsy:

1. Developing preeclampsia (after 20 weeks of gestation).
2. No pregnancy complications occur, and proteinuria resolves postpartum (known as *gestational proteinuria*).
3. Intrinsic glomerular disease has developed and remains postpartum (uncommon).

Because serum albumin falls in most pregnancies as a result of volume expansion and may be below 30 g/l, hypoalbuminemia is not a reliable indicator of nephrotic syndrome. Similarly, peripheral edema and a rise in serum cholesterol are commonly seen in healthy pregnancy. A spot uPCR greater than 230 mg/mmol generally indicates protein excretion is above 3 g/day and this should be confirmed by 24-hour urine collection. Diuretic therapy is rarely needed, but is indicated if edema is causing blistering and skin infections. Dietary sodium restriction should be avoided in pregnancy.

Nephrotic syndrome in pregnancy may be associated with urinary loss of vitamin D binding protein, transferrin, immunoglobulins, antithrombin III (accompanied by increased hepatic synthesis of clotting factors), and a propensity for intravascular volume contraction that may lead to reduced uteroplacental blood flow with fetal growth restriction or death and worsening renal function. Treatment requires oral calcium, vitamin D, and iron supplementation, subcutaneous heparin for thrombosis prophylaxis, and reassessment of maternal serum creatinine on a regular basis. Thresholds for commencing thromboprophylaxis are undefined, but most clinicians initiate treatment at higher serum albumin and/or lower proteinuria concentrations than in the nonpregnant state because of the prothrombotic nature of pregnancy, with consideration for additional risk factors such as dehydration secondary to hyperemesis, or obesity. We recommend this for all pregnant women with nephrotic syndrome and for women with nephrotic range proteinuria but serum albumin above 20 g/l if they have a body mass index above 35, dehydration, or another known clinical risk factor for thrombosis. Warfarin should not be used during pregnancy because of increased risk for fetal anomalies. Low-molecular-weight heparin is safe during pregnancy and does not cross the placenta. Dose adjustment should be made for increased renal clearance in pregnancy and weight. Unfractionated heparin is recommended in women with GFR less than 30 ml/min/1.73 m^2 to avoid accumulation.

Data comparing pregnancy outcomes in women with different glomerular diseases associated with nephrotic syndrome are limited. Nonetheless there are no data to suggest that any particular glomerular disease is associated with worse outcomes independent from the severity of renal disease and hypertension.

Hypertension

Many pregnant women with CKD will not exhibit the usual first-trimester fall in BP, and, in many women, BP increases as the pregnancy progresses. Normal pregnancy is accompanied by significant volume expansion, which does not usually induce hypertension. However, in CKD there is often inability to excrete a sodium load with accompanying hypertension, and it is likely that this mechanism contributes in pregnancy. Other potential contributory factors include stimulation of the renin-angiotensin and sympathetic nervous systems; alterations in endothelial factors such as prostacyclin, nitric oxide, and endothelin; and drugs such as calcineurin inhibitors and corticosteroids. Regardless of its cause, persistence of hypertension is an adverse factor in pregnancy outcome and inadequate use of antihypertensives in pregnancy has been associated with poorer pregnancy outcomes, at least in women with renal transplants.[11] BP often will rise significantly soon after delivery and should be measured diligently postpartum and treated if necessary.

Hypertension in pregnancy is defined as BP of 140/90 mm Hg or greater and has historically been the threshold for commencing treatment. A large randomised controlled trial comparing tight BP control (target diastolic blood pressure [DBP], 85 mm Hg) or less tight control (target DBP, 100 mm Hg) reported no difference in neonatal outcomes but a reduction in episodes of severe maternal hypertension including requirement for intravenous antihypertensive treatment, in those with more tight BP control[12]; thus stricter hypertension control is now generally recommended for pregnant women with hypertension.

Target BP for nonpregnant women with CKD are lower in the presence of proteinuria; therefore pregnant women with proteinuric CKD may have a prolonged period when BP is above the usual target if standard pregnancy targets are used, which may contribute to progressive renal impairment, and thus strict BP control is imperative for women with CKD. Although there is no direct evidence for optimum BP thresholds in women with CKD, the authors recommend aiming for 110 to 140/80 to 85 mm Hg. Nevertheless, if a pregnant woman develops BP below 110/80 mm Hg, it is the authors' practice to reduce antihypertensives so as to avoid the potential risk for fetal hypoperfusion.

There is limited understanding of the role of nonpharmacologic interventions for treatment of hypertension in pregnancy. However, salt restriction is not recommended because of the increased net requirement of sodium in pregnancy to facilitate plasma volume expansion. Suitable antihypertensive agents include methyldopa, labetalol, oxprenolol, hydralazine, prazosin, and nifedipine, and they all may be used in conventional doses. There is no evidence to prioritize these agents, and choice of first-line agent is based on clinician preference and experience. The frequency of dosing often needs to be increased because of altered drug metabolism in pregnancy. Diltiazem may have a small benefit in reducing proteinuria, but this has not been addressed specifically for pregnancy. Diuretics are not recommended during pregnancy because any reduction in maternal plasma volume may have adverse effects on uteroplacental or renal perfusion, but may be used in extreme circumstances such as pulmonary edema or substantial peripheral edema leading to skin breakdown. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) must be discontinued as soon as pregnancy is diagnosed, because of increased risk for fetal growth restriction, oligohydramnios, neonatal renal failure, and probably cardiac and neurologic development abnormalities. Although it remains usual practice to cease ACE inhibitors or ARBs before pregnancy, it is acceptable to continue these until the time of conception for some women, often those with heavy proteinuria, provided the woman understands the need to cease these on learning she is pregnant. Aldosterone antagonists also should be avoided, and atenolol has been associated with fetal growth restriction. Enalapril or captopril may be used in women after delivery for those who wish to breastfeed.

RENAL BIOPSY IN PREGNANCY

It is rare to require renal biopsy in pregnancy. Situations in which biopsy may inform treatment that could significantly affect the pregnancy outcome for mother and baby are as follows:

1. *De novo* onset of nephrotic syndrome or unexplained impaired GFR with abnormal urine sediment before fetal viability, that is, before 24 weeks of gestation. Nephrotic syndrome after this stage can generally be managed conservatively until delivery, usually at about 32 to 34 weeks; most such cases are due to preeclampsia.
2. Situations before 32 weeks of gestation in which clinician and patient have agreed that immunosuppression and/or plasma exchange will be used if necessary, while prolonging the pregnancy to about 32 weeks.
    a. Rapidly declining GFR without apparent reversible cause in women with underlying primary glomerulonephritis (GN).
    b. Acute kidney injury with active urine sediment.
    c. Declining GFR or increasing proteinuria in a woman with lupus nephritis or lupus without previously known nephritis.
3. Deteriorating GFR before 32 weeks of gestation without obvious cause in a woman with a kidney transplant, to exclude acute rejection.

Complication rates of renal biopsy in pregnancy are probably comparable to those in general nephrology practice, but one systematic review reported complications in 7% of biopsies performed in pregnancy compared with 1% performed postpartum.[13]

SUPERIMPOSED PREECLAMPSIA

Preeclampsia (see Chapter 42) is a placental disorder of unknown cause that is rarely diagnosed before 20 weeks of gestation that has several predisposing risk factors, including an association with increasing severity of CKD. Superimposed preeclampsia in a woman with underlying renal impairment frequently will lead to exaggerated hypertension and proteinuria with risks for nephrotic syndrome, short-term and long-term progression of maternal renal impairment, fetal growth restriction, prematurity and perinatal mortality.

Superimposed preeclampsia may be challenging to diagnose in a woman with preexisting hypertension, renal impairment, and/or proteinuria. However, when these features are accompanied by additional features such as hyperreflexia with clonus, abnormal liver transaminases, or new-onset thrombocytopenia (except in systemic lupus), superimposed preeclampsia is likely, although relatively few patients with superimposed preeclampsia present with extrarenal manifestations.[8]

It has been proposed that an elevated ratio of soluble fms-like tyrosine kinase 1 to placental growth factor (sFlt-1/PlGF) is diagnostic of preeclampsia and distinguishes this condition from pregnant women with CKD[14]; a prospective cohort study reported comparable diagnostic performance for superimposed preeclampsia and preeclampsia without preexisting disease[8]; although these data are promising, measurement of the sFlt-1/PlGF ratio is not yet recommended for routine clinical practice. Confirmation of superimposed preeclampsia in women with CKD is to some extent unnecessary because clinicians should be vigilant for changes in maternal and fetal condition in all cases and the indications for delivery in women with preeclampsia are comparable to those for progressive underlying renal disease (Box 43.5).

Limited studies suggest that aspirin is of benefit in reducing superimposed preeclampsia and perinatal death in women with underlying renal disease.[15] Our practice is to use low-dose aspirin 75 to 150 mg/day for all women with CKD, giving reassurance regarding safety for both fetus and maternal renal disease. We also use calcium 1200 mg/day as prophylaxis against preeclampsia when there is no concern about hypercalcemia; data for calcium as prophylaxis are less convincing than for aspirin, but this causes little harm and may have some benefit.

BOX 43.5 **Indications for Delivery in Women With Preeclampsia or Chronic Kidney Disease**

- Inability to control blood pressure
- Deteriorating glomerular filtration rate
- Neurologic abnormalities, such as eclampsia, headaches with accompanying clonus and hyperreflexia, or repeated visual scotomata
- Worsening thrombocytopenia
- Increasing liver transaminase levels
- Failure of fetal growth
- Reversed or absent end diastolic flow on cardiotocography

The decision to deliver is based on a global clinical assessment rather than on specific thresholds for each parameter.

ASSESSMENT OF FETAL WELL-BEING

Prematurity, fetal growth restriction, and stillbirth are the major concerns for neonatal outcomes of women with renal impairment, particularly if superimposed preeclampsia develops. Avoidance of prematurity is not just for the immediate effects on the baby but the association with higher mortality in later life.

Early pregnancy ultrasound (before 12 weeks) is advised to estimate accurately the expected date of delivery, followed by a nuchal translucency scan at 12 weeks, and then fetal morphology scan at 18 to 20 weeks of gestation to screen for fetal anomalies, assess fetal well-being, and check placental function and position. An important point is that blood human chorionic gonadotropin (hCG) levels are often elevated in women with renal impairment and may overestimate the risk for a fetal abnormality.[16]

In women with stages 3 to 5 CKD and all women with hypertension, additional ultrasound scans should be done at 2- to 4-weekly intervals to assess fetal growth and amniotic fluid volume, with Doppler studies of umbilical artery blood flow from 28 weeks of gestation. Asymmetric intrauterine growth restriction (IUGR) in which the abdominal measurements are more decreased than the fetal head and femur measurements is characteristic of IUGR related to maternal CKD and reflects reduced placental function.

Amniotic fluid volume correlates well with perinatal outcome, and reduced volume helps distinguish babies who are small due to IUGR from those who are constitutionally small. However, women with diabetes and severe renal impairment may have disproportionately increased amniotic fluid because of excess urine fetal urine excretion.

Absent end diastolic flow on umbilical artery velocimetry is usually an indication for delivery, depending on gestation. The development of reversed end diastolic flow indicates a high risk for fetal hypoxia, acidosis, and death.

TIMING OF DELIVERY

In women with stable CKD and no evidence of fetal compromise, pregnancies should be continued to term and spontaneous labor awaited. The method of delivery, either vaginal or by cesarean section, is determined by obstetric issues rather than CKD. Indications for delivery are described in Box 43.5.

The goal is to time delivery such that the risks of delivery (to both mother and fetus) are less than the risks of the pregnancy continuing, which often requires consultation among nephrologist or obstetric medicine physician, obstetrician, midwife, and neonatologist. The following issues should be considered:

1. *Gestational age:* Decisions are difficult to make at the borderlines of viability (23 to 25 weeks of gestation). Although outcome data vary from country to country, approximate survival rates increase from 30% at 23 weeks to 75% at 25 weeks to 95% at 28 weeks of gestation. Babies born at less than 30 weeks of gestation have significant risk for long-term morbidity, including chronic lung disease and cerebral palsy.
2. *Prevention of respiratory distress syndrome:* Maternally administered antenatal corticosteroids, generally intramuscular betamethasone 12 mg two doses 12 hours apart ideally at least 24 hours before delivery, which has been shown to reduce respiratory distress syndrome by 50%.
3. *Transfer to a unit with neonatal support:* There is less neonatal morbidity and mortality if babies are born in hospitals where there is appropriate neonatal care rather than being transferred after delivery.

The final pregnancy outcome in most cases is successful for both mother and baby, albeit with long-term implications for both. Clinicians can take a positive approach, at all times emphasizing the need for diligence and assessment for potential complications, and aim to relieve some of the stress that accompanies pregnancy for women with CKD.

COURSE OF CHRONIC KIDNEY DISEASE DURING AND AFTER PREGNANCY

The risk for progression of renal disease during pregnancy depends on severity of renal disease, hypertension, increasing proteinuria, or onset of superimposed preeclampsia, rather than underlying cause of CKD.

Rapid deterioration during a pregnancy is unlikely in women with mild CKD, other than lupus, which may flare. However, 50% of women with moderate baseline renal impairment (serum creatinine >1.5 mg/dl [130 μmol/l]) or worse have a significant rise in serum creatinine in the third trimester or early postpartum and almost 1 in 5 of these will progress to ESRD within 6 months.[17] In a series of 49 women with stage 3 to 5 CKD before conception whose pregnancy proceeded beyond 20 weeks, GFR was lower after pregnancy than before conception, and this fall was predicted by the combination of preconception GFR less than 40 ml/min/1.73 m^2 and proteinuria greater than 1 g/day, but not by GFR alone.[18]

The course of renal disease postpartum is unpredictable. Even some women with stable renal function throughout their pregnancy develop an acute deterioration postpartum. Surveillance by the nephrologist therefore should be just as diligent in the first 3 to 6 months postpartum as during pregnancy. ACE inhibitors or ARBs should be commenced soon after delivery for their antiproteinuric effect if GFR is stable.

A Norwegian study showed that women with biopsy-proven kidney disease had slightly faster progression to ESRD if their pregnancy required preterm delivery but not if they had preeclampsia.[19] A neglected issue is the association between preterm birth, low birth weight, and later life cardiovascular and renal disease; because many women with CKD are delivered prematurely, this in turn may transmit an increased risk for renal disease to their offspring even if the renal disease is not hereditary. On balance it is prudent to consider both preeclampsia and preterm delivery as risk factors for later kidney disease. It is imperative that women with CKD have close attention postpartum, with a strong emphasis on BP control.[20]

MANAGEMENT OF SPECIFIC RENAL DISORDERS DURING PREGNANCY

The most common CKDs predating pregnancy are primary GN, diabetic nephropathy, lupus nephritis, and reflux nephropathy.

IgA Nephropathy

Pregnancy outcomes for women with IgA nephropathy are generally good, with outcomes comparable to those with other causes of CKD. Long-term follow-up of women with IgA nephropathy diagnosed in childhood showed that pregnancy was complicated by hypertension in half the cases and premature delivery in one third.[21] Pregnancy in IgA nephropathy does not appear to cause accelerated renal dysfunction, at least in those with CKD stage 1 or 2, compared with nulliparous women,[22] but proteinuria may increase in the third trimester.[23] However, there is limited evidence that women with proteinuria before pregnancy have a more rapid decline in function postpartum.[24] Visible hematuria is not more likely during pregnancy unless there is intercurrent upper respiratory tract or gastrointestinal tract infection.

Diabetic Nephropathy

Studies in the United Kingdom reported that 8% of pregnant women with type 1 diabetes and 5% with type 2 diabetes had nephropathy. Diabetes *per se* increases risks for preterm birth, cesarean section, and perinatal mortality. The presence of overt nephropathy more than doubles the risk for fetal death after 20 weeks. There is an added risk for congenital abnormalities if blood sugar was not adequately controlled at the time of conception, and a large cohort study reported that the presence of nephropathy also was an independent risk factor for congenital abnormalities.[25]

The Diabetes Control and Complications Trial and EURODIAB trial both concluded that pregnancy does not increase the progression of diabetes to early diabetic nephropathy (microalbuminuria). Although microalbuminuria alone did not correlate with increased perinatal risk, both prematurity and superimposed preeclampsia rates were higher than in women with type 1 diabetes without microalbuminuria. It is likely that women with diabetic nephropathy have worse pregnancy outcomes than women with other causes of CKD and comparable renal function. For example, a recent Finnish retrospective cohort study of women with type 1 diabetes and nephropathy (median prepregnancy serum creatinine 0.8 mg/dl [68 μmol/l]) reported high complication rates (e.g., preeclampsia 42%, preterm before 34 weeks 21%, neonatal care admission 49%).[26]

The outcome of established diabetic nephropathy during pregnancy depends on the usual factors of severity of renal impairment and hypertension. Meticulous control of blood glucose and BP during pregnancy is required in all women with diabetic nephropathy. One study showed that failure to achieve mean arterial pressure below 100 mm Hg was associated with increased risk for early delivery even after adjusting for glucose control.[27] Risk for permanent decline in renal function for women with more severe diabetic nephropathy has not been formally evaluated, but the incidence of CKD progression is likely to be comparable, if not higher, than for women with CKD without diabetes. Ideally, ACE inhibitors (enalapril or captopril if breastfeeding) should be introduced soon after delivery for prevention of progression of diabetic nephropathy.

Having gestational diabetes mellitus (GDM) without developing overt diabetes after the pregnancy is still associated with about a 10% risk for microalbuminuria by age 50, an intermediate risk between that of nondiabetic and diabetic women.[28] This means that women with a history of GDM, not just those with type 1 or 2 diabetes, should be followed after pregnancy assessing renal function and urine albumin excretion because of their risk for later developing diabetes.

Lupus Nephritis

Ideally, women with lupus should be in remission for at least 6 months before conception and on maintenance corticosteroids in doses less than prednisolone 20 mg/day, with or without azathioprine; all such women should receive aspirin and hydroxychloroquine during pregnancy.[29] Women with active disease at conception have a higher likelihood of developing acute lupus nephritis during pregnancy that is then associated with high fetal risk, about 20% having miscarriage, stillbirth, or neonatal death[30]; thus it is important to establish remission before pregnancy. This assessment may include cessation of ACE inhibitors and repeat renal biopsy to exclude active disease in women with persistent proteinuria more than 1 g/24 h. If such a woman has worsening proteinuria (at least >1 g/day) and there is ongoing delay to conception, we now advocate continuing ACE or ARB therapy until conception because the first-trimester risks of these drugs are small. We discuss the rationale for this approach clearly with each woman.

Lupus nephritis may flare during pregnancy in about 30% or postpartum in 15%,[31] but a prophylactic postpartum increase in corticosteroid dosing in those who have not had a flare during the pregnancy is not indicated. The major cause of maternal death in lupus nephritis is sepsis, and immunosuppression should be used with care in pregnant women.[32] New onset or a flare of lupus nephritis, evidenced by increasing proteinuria, active urine sediment, and rising serum creatinine, is a major concern, and such cases have sometimes been associated with maternal death. These women should be treated by increasing doses of prednisolone and early introduction of azathioprine. Some prefer to undertake renal biopsy at this point to confirm the histologic changes before introducing immunosuppression. Either approach is reasonable, but our approach is to introduce steroids and azathioprine and reserve biopsy for after delivery.

Cyclophosphamide and mycophenolate mofetil (MMF) are contraindicated in pregnancy because of teratogenicity, including (for MMF) microtia (underdeveloped external ear), auditory canal atresia, cleft lip and palate, and micrognathia; although cyclophosphamide has been used successfully in a few cases of lupus nephritis in later pregnancy, its use is not recommended. Tacrolimus is an alternative agent that has been used with increasing success in women with active lupus nephritis in pregnancy.[33]

Prior histologic class of lupus nephritis has no influence on pregnancy outcome. Predictors of poor pregnancy outcome include baseline creatinine greater than 0.9 mg/dl (100 µmol/l), proteinuria greater than 0.5 g/24 h, antiphospholipid syndrome, hypertension, non-White ethnicity, and maternal disease flare.[34] A prospective cohort study of women with lupus, including those with mild nephritis, recently reported that pregnancy outcomes were favorable for women without adverse risk factors (including lupus anticoagulant, antihypertensive use, active disease, or low platelets), with 92% having uncomplicated pregnancies. However, when counseling about future pregnancies women should be advised that even if their lupus nephritis has been well treated, they appear to have a greater risk for maternal complications and lupus flare in their next pregnancy than do women with systemic lupus erythematosus (SLE) who have never had nephritis; this appears only partly explained by increased activity of the SLE at conception. Fortunately, fetal outcomes are not affected adversely in this group and postpartum renal function appeared unaffected.[35] This means that such women need more surveillance during pregnancy than usual, to detect a renal flare or preeclampsia, their two biggest maternal risks.

Women with anti-Ro and anti-La antibodies should be counseled regarding the risk for fetal heart block and neonatal cutaneous lupus, respectively. Hydroxychloroquine may reduce the risk for recurrent fetal heart block in women with a previously affected infant, and this should be encouraged.[36]

Reflux Nephropathy

Pregnancy outcome in women with reflux nephropathy depends on preexisting renal function and BP control rather than the disorder itself, as for other renal diseases. There is an increased incidence of gestational hypertension, preeclampsia, and fetal morbidity in women with reflux with renal scarring but not in those without scarring compared with the general population.[37] These women are more predisposed to urinary tract infection (UTI) throughout pregnancy, as are women who have had surgically corrected reflux in childhood. Around 20% of women with reflux nephropathy will develop UTI in pregnancy, with about 6% of these due to acute pyelonephritis. This is important because UTI can be associated with premature labor or spontaneous rupture of membranes; hence regular urine culture should be performed throughout pregnancy in women with underlying reflux nephropathy. Management of UTI in pregnancy is further discussed in Chapter 42. About 40% of offspring have vesicoureteral reflux, and testing of offspring is recommended offspring is recommended.

Inherited Renal Disorders

Inherited renal disorders are likely to have been diagnosed before the pregnancy, and the specific implications of this for the offspring will have been discussed, for example, autosomal dominant polycystic kidney disease and Alport syndrome. For single-gene disorders preimplantation diagnosis may be available, and referral to a specialist is recommended.

DIALYSIS IN PREGNANCY

Significant improvements in outcomes of pregnant women requiring dialysis during pregnancy have occurred over the past two decades, with fetal survival rising from less than 50% to almost 85%.[38] Enhanced outcomes have been associated with more intensive dialysis regimens and advances in neonatal care enable survival for premature and growth-restricted infants. Evidence for the benefit of increased dialysis in pregnancy came from a Canadian cohort study that reported significant improvement in birth weight and length of gestation in women with ESRD who received prolonged dialysis (43 ± 6 h/wk) compared with those with a more modest increment (17 ± 5 h/wk).[39] A meta-analysis of 574 pregnancies in 543 patients, reported that fewer dialysis hours per week was strongly associated with preterm delivery before 37 weeks.[40] Recommendations for managing hemodialysis during pregnancy are listed in Box 43.6.

Women of childbearing age undergoing dialysis have around a 1 in 20 chance of conceiving,[38] but increments in dialysis dose also appear to be associated with increased fertility, for example, nocturnal home dialysis.[39] Women of childbearing age on maintenance dialysis therefore need to be counseled about adequate contraception.

Initiating Dialysis for Progressive Chronic Kidney Disease

Dialysis should be commenced for the standard indications of hyperkalemia, acidosis, and/or fluid overload. In addition, it is generally recommended to commence dialysis at a blood urea nitrogen (BUN)

BOX 43.6 Managing Hemodialysis During Pregnancy

Prepregnancy

- Discuss risks of pregnancy (miscarriage, fetal death, fetal growth restriction, prematurity, preeclampsia).
- Ensure all medications safe in pregnancy.
- Aspirin: 75 to 150 mg daily.
- Folic acid: 5 mg daily.

During Pregnancy

Dialysis	20 h/wk in four or more sessions. Aim for predialysis BUN <40 mg/dl (serum urea 15 mmol/l). Heparin requirement may increase because of hypercoagulability of pregnancy.
Anemia	Intravenous iron to maintain iron stores. Dose ESA to achieve hemoglobin 10 to 11 g/dl.
Bicarbonate	Adjust oral and dialysate bicarbonate to achieve normal serum bicarbonate for pregnancy (18 to 22 mmol/l).
Nutrition	Dietician advice to ensure adequate protein and nutrient intake. Supplement oral or dialysate phosphate to maintain postdialysis serum phosphate in normal range.
Calcium	Maintain normal serum calcium with additional oral calcium and vitamin D, as well as increased dialysate calcium. Hypercalcemia occasionally provoked by placental PTHrP and vitamin D–like substances.
Phosphate	Supplement oral or dialysate phosphate to maintain postdialysis serum phosphate in normal range.

After Pregnancy

- Return to usual dialysis schedule immediately.
- Readjust dry weight and antihypertensives weekly for 6 weeks.

BUN, Blood urea nitrogen; *ESA,* erythropoiesis-stimulating agents; *PTHrP,* parathyroid hormone–related protein.

>40 mg/dl (serum urea >15 mmol/l) and aim for predialysis blood urea below 10 mmol/l (BUN 28 mg/dl).[38] Dialysis initiated during pregnancy is probably associated with greater likelihood of successful pregnancy than for those on maintenance dialysis, perhaps because of the benefits of residual renal function,[41] although this is not a consistent finding.[39]

Dialysis Regimens in Pregnancy

In addition to augmentation of dialysis dose as practically possible, ensuring the above biochemical goals are achieved, and weekly surveillance, the following also should be considered:

- Control of maternal blood pressure, generally to 110 to 140/80 to 90 mm Hg. This is difficult to achieve in many cases. There still appears to be volume expansion in women on maintenance hemodialysis who become pregnant, as evidenced by anemia and fall in serum albumin. As yet there are no data to recommend assessment of volume status in pregnant women on dialysis using ultrasound measurement of inferior vena cava diameter or bioimpedance.
- Intravenous iron and erythropoiesis-stimulating agents aiming for a hemoglobin level of 10 to 11 g/dl. No adverse consequences in pregnancy have been reported with either intravenous iron or erythropoiesis-stimulating agents, although there is a theoretic risk for exacerbation of hypertension with the latter agents.
- Detection and early treatment of sepsis, which may precipitate premature labor or premature rupture of membranes.
- Phosphate monitoring if supplementary phosphate in the dialysate is required.
- Fetal monitoring with at least 2- to 4-weekly ultrasound scanning from the time of fetal viability, around 24 weeks of gestation.

Peritoneal Dialysis and Pregnancy

There is little information concerning specific requirements of women on peritoneal dialysis (PD) during pregnancy. A systematic review and meta-analysis compared pregnancy outcomes in women on hemodialysis (HD) with PD and reported a higher incidence of infants who are small for gestational age in those receiving PD,[40] although successful pregnancies have been reported. A major risk is that PD peritonitis may provoke premature labor or premature rupture of membranes. Although some women have had successful outcomes remaining on PD throughout pregnancy, we recommend switching to HD to augment dialysis dose in a controlled manner. This recommendation is predicated on the greater available evidence for HD in pregnancy and may change when more data emerge about PD in pregnancy.

RENAL TRANSPLANTATION AND PREGNANCY

Successful renal transplantation is an excellent way of restoring fertility in women with ESRD. It is surprising therefore that the pregnancy rate amongst female transplant recipients more than halved between 1990 and 2003, which is unexplained by a change in age of women being transplanted, but may be related to the introduction of MMF, which is teratogenic.[42] Women with transplants appear less likely to conceive if ESRD is caused by diabetes compared with women without diabetes and in those with preemptive transplants compared with those on dialysis for 3 or more years before transplant.

Timing of Pregnancy

Women are recommended to wait at least 12 months after a successful renal transplant before embarking on pregnancy, to ensure stable transplant function and maintenance immunosuppression, although evidence is conflicting. A meta-analysis of pregnancy outcomes in women with renal transplants reported that live-birth rates were higher if conception occurred within 2 years of transplantation compared with 4 years or more, but in a study in the United States, rates of preeclampsia, gestational diabetes, caesarean section, and preterm delivery also were higher than for the general population in those who conceived within 2 years.[43] One to two years after transplantation seems a practical time for ensuring clinical stability and having optimal BP control and stable immunosuppression.

Immunosuppression in Pregnancy

There are usually opportunities to ensure that conception is carefully planned, immunosuppression optimized, and folic acid commenced, but, unfortunately, many pregnancies in women with renal transplants are still unplanned. Immunosuppressive drugs considered safe in pregnancy include prednisolone, azathioprine, and cyclosporine. Tacrolimus has been associated with neonatal hyperkalemia, but overall data support its safety. MMF is associated with embryotoxic effects and should be avoided in pregnancy, as should sirolimus and everolimus. We suggest ceasing such drugs 6 months before pregnancy.

Gestational diabetes occurs in 3% to 12% of pregnancies of women with renal transplants but no more frequently in tacrolimus-treated women than in those receiving cyclosporine. Screening for gestational diabetes is recommended for all transplant recipients at 12 and 28 weeks.

Dosing of tacrolimus in pregnancy remains problematic until assays for free tacrolimus become readily available. Tacrolimus pharmacokinetics alter during pregnancy with increased metabolism but altered protein binding. Our practice is to change dose from prepregnancy doses only if trough levels fall very low.

Azathioprine, tacrolimus, and prednisone appear safe to use for women who are breastfeeding, but the decision to breastfeed remains an individual one. Women should be informed that effects on the baby are not completely known but that breastfeeding may have considerable advantages, particularly in premature and growth-restricted babies.

Pregnancy Outcomes

A favorable view of pregnancy in women who have undergone successful renal transplantation was supported early on by observations in over 3000 pregnancies from 2000 women mostly receiving azathioprine and prednisone.[44] About 15% of these pregnancies miscarried spontaneously, and of those going past the first trimester, pregnancy was successful in over 90% of cases, provided that hypertension or a decline in renal function had not occurred before 28 weeks of gestation, in which case successful pregnancy outcome was reduced to about 70%. Women with preconception serum creatinine of 1.4 mg/dl (125 μmol/l) had 96% pregnancy success, whereas those with higher serum creatinine had a 75% success rate. In keeping with the data for all women with CKD, long-term decline in renal function occurred significantly more often (27%) in those with preconception serum creatinine greater than 1.4 mg/dl.

Hypertension, either accelerated from preexisting hypertension or *de novo* during pregnancy, is present in 58% to 72% of cases. Even with these relatively good outcomes, somewhere between 30% and 70% of women will have hypertension requiring treatment as the pregnancy progresses (sometimes superimposed preeclampsia), fetal growth restriction occurs in 40% to 50% of cases, and preterm delivery occurs in as many as 40% to 50%, with attendant long-term risks for prematurity. Cesarean section is necessary in approximately half of cases.[43,44]

The United States National Transplantation Pregnancy Registry (NTPR) reported in 2014 on the outcomes of 1742 pregnancies from 986 women who had received kidney transplants.[45,46] Because this is a voluntary registry, there is potential for reporting bias. Data are reported according to immunosuppression taken during pregnancy and include azathioprine without calcineurin inhibitor (26.4%), cyclosporine (48.4%), or tacrolimus (25.2%). Overall live birth rates were about 76%, 30% of women had preeclampsia, 51% of live births required delivery before 37 weeks of gestation, and 41% of babies weighed less than 2500 g. Biopsy-proven acute rejection occurred in 1% of pregnancies, and 4.4% of babies had a birth defect, a figure not dissimilar to that of the general population. Graft loss within 2 years after delivery occurred in approximately 6% of women. Maternal and fetal risks for pregnancy in women with a renal transplant are summarized in Box 43.7.

Graft and patient survival are similar in those with and without any pregnancy over follow-up as long as 15 to 20 years. This was observed in data from 577 pregnancies in the Australian and New Zealand Data registry, most of whom had GN or reflux nephropathy as their primary diagnosis[47] and in most single-center cohort studies.

A postpregnancy increase in serum creatinine has been associated with cyclosporine use, possibly because cyclosporine doses were increased during pregnancy as blood concentrations fell. Thus it is very important to check tacrolimus or cyclosporine levels frequently in the early postpartum period.

Acute transplant rejection is uncommon—reported in fewer than 1 in 20 cases.[43] Presentation as acute graft dysfunction is not different in pregnancy; renal biopsy is required to confirm the diagnosis. Treatment is limited to intravenous methylprednisolone and increments in oral immunosuppression, because safety of more potent agents (e.g., antithymocyte globulin) is unproven in pregnancy and likely to cause harm to the developing fetus.

BOX 43.7 Maternal and Fetal Outcomes in Renal Transplant Pregnancies

Maternal

- Long-term decline in glomerular filtration rate if preconception serum creatinine below 1.4 mg/dl (125 μmol/l); rate of decline not usually different from transplant women without pregnancy
- Graft loss in 5% to 10% at 2 years postpartum
- Hypertension in about two thirds
- Rejection risk in 2% to 4%
- Infection in 20% to 35%
- Gestational diabetes mellitus in 10%

Fetal

- Overall live birth rate: 75% to 80%
- Spontaneous miscarriage: 15%
- Prematurity: 50%
- Fetal growth restriction: 50%
- Birth defects in about 5%, probably no more than in the general population
- Long-term consequences of prematurity, although most infants have normal postnatal growth and development

Infection in Pregnant Transplant Recipients

There is an increased risk for infection (20% to 35%), particularly UTI but also cytomegalovirus (CMV) infection with attendant maternal and fetal risks. The consequences of any infection can include premature labor and preterm rupture of membranes. CMV can cause congenital malformations and fetal demise, but delay in conception to after at least 1 year post-transplantation makes new infection or reactivation unlikely. Valganciclovir prophylaxis is not advised because of teratogenicity in animals, but there are case reports of successful use in women with severe CMV infection in pregnancy.

Recommendations for management of pregnancy in women with a renal transplant are summarized in Box 43.8.

Male Transplant Recipients

Outcomes of pregnancies fathered by male transplant recipients showed mean gestational age and mean birth weight similar to those of the general population. There have been recent concerns about teratogenicity of MMF in the offspring of fathers with renal transplants, and the manufacturers have advised switching to a different agent before conception. We agree with this approach for stable grafts, but because these recommendations are largely theoretical, this should be balanced against the risk for inadequate immunosuppression for a prolonged period in men with higher risk transplants.

PREGNANCY IN THE KIDNEY DONOR

It is usually stated that being a kidney donor does not adversely affect future pregnancy outcomes in terms of fetal birth weight, stillbirth, or prematurity; although recent studies suggest there may be an increased risk for preeclampsia in pregnancy after organ donation, and some reports suggest that fetal outcomes also may be slightly worse.[48,49] A Canadian population study also reported a higher incidence of preeclampsia and gestational hypertension in women after donation compared with controls. Importantly, there were no differences in neonatal outcomes, including gestation at delivery or birth weight, and thus placental insufficiency is unlikely to be severe.[50] These studies have some limitations, and pregnancy should not be discouraged in women

BOX 43.8 Management of Renal Transplant Patients During Pregnancy

Prepregnancy

- Stable graft function at least 1 year after transplantation.
- Discuss risks with transplant recipient and her partner.
- Best pregnancy outcome will occur if:
  - Prepregnancy serum creatinine is less than 1 mg/dl (125 μmol/l)
  - Proteinuria <500 mg/day
  - Blood pressure <140/90 mm Hg
- Aspirin 75 to 150 mg/day if creatinine is ≥1.5 mg/dl (130 μmol/l) or 0.9 to 1.5 mg/dl (100 to 130 μmol/l) and proteinuria is >1 g/day.
- Replace all medications that are not safe in pregnancy.
- Eradicate UTI before pregnancy; prophylactic antibiotics indicated if there has been recurrent UTI since transplant.
- Stable cyclosporine or tacrolimus blood levels.
- Test for and control diabetes.

During Pregnancy

- Visits every 2 weeks until 24 weeks of gestation (alternating between obstetrician and nephrologist), then weekly.
- Assess fetal growth by ultrasound at least every 4 weeks from 24 weeks of gestation.
- Do not adjust CNI dose during pregnancy unless there are extreme variations from stable prepregnancy levels.
- Screen for gestational diabetes at 28 weeks of gestation with 1-hour 50-g glucose challenge test.
- At each visit, assess BP (goal 110 to 140/80 to 90 mm Hg), proteinuria (dipstick, then uPCR if dipstick result is positive), urine culture (if history of recurrent UTI, otherwise at 24, 28, and 32 weeks of gestation), electrolytes, creatinine, full blood count, CNI level, and fetal growth.
- Reassess at each visit whether there is an impending indication for delivery (see Box 43.5).

During Delivery

- Vaginal delivery is usually possible despite pelvic kidney.
- Prophylactic antibiotics are not required routinely.

Postpartum

- Monitor CNI and serum creatinine levels daily in hospital.
- Breastfeeding appears safe with CNI drugs, azathioprine, and corticosteroids, but discuss individual case with neonatologist.
- Review weekly or every other week for the first 3 months.

ACE, Angiotensin-converting enzyme; *BP,* blood pressure; *CNI,* calcineurin inhibitor; *uPCR,* urine protein-to-creatinine ratio; *UTI,* urinary tract infection.

BOX 43.9 Managing Women With Preexisting Renal Disease During Pregnancy

1. Women with chronic kidney disease should be managed by a team comprising obstetrician, nephrologist, and experienced midwife or specialty nurse, preferable in a high-risk pregnancy clinic.
2. Main determinants of pregnancy outcome are prepregnancy GFR, proteinuria, and BP. These should be the focus in counseling.
3. GFR should be estimated using serum creatinine and proteinuria using changes in spot uPCR after calculation of initial ratio on 24-hour urine collection.
4. Low-dose aspirin should be given to reduce risk for preeclampsia or perinatal death. Subcutaneous heparin if nephrotic syndrome develops.
5. Primary issues during pregnancy are BP control, watching for emerging preeclampsia, and regular assessment of fetal well-being.
6. An appropriate schedule of visits is every 2 weeks until 24 weeks of gestation (alternating between obstetrician and nephrologist) and then weekly until delivery.
7. Appropriate laboratory evaluations are:
   Initial visit at 12 weeks of gestation: Full blood count, serum creatinine and electrolytes, liver function, 24-hour uPCR if proteinuria on dipstick testing.
   If baseline GFR is normal, repeat at 24 weeks of gestation.
   If baseline GFR is abnormal, repeat every 4 weeks.
   Mid-stream urine culture at 24, 28, and 32 to 34 weeks of gestation (monthly throughout pregnancy if woman has history of UTI).
8. Fetal assessment by ultrasound, in those with impaired GFR, or with heavy proteinuria.
   At 20 weeks: Uterine artery pulsatility index.
   Monthly from 24 weeks: Fetal growth, blood flow, amniotic fluid index.
9. Obstetric review at 6 weeks postpartum, nephrology review within the first 4 weeks because impairment of renal function can occur after delivery. Transplant patients should be seen more often.

GFR, Glomerular filtration rate; *uPCR*, urine protein-to-creatinine ratio.

who have been kidney donors; rather, the key message is that all such women should be treated as “at risk” pregnancies and have a higher number of clinical reviews, focusing on maternal BP and urinalysis and fetal growth, than in normal low-risk pregnancies.

SUMMARY

A summary of factors to be considered in managing a pregnant woman with renal disease is shown in Box 43.9. Attention to these issues from preconception through to postpartum can result in good pregnancy outcomes with preservation of maternal health. These women and in many cases their offspring require lifelong assessment for progressive renal and/or cardiovascular disease.

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SELF-ASSESSMENT QUESTIONS

1. A 32-year-old woman with autosomal dominant polycystic kidney disease (ADPKD) wishes to become pregnant. Her estimated glomerular filtration rate (eGFR) is 110 ml/min/1.73 m^2. Her blood pressure (BP) is 142/89 mm Hg, and she has no proteinuria. She is taking amlodipine 5 mg once daily. Which of the following is correct advice about a future pregnancy?
   - **A.** Her pregnancy will be low risk.
   - **B.** She should have preimplantation genetic testing.
   - **C.** She should take aspirin daily.
   - **D.** She should stop amlodipine when she becomes pregnant.
2. A 39-year-old woman with end-stage renal disease secondary to lupus nephritis received a kidney transplant from her partner 9 months ago and wishes to conceive. She has had no episodes of rejection. Her eGFR is 84 ml/min/1.73 m^2, and her BP is 124/77 mm Hg. She is currently taking prednisolone, tacrolimus, mycophenolate mofetil (MMF), and aspirin. What would you recommend to have the best outcome?
   - **A.** She should not conceive until at least 24 months after transplantation.
   - **B.** Breastfeeding is not recommended with immunosuppressant medication.
   - **C.** Her steroid dose should be increased and MMF stopped.
   - **D.** Anti-Ro and La antibody should be assessed to inform fetal monitoring.
3. A 28-year-old woman with immunoglobulin A (IgA) nephropathy is at 32 weeks of gestation. Her prepregnancy GFR is 45 ml/min/1.73 m^2 and ratio of urine protein to creatinine (uPCR) is 120 mg/mmol. She presents with headache and peripheral edema; her BP is 166/100 mm Hg and uPCR is 245 mg/mmol. Her serum creatinine has increased from 70 µmol/l 4 weeks ago to 84 µmol/l. What is the best approach to management?
   - **A.** Admit for BP control and assess by fetal artery Doppler to determine timing of delivery.
   - **B.** Admit for BP control and urgent cesarean section delivery to preserve renal function.
   - **C.** Give intravenous magnesium sulfate to prevent eclampsia, then plan delivery within 24 hours.
   - **D.** Start aspirin 75 mg daily and labetalol 200 mg three times daily with escalation to intravenous antihypertensives if no response.

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Autosomal Dominant Polycystic Kidney Disease

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DEFINITION

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder characterized by multiple, bilateral renal cysts and associated with cysts in other organs, such as liver, pancreas, and arachnoid membranes.[1] It is a genetic disorder caused by mutations in either of two major genes and is inherited in an autosomal dominant pattern, with variable expression. Although benign (nongenetic) renal cysts are common with aging, an underlying inherited disease should be suspected in patients with multiple bilateral renal cysts, even if the renal function is normal.

ETIOLOGY AND PATHOGENESIS

The common ADPKD proteins, polycystin-1 and polycystin-2, play a critical role in the normal function of the primary cilium that is essential to maintaining the differentiated phenotype of tubular epithelium.[2]

Genetic Mechanisms

ADPKD is genetically heterogeneous with two common genes identified (Fig. 44.1), *PKD1* (chromosome 16p13.3) and *PKD2* (4q21). Recently, mutations in a third gene, *GANAB,* have been identified in families with mild polycystic kidney and more variable polycystic liver disease (PLD).[3] Autosomal dominant polycystic liver disease (ADPLD) also exists as an independent entity and is genetically heterogeneous; the first two genes identified (*PRKCSH* in chromosome 19 and *SEC63* in chromosome 6) account for about one third of isolated ADPLD cases, with *GANAB,* also an ADPLD gene.

Evidence from animal models of ADPKD and analysis of cystic epithelia has shown that renal cysts may develop from loss of functional polycystin with somatic inactivation of the normal allele. However, cysts can develop even if the protein is not completely lost, as demonstrated by animal models expressing incompletely penetrant alleles.[4] Furthermore, transgenic rodents overexpressing *Pkd1* or *Pkd2* develop renal cystic disease, which suggests that multiple genetic mechanisms causing an imbalance in expression of polycystins can lead to the development of cysts.[2]

Polycystic Kidney Disease Proteins

Polycystin-1 (PC1; PKD1 protein) and polycystin-2 (PC2; PKD2 protein) belong to a subfamily of transient receptor potential (TRP) channels. PC1 (TRPP1; ~440 kDa) has the structure of a receptor or adhesion molecule and contains a large extracellular N region, 11 transmembrane regions, and a short intracellular C region (see Fig. 44.1). PC1 interacts with PC2 through a coiled-coil domain in the C-terminal portion and with multiple other proteins at different extracellular and intracellular sites. PC1 is found in the primary cilia, plasma membrane at focal adhesions, desmosomes, adherens junctions, and possibly endoplasmic reticulum and nuclei. PC1 may regulate the mechanical strength of adhesion between cells by controlling the formation of stabilized, actin-associated adherens junctions. PC2 (TRPP2; ~110 kDa) contains a short N-terminal cytoplasmic region, six transmembrane domains, and a short C-terminal portion. PC2 is localized predominantly to the endoplasmic reticulum but also to the plasma membrane, primary cilium, centrosome, and mitotic spindles in dividing cells.[2] PC1 and PC2 are also found at high concentrations in exosomes, which are shed into the urine and physically interact with primary cilia, possibly exerting a urocrine function of cell-cell communication.

Mechanisms of Cyst Formation

Experimental data indicate that the timing of ciliary loss or *Pkd1* inactivation determines the rate of development of cystic disease. Inactivation in the developing kidney results in rapid progression.[5] Interestingly, the loss of *Pkd1* and cilia results in less severe PKD than loss of *Pkd1* alone.[6]

The polycystins are involved in the detection of extracellular cues at primary cilia, cell-cell contacts, and cell-matrix contacts and are essential to maintain the differentiated phenotype of the tubular epithelium. Reduction in one of the polycystins below a critical threshold results in inability to maintain planar polarity, increased rates of proliferation and apoptosis, expression of a secretory phenotype, and remodeling of the extracellular matrix.[2] PC1 and PC2 in the primary cilium may be required for the increase in cytosolic calcium that occurs in response to ciliary bending.[7] PC2 is a TRP channel (TRPP2) and functions as a calcium release channel in the endoplasmic reticulum.[8] PC1 interacts with and modulates the maturation and function of PC2, and vice versa.[9] PC1 and PC2 also interact with additional calcium channel proteins. Precisely how intracellular calcium homeostasis is altered in ADPKD remains uncertain, but many studies show reduced resting intracellular calcium, endoplasmic reticulum calcium stores, and store-operated calcium entry in primary cell cultures or microdissected samples from human and rodent polycystic tissues[2] (Fig. 44.2).

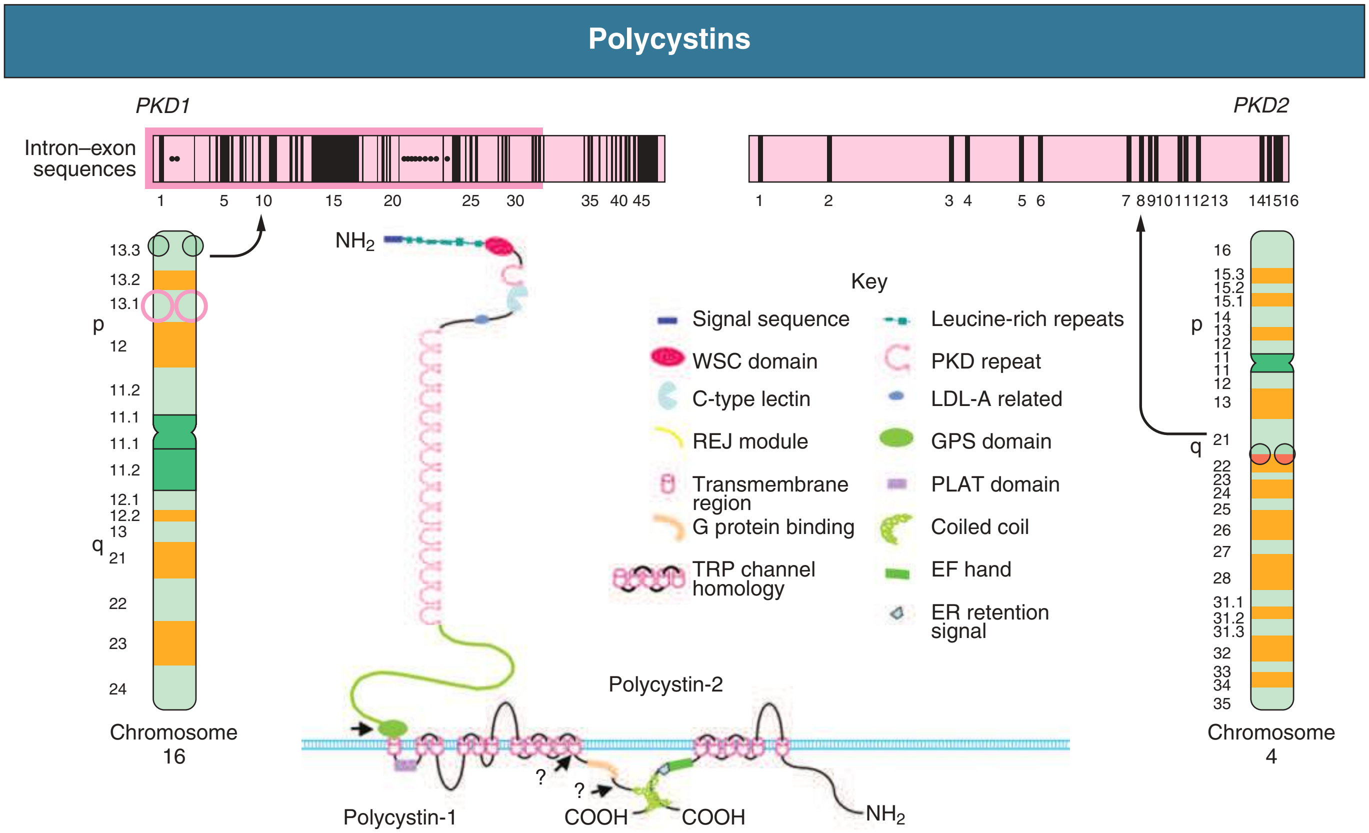
Polycystins
PKD1
PKD2
Intron–exon sequences
1 5 10 15 20 25 30 35 40 45
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
NH2
Key
Signal sequence
Leucine-rich repeats
WSC domain
PKD repeat
C-type lectin
LDL-A related
REJ module
GPS domain
Transmembrane region
PLAT domain
G protein binding
Coiled coil
TRP channel homology
EF hand
ER retention signal
Polycystin-2
Polycystin-1
COOH
COOH
NH2
?
?
p
q
13.3
13.2
13.1
12
11.2
11.1
11.1
11.2
12.1
12.2
13
21
22
23
24
Chromosome 16
16
15.3
15.2
15.1
14
13
12
11
11
12
13
21
22
23
24
25
26
27
28
31.1
31.2
31.3
32
33
34
35
Chromosome 4

Fig. 44.1 Polycystins: Genes, messenger RNAs, and proteins. Diagrammatic representation of chromosome 16 *(left)* and chromosome 4 *(right)*. Intron–exon sequences of *PKD1 (upper left)* and *PKD2 (upper right)*. Diagram of proposed structural features of the polycystin-1 and polycystin-2 proteins *(center)*.

A common finding in animal models of PKD is increased levels of cyclic adenosine monophosphate (cAMP), not only in the kidney but also in the liver and vascular smooth muscle.[10] Tissue levels of cAMP are determined by the activities of membrane-bound and soluble adenylyl cyclases and cAMP phosphodiesterases (PDEs), themselves subject to complex regulatory mechanisms. Reduced intracellular calcium in PKD may activate calcium inhibitable AC6 or AC5, directly inhibit calcium/calmodulin-dependent PDE1, and indirectly inhibit cGMP inhibitable PDE3, thereby accounting for the accumulation of cAMP and activation of protein kinase A (PKA), which in turn contributes to the development and progression of PKD by stimulating cystic fibrosis transmembrane conductance regulator (CFTR)-driven chloride and fluid secretion and cell proliferation (see Fig. 44.2).

Chloride enters across basolateral Na-K-2Cl cotransporters, driven by the sodium gradient generated by basolateral Na^+,K^+-ATPase, and exits across apical PKA–stimulated CFTR. Basolateral recycling of potassium occurs through the KCa3.1 channel.

cAMP exerts opposite effects on cell proliferation in different cell types. cAMP and PKA signaling enhance several pro-proliferative pathways (extracellular signal–regulated kinase [ERK]) in cells derived from polycystic kidneys, while inhibiting proliferation in cells derived from normal human kidney cortex.[11,12] Treatment of normal human kidney or murine collecting duct cells with calcium channel blockers replicates the proliferative response of the ADPKD cells to cAMP, thus linking this response to the reduction in intracellular calcium that results from disrupting the polycystin pathway.[13] Conversely, treatment of ADPKD cyst–derived cells with calcium channel activators or calcium ionophores restores the normal antimitogenic response to cAMP (see Fig. 44.2).

Liver Cyst Development

Liver cysts arise by excessive proliferation and dilation of biliary ductules and peribiliary glands. Estrogen receptors, insulin-like growth factor 1 (IGF-1), IGF-1 receptors, and growth hormone receptor are expressed in the epithelium lining the hepatic cysts, and estrogens and IGF-1 stimulate hepatic cyst–derived cell proliferation. Cyst growth is also promoted by growth factors and cytokines secreted into the cyst fluid.

Hypertension

Hypertension is a major clinical manifestation and predictor of outcome in ADPKD (see Clinical Manifestations in this chapter). Several factors contribute to the development of hypertension in ADPKD. Activation of the intrarenal renin-angiotensin system (RAS) likely plays an important role, but whether the circulating RAS is inappropriately activated is controversial. The expression of PC1 and PC2 in vascular smooth muscle and endothelium, along with enhanced vascular smooth muscle contractility and impaired endothelium-dependent vasorelaxation in ADPKD, suggest that disruption of polycystin function directly contributes to hypertension. Other factors include increased sympathetic nerve activity and plasma endothelin-1 levels and insulin resistance.[1]

Endothelial vasodilation and constitutive nitric oxide synthase activity are reduced in subcutaneous resistance vessels from patients with ADPKD and normal glomerular filtration rate (GFR). Flow-induced vasodilation of the brachial artery is inconsistently impaired, whereas pulse wave reflection is amplified, suggesting a predominant involvement of small resistance vessels. Reduced coronary flow velocity reserve and increased carotid intima-media thickness in normotensive patients

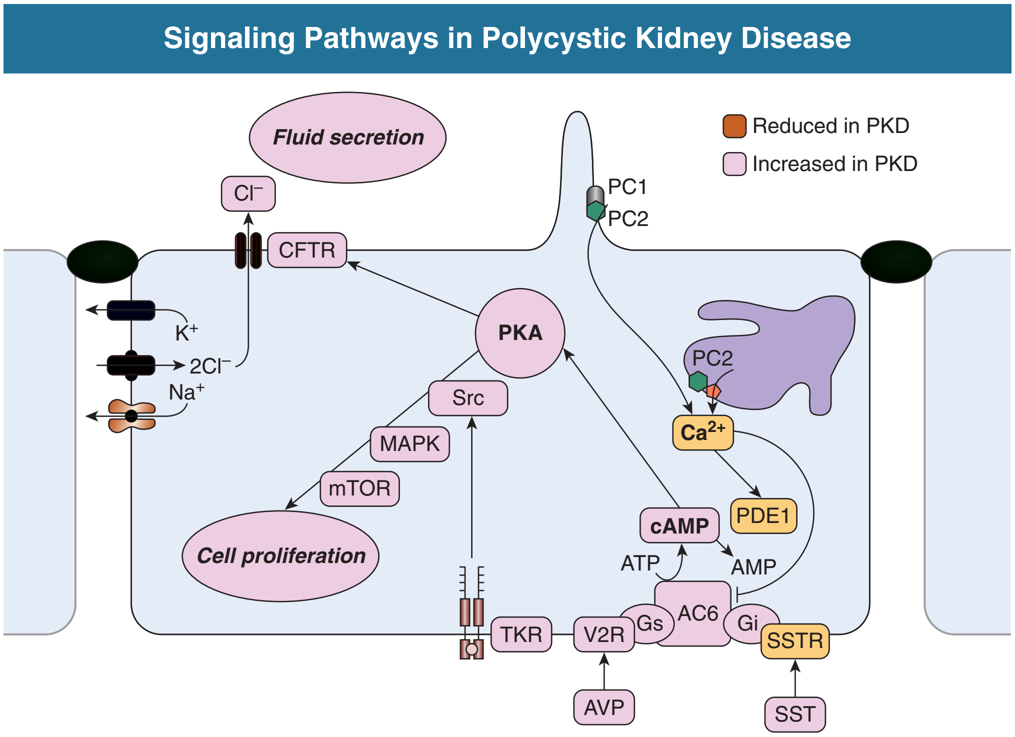

Fig. 44.2 Signaling pathways in polycystic kidney disease (PKD). Pathways that are upregulated or downregulated in polycystic kidney disease and rationale for potential therapies. Dysregulation of intracellular calcium homeostasis leads to intracellular accumulation of cyclic adenosine monophosphate *(cAMP),* activation of protein kinase A *(PKA),* cystic fibrosis transmembrane conductance regulator *(CFTR)* phosphorylation, and stimulation of chloride-driven fluid secretion. In the setting of reduced intracellular calcium, PKA activates Src, mitogen-activated protein kinase *(MAPK)*/extracellular signal–regulated kinase (ERK), and mammalian target of rapamycin *(mTOR)* signaling. Activation of tyrosine kinase receptors *(TKR)* for several growth factors contributes to the activation of Src and downstream pro-proliferative pathways. Therapies currently under clinical investigation target G protein–coupled receptors (modulating activity of adenylyl cyclase 6 *[AC6]* and generation of cAMP), Src, mTOR, and TKRs. *AVP,* Arginine vasopressin; *PDE1,* phosphodiesterase-1; *SST,* somatostatin; *SSTR,* somatostatin receptor.

with normal GFR suggest that atherosclerosis starts early in the course of ADPKD.

Reduced nitric oxide endothelium-dependent vasorelaxation in ADPKD may be caused by increased plasma levels of asymmetric dimethylarginine, a mechanism common to all hypertension associated with kidney disease.

Altered polycystin function in cardiac fibroblasts likely accounts for the increased frequency of valvular heart disease in ADPKD.

EPIDEMIOLOGY

ADPKD occurs worldwide and in all races, with a prevalence of genetically affected individuals at birth estimated at 1 in 400 to 1 in 1000. In most patients the diagnosis is made decades later, and some patients are never diagnosed. Therefore, at any point in time, only a fraction of genetically affected individuals are aware of having the disease. Clinical registry data suggest point prevalence rates of diagnosed cases ranging from 1 in 543 to 1 in 4000. The proportion of end-stage renal disease (ESRD) caused by ADPKD is less among African Americans than among Whites because of a higher incidence of other causes of ESRD. Yearly incidence rates for ESRD caused by ADPKD in men and women, respectively, are 8.7 and 6.9 per 1 million (1998 to 2001, United States), 7.8 and 6.0 per million (1998 and 1999, Europe), and 5.6 and 4.0 per million (1999 and 2000, Japan). Age-adjusted gender ratios greater than unity (1.2 to 1.3) and recent genotype/phenotype studies suggest more progressive disease in men than in women.[14,15] In recent studies, the age of onset of ESRD has increased in both genders; and all-cause mortality has decreased, possibly because of improved detection and control of hypertension.[1]

PHENOTYPIC VARIABILITY

Genic, allelic, and gene-modifier effects contribute to the high phenotypic variability of ADPKD. *PKD1*-associated disease is more severe than *PKD2*-associated disease (age at ESRD, 58 years vs. 79 years for *PKD1* and *PKD2,* respectively).[16] The greater severity of *PKD1* is caused by development of more cysts at an early age, not faster cyst growth.[1] Both *PKD1* and *PKD2* can be associated with severe PLD and vascular abnormalities.[17] Because of the lesser severity of the renal involvement, the prevalence of *PKD2*-associated disease has likely been underestimated in clinical studies.

Mutations in *PKD1* and *PKD2* are highly variable and often “private” (unique to a kindred). The ADPKD Mutation Database (www.pkdb.mayo.edu) lists 1273 likely pathogenic *PKD1* mutations identified in 1895 families with a total of 2323 variants, including silent polymorphisms. Also, 202 likely pathogenic *PKD2* mutations are listed in 438 families, with a total of 278 different variants. So far 9 families (20 patients) with *GANAB* mutations have been described.[3]

Allelic factors have an effect on the severity of ADPKD. Recent studies in large cohorts have shown that the type of *PKD1* mutation, but not its position, correlates strongly with renal survival. The median age at onset of ESRD was 55 years for carriers of a truncating mutation and 67 years for carriers of a nontruncating mutation.[16] Hypomorphic or incompletely penetrant *PKD1* or *PKD2* alleles have been described. These alleles alone may result in mild cystic disease; two such alleles cause typical to severe disease and in combination with an inactivating allele, may be associated with early-onset disease that mimics ARPKD.[1] A new prognostic score (PRO-PKD score) based on the gene mutated and type of mutation helps predict renal outcomes and enable the personalization of therapeutic management in patients with ADPKD.[2,18]

The large intrafamilial variability of ADPKD highlights a role for genetic background in disease presentation. Age at clinical manifestations in ADPKD is less variable within than between families, which suggests a common familial modifying background for early and severe disease expression (e.g., mutations or variants in genes encoding other cystoproteins). The contiguous deletion of the adjacent *PKD1* and *TSC2* is characterized by childhood PKD with additional clinical signs of tuberous sclerosis complex. Other modifying loci are likely to account for more common and subtle intrafamilial variability.

DIAGNOSIS

Only individuals who have been properly informed about the advantages and disadvantages of screening should be offered presymptomatic screening. If ADPKD is diagnosed, the patient should receive appropriate genetic counseling, and risk factors such as hypertension can be identified and treated early. If ADPKD is absent, the patient can be reassured. Disadvantages of presymptomatic screening relate to insurability and employability. Presymptomatic screening of children is not recommended until more effective therapy for the disease becomes available.

Renal Ultrasound

Renal ultrasound is used for presymptomatic testing because of cost and safety. Revised criteria have been proposed to improve the diagnostic performance of ultrasound in ADPKD (Table 44.1). At least three (unilateral or bilateral) renal cysts are sufficient for diagnosis of at-risk individuals 15 to 39 years of age; two cysts in each kidney sufficient for diagnosis for ages 40 to 59 years.[19] For at-risk individuals age 60 and older, four or more cysts in each kidney is required.

The specificity and positive predictive value (PPV) of ultrasound are high using these criteria, but their sensitivity and negative predictive value (NPV) when applied to PKD2 patients age 15 to 59 are low. This is a problem in the evaluation of potential kidney donors, in which exclusion of the diagnosis is important. Different criteria have therefore been proposed to exclude a diagnosis of ADPKD in an individual at risk from a family with an unknown genotype. An ultrasound finding of normal kidneys or one renal cyst in an individual age 40 or older has an NPV of 100%. The absence of any renal cysts provides near certainty that ADPKD is absent in at-risk individuals age 30 to 39, with a false-negative rate of 0.7% and NPV of 98.7%. A normal or indeterminate ultrasound scan does not exclude ADPKD with certainty in an at-risk individual younger than 30 years. A recent study of 73 affected and 82 nonaffected individuals suggested that finding fewer than five cysts by magnetic resonance imaging (MRI) is sufficient to exclude the diagnosis of ADPKD in potential living related kidney donors.[20] Contrast-enhanced computed tomography (CT) scanning with thin slices likely provides similar information, but this has not been proven.

TABLE 44.1 Ultrasound Criteria for the Diagnosis of Autosomal Dominant Polycystic Kidney Disease

Age (y)	Criteria	PPV	NPV
Original Ravine's PKD1 Diagnostic Criteria			
15-29	≥2 cysts, unilateral or bilateral	99	88
30-39	≥2 cysts in each kidney	100	88
40-59	≥2 cysts in each kidney	100	95
≥60	≥4 cysts in each kidney	100	100
Revised Unified Diagnostic Criteria			
15-29	≥3 cysts, unilateral or bilateral	100	86
30-39	≥3 cysts, unilateral or bilateral	100	86
40-59	≥2 cysts in each kidney	100	95
≥60	≥4 cysts in each kidney	100	100
Revised Diagnostic Criteria (when diagnosis needs to be excluded)			
15-29	≥1 cyst	97	91
30-39	≥1 cyst	94	98
40-59	≥2 cysts	97	100
≥60	≥3 cysts in each kidney	100	100

NPV, Negative predictive value; *PPV*, positive predictive value.

Genetic Testing

Genetic testing can be performed when a precise diagnosis is needed and the results of imaging are indeterminate. Molecular diagnosis of ADPKD is complicated by duplication of the *PKD1* gene, which means it may not be efficiently screened by whole-exome sequencing. For diagnostic purposes, direct mutation screening by Sanger or next-generation sequencing of the *PKD1* and *PKD2* genes is generally performed with multiplex-dependent probe amplification to identify larger rearrangements. However, next-generation sequencing panels of PKD genes are increasingly being employed that have the potential for higher throughput screening and lower costs.[21] Molecular testing by direct DNA sequencing is now informative in about 90% of patients. However, because many mutations are unique and up to one third of *PKD1* changes are missense, the pathogenicity of some changes is difficult to prove. *De novo* mutations and mosaicism also can complicate interpretation of results.

In preimplantation genetic diagnosis (PGD), genetic analysis is performed on single blastomeres from preimplantation embryo biopsy specimens obtained after in vitro fertilization (IVF), and only embryos unaffected by the disease are selected for transfer. PGD for ADPKD is complicated by the genetic heterogeneity of the disease and the large size and complex structure of the *PKD1* gene but has been performed for ADPKD. PGD should be included in the discussion of reproductive choices with patients with ADPKD, but it is only available in certain countries and the acceptance of this technique is influenced by personal values as well as the severity of the disease.[1]

DIFFERENTIAL DIAGNOSIS

Renal cysts can be a manifestation of many other systemic diseases. Conditions to consider when presentation is not typical of ADPKD include autosomal recessive PKD, tuberous sclerosis complex, von Hippel–Lindau disease, renal cysts and diabetes from *HNF1β* mutations, and orofaciodigital syndrome type I, as well as medullary sponge kidney and simple renal cysts. These are discussed further, including differential diagnosis, in Chapter 45. If the patient has ESRD, acquired cystic disease also should be considered (see Chapter 88).

CLINICAL MANIFESTATIONS

ADPKD is a multisystem disorder. Multiple renal and extrarenal manifestations of ADPKD have been described that cause significant complications.

Renal Manifestations

A number of clinical features that result from renal damage can be identified (Box 44.1). Reduction in urinary concentrating capacity and glomerular hyperfiltration are early functional abnormalities that can be observed in some children and adolescents with ADPKD.

Renal Size

Renal size increases with age, and renal enlargement eventually occurs in 100% of patients with ADPKD. The severity of the structural abnormality correlates with the manifestations of ADPKD, such as pain, hematuria, hypertension, and renal impairment.[1] Massive renal enlargement can lead to compression of local structures, resulting in such complications as inferior vena cava (IVC) compression and digestive symptoms. Most manifestations are directly related to the development and enlargement of renal cysts. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP), a prospective study of 241 patients by annual MRI, has shown that total kidney volume and cyst volumes increased exponentially.[22] Rates of growth were relatively constant, averaging 5.3% per year, but highly variable from patient to patient. Baseline total kidney volume predicted the subsequent rate of increase in renal volume and decline in GFR.[23] An imaging classification of ADPKD based on height adjusted total kidney volume and age has been proposed to facilitate the selection of patients for enrollment into clinical trials and for treatment when one becomes available.[24]

BOX 44.1 Renal Manifestations of Autosomal Dominant Polycystic Kidney Disease

Functional Manifestations
- Concentrating defect
- Reduced renal blood flow

Hypertension → Target Organ Damage
- Cardiac
- Cerebrovascular
- Arteriolosclerosis and glomerulosclerosis
- Peripheral vascular disease

Pain, Caused by
- Cyst hemorrhage
- Gross hematuria
- Nephrolithiasis
- Infection
- Renal enlargement

Reduced Glomerulat Filtration Rate, Possible Caused by
- Interstitial inflammation
- Apoptosis of tubular epithelial cells
- Hypertensive glomerulosclerosis
- Compression atrophy

Pain

Episodes of acute renal pain are seen frequently; causes include cyst hemorrhage, infection, stone, and, rarely, tumor, and these must be investigated thoroughly. A few patients with ADPKD with renal enlargement and structural distortion develop chronic flank pain without specifically identifiable cause.

Hematuria and Cyst Hemorrhage

Visible hematuria may be the initial presenting symptom and occurs in up to 40% of patients with ADPKD over the course of the disease. Many have recurrent episodes. Differential diagnosis includes cyst hemorrhage, stone, infection, and tumor. Cyst hemorrhage is a frequent complication and produces gross hematuria when the cyst communicates with the collecting system. Frequently, the cyst does not communicate with the collecting system, and flank pain without hematuria occurs. It can manifest with fever, raising the possibility of cyst infection. On occasion, a hemorrhagic cyst will rupture, resulting in a retroperitoneal bleed that can be significant, potentially requiring transfusion. In most patients, cyst hemorrhage is self-limited, resolving within 2 to 7 days. If symptoms of hematuria or flank pain last longer than 1 week or if the initial episode of hematuria occurs after age 50 years, neoplasm should be excluded.

Urinary Tract Infection and Cyst Infection

Urinary tract infection (UTI) is common in ADPKD, but its incidence may have been overestimated because sterile pyuria is common in these patients. UTI presents as cystitis, acute pyelonephritis, cyst infection, and perinephric abscesses. As in the general population, women are affected more frequently than men. Most infections are caused by *Escherichia coli, Klebsiella* and *Proteus* species, and other Enterobacteriaceae. The route of infection in acute pyelonephritis and cyst infection is usually retrograde from the bladder; therefore cystitis should be promptly treated to prevent complicated infections.

Both CT and MRI are sensitive to detect complicated cysts and can provide anatomic definition, but the findings are not specific for infection. Nuclear imaging, especially indium-labeled white blood cell scanning, is useful, but false-negative and false-positive results are possible. F-Labeled fluorodeoxyglucose (FDG) positron emission tomography (PET) has recently been used for detection of infected cysts.[1] FDG is taken up by inflammatory cells because of their high metabolic rate but is filtered by the kidneys, is not reabsorbed, and appears in the collecting system, which may limit its use in diagnosis of renal cyst infections; its present role is for diagnosis of infected liver cysts. FDG-PET is expensive and not widely available, but it provides rapid imaging with high spatial resolution, high target-to-background ratio, low radiation burden, and high interobserver agreement.

When there is fever and flank pain with suggestive diagnostic imaging but blood and urine cultures are negative, cyst aspiration under ultrasound or CT guidance should be undertaken to culture the organism and inform the selection of antimicrobial therapy.

Nephrolithiasis

Renal stone disease occurs in about 20% of patients with ADPKD. Most stones are composed of uric acid, calcium oxalate, or both. Uric acid stones are more common in ADPKD than in stone formers without ADPKD. Urinary stasis secondary to distorted renal anatomy may play a role in the pathogenesis of nephrolithiasis. Predisposing metabolic factors include decreased ammonia excretion, low urinary pH, and low urinary citrate concentration.

Stones can be difficult to diagnose on imaging in ADPKD because of cyst wall and parenchymal calcification. The distorted anatomy can cause difficulty in localizing stones to the collecting system on plain radiographs. Intravenous (IV) urography has the advantage of specifically localizing stone material to the collecting system and may provide clues to stone composition. IV urography also can detect precalyceal tubular ectasia, found in 15% of patients with ADPKD. CT urography has replaced IV urography in many centers; it is more sensitive in detecting small or radiolucent stones and for differentiating stones from tumor, clot, and cyst wall or parenchymal calcification. Dual-energy CT is increasingly used to distinguish between calcium and uric acid stones.

Hypertension

Hypertension is the most common manifestation of ADPKD and a major contributor to renal disease progression and cardiovascular morbidity and mortality (Fig. 44.3). Microalbuminuria, proteinuria, and hematuria, which are independent risk factors for renal functional decline, are more common in hypertensive patients with ADPKD. Hypertension also may increase morbidity from valvular heart disease and intracranial aneurysms, which are common in ADPKD.

Ambulatory blood pressure (BP) monitoring of children or young adults without diagnosed hypertension often reveals elevated BP, attenuated nocturnal BP dipping, and exaggerated BP response during exercise. A study stratified 65 children by BP into three cohorts: hypertensive (≥95th percentile), borderline hypertensive (75th to 95th percentile), and normotensive (≤75th percentile).[25] Both the hypertensive and the borderline hypertensive children had significantly higher left ventricular mass indices than the normotensive children. Among normotensive children, indices were significantly higher in those within the upper quartile of normal BP. These observations suggest that target organ damage develops early in ADPKD and that antihypertensive treatment may be indicated in children with ADPKD and borderline hypertension.

End-Stage Renal Disease

In most patients, renal function is maintained within the normal range, despite relentless growth of cysts, until the fourth to sixth decade of life. By the time renal function starts declining, the kidneys usually are greatly enlarged and distorted with little recognizable parenchyma on imaging studies. At this stage, the average rate of GFR decline is 4.4 to 5.9 ml/min per year. Nevertheless, ESRD is not inevitable in ADPKD. Up to 77% of patients are alive with preserved renal function at age 50 years, and 52% at age 73. Men tend to progress to renal failure more rapidly and require renal replacement therapy at a younger age than women. Other risk factors for renal failure include Black race, diagnosis of ADPKD before age 30, first episode of hematuria before age 30, onset of hypertension before age 35, hyperlipidemia, low level of high-density lipoprotein cholesterol, sickle cell trait, and *PKD1* truncating mutations. Recently, a post hoc analysis of the HALT PKD clinical trials showed an association of dietary sodium with the rate of kidney growth in patients with ADPKD with estimated GFR (eGFR) over 60 ml/min/1.73 m^2 and with the rate of decline in kidney function in those with eGFR between 25 and 60 ml/min/1.73 m^2.[26]

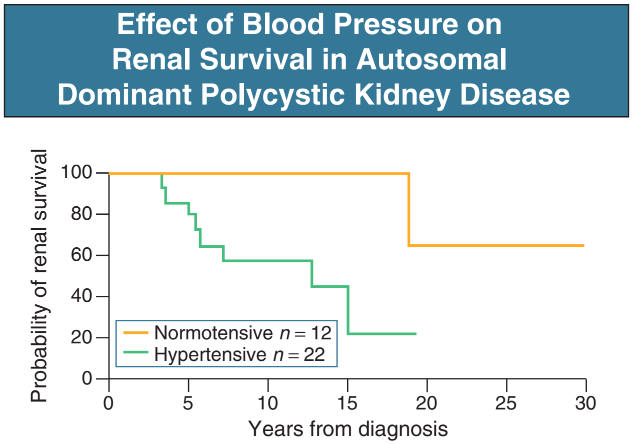
Effect of Blood Pressure on Renal Survival in Autosomal Dominant Polycystic Kidney Disease

Fig. 44.3 Patients with polycystic kidney disease and hypertension at diagnosis have less probability of renal survival than those with normal blood pressure.

Several mechanisms account for renal function decline. The CRISP study confirmed that kidney and cyst volumes are the strongest predictors of renal functional decline.[23] CRISP also found that renal blood flow (or vascular resistance) is an independent predictor.[27] This points to the importance of vascular remodeling in the progression of the disease and may account for cases in which the decline of renal function seems disproportionate to the severity of the cystic disease. Other factors, such as heavy use of analgesics, may contribute to chronic kidney disease progression in some patients.

Extrarenal Manifestations

Polycystic Liver Disease

PLD is the most common extrarenal manifestation of ADPKD. PLD is associated with both *PKD1* and *PKD2* genotypes. In contrast to the renal phenotype, the ADPKD genotype is not associated with the severity or growth rate of PLD in patients with ADKPD.[17] In addition, PLD also occurs as a genetically distinct disease in the absence of renal cysts (ADPLD). Most simple hepatic cysts are solitary, and PLD should be suspected when four or more cysts are present in the hepatic parenchyma. The liver in PLD contains multiple microscopic or macroscopic cysts that result in hepatomegaly (Fig. 44.4), but typically there is preservation of normal hepatic parenchyma and liver function.

Hepatic cysts are exceedingly rare in children with ADPKD. Their frequency increases with age and may have been underestimated by ultrasound and CT studies. Their prevalence by MRI in the CRISP study was 58%, 85%, and 94%, respectively, in participants age 15 to 24, 25 to 34, and 35 to 44 years. Women develop more cysts at an earlier age than men. Women who have multiple pregnancies or who have used oral contraceptives (OCs) or estrogen replacement therapy (ERT) in the postmenopausal period may have worse disease. After menopause the volume of polycystic livers often remains stable or may even decrease.[17]

Typically, PLD is asymptomatic, but reported symptoms have become more frequent as the life span of patients with ADPKD is prolonged with dialysis and transplantation. Symptoms result from mass effect or from complications related to the cysts themselves.[28] Symptoms include dyspnea, orthopnea, early satiety, gastroesophageal reflux, mechanical low back pain, uterine prolapse, and even rib fracture. Other complications caused directly by mass effect include hepatic venous outflow obstruction, IVC compression, portal vein compression, and bile duct compression presenting as obstructive jaundice. Hepatic venous outflow obstruction is an uncommon condition caused by severe extrinsic compression of the intrahepatic IVC and hepatic veins by cysts, rarely with superimposed thrombosis. Symptomatic cyst complications include cyst hemorrhage, which occurs less frequently than renal cyst hemorrhage, cyst infection, and the rare occurrence of torsion or rupture of cysts. Hepatic cyst infection can be a serious complication and typically presents with localized pain, fever, leukocytosis, elevated sedimentation rate, and often elevated alkaline phosphatase. Enterobacteriaceae are the most common microorganisms causing cyst infection. The same imaging techniques discussed for the investigation of renal cyst infections may be useful for the localization of infected cysts in the liver.

Congenital hepatic fibrosis, always found in association with autosomal recessive PKD, can, rarely, coexist with ADPKD. Contrary to PKD, which affects members of several generations in these families, congenital hepatic fibrosis is seen in only one generation and is not

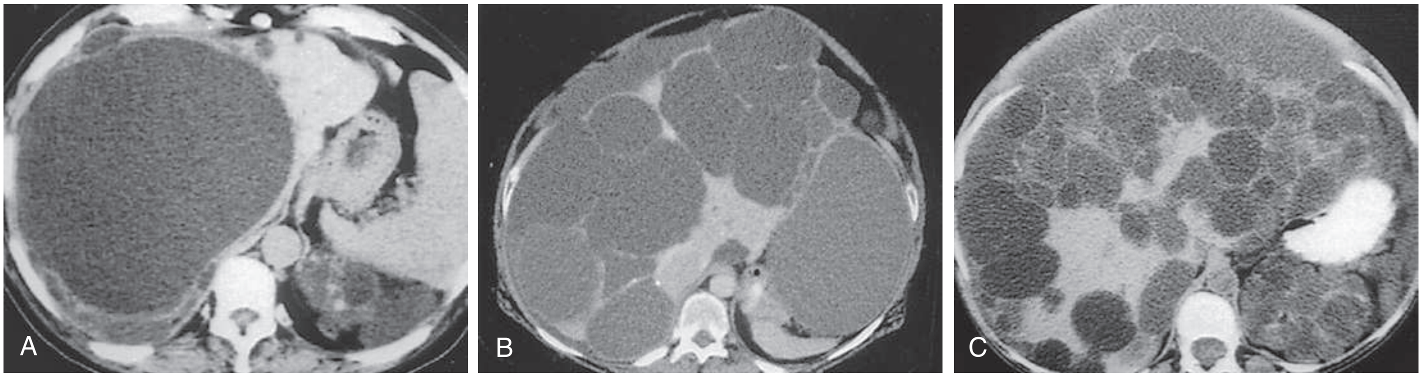

Fig. 44.4 Variable presentation of symptomatic polycystic liver disease. (A) Hepatomegaly caused by a very large, isolated, dominant cyst. (B) Hepatomegaly caused by several large cysts. (C) Hepatomegaly caused by multiple smaller cysts throughout the hepatic parenchyma.

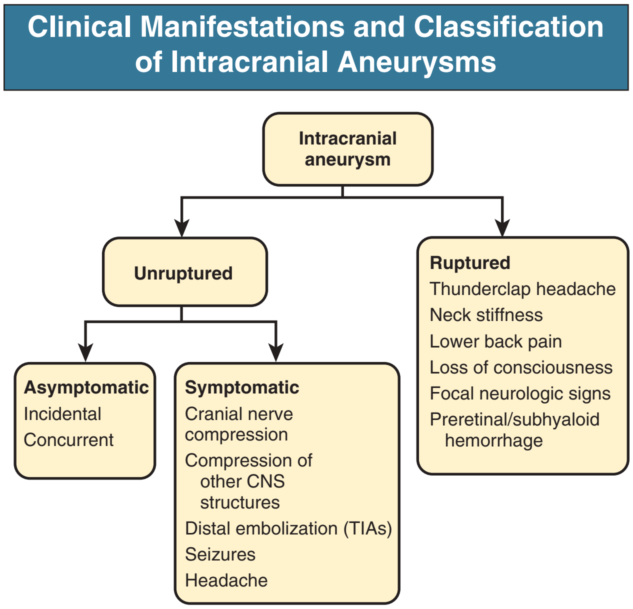

Fig. 44.5 Intracranial aneurysms. Clinical manifestations and classification. *CNS,* Central nervous system; *TIAs,* transient ischemic attacks.

transmitted vertically, suggesting the importance of modifier genes. These patients present with manifestations of portal hypertension, but hepatocellular function is normal.

Intracranial Aneurysms

Intracranial aneurysms occur in about 8% of patients with ADPKD. There is some familial clustering; intracranial aneurysms occur in 6% of patients with a negative family history and 16% of those with a positive family history. Most are asymptomatic. Focal findings, such as cranial nerve palsy and seizure, may result from compression of local structures by an enlarging aneurysm (Fig. 44.5). Yearly rupture rates increase with size, ranging from less than 0.5% for aneurysms smaller than 5 mm in diameter to 4% for aneurysms larger than 10 mm. Rupture carries a 35% to 55% risk for combined severe morbidity and mortality. The mean age at rupture in ADPKD is 39 years (vs. 51 years in the general population), with a range of 15 to 69 years. Most patients have normal renal function, and up to 29% have normal BP at rupture.

Screening is not indicated for all patients with ADPKD because most intracranial aneurysms found by presymptomatic screening are small, have a low risk for rupture, and require no treatment because the risks of intervention exceed any risk for rupture.[29] Indications for screening in patients with a good life expectancy include family history of intracranial aneurysm or subarachnoid hemorrhage, previous aneurysmal rupture, preparation for elective surgery with potential hemodynamic instability, high-risk occupations (e.g., airline pilots), and significant patient anxiety despite adequate information about the risks. Magnetic resonance angiography is the diagnostic imaging modality of choice for presymptomatic screening because it is noninvasive and does not require IV contrast administration. CT angiography is a satisfactory alternative if there is no contraindication to IV contrast. Repeated screening of patients with a strong family history of intracranial aneurysms or aneurysmal rupture after 5 to 10 years is recommended.

Other Vascular Abnormalities

In addition to intracranial aneurysms, ADPKD is associated with other vascular abnormalities, such as thoracic aortic and cervicocephalic arterial dissections, coronary artery aneurysms, and retinal artery and vein occlusions (Fig. 44.6). Thoracic aortic dissection is seven times more common in ADPKD than in the general population in autopsy series, but reported cases are rare. Rare patients with coronary aneurysms can present with cardiac ischemia and thrombus in the aneurysm in the absence of atherosclerotic disease. Several case reports describe abdominal aortic aneurysms in ADPKD. However, a prospective ultrasound study showed neither a wider aortic diameter nor a higher prevalence of abdominal aortic aneurysms in patients with ADPKD compared with an unaffected kindred in any age group.

Valvular Heart Disease and Other Cardiac Manifestations

Mitral valve prolapse is the most common valvular abnormality and has been demonstrated in up to 25% of patients with ADPKD by echocardiography. Mitral regurgitation, tricuspid regurgitation, and tricuspid prolapse also occur more frequently in ADPKD than in unaffected kindred. Aortic regurgitation may be associated with dilation of the aortic root. On histologic examination, valvular tissue shows myxoid degeneration with disruption of collagen, as seen in Marfan and Ehlers-Danlos syndromes. Although the lesions may progress with time, they rarely require valve replacement. Screening echocardiography is not indicated unless a murmur is detected on physical examination. Small, hemodynamically insignificant pericardial effusion can be detected by CT scanning in up to 35% of patients with ADPKD.

Other Associated Conditions

Cyst formation has been described in such diverse organs as the pancreas, seminal vesicles, and arachnoid membrane (Fig. 44.7). Seminal

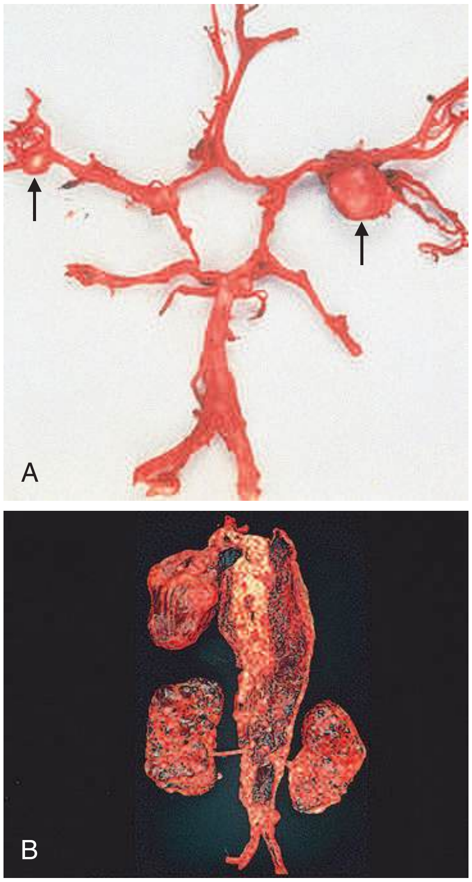

Fig. 44.6 Vascular manifestations of autosomal dominant polycystic kidney disease (ADPKD). (A) Gross specimen demonstrating bilateral aneurysms of the middle cerebral arteries *(arrows)*. (B) Gross specimen demonstrating a thoracic aortic dissection extending into the abdominal aorta in a patient with ADPKD.

vesicle cysts, usually multiple and bilateral, are found in 40% of ADPKD compared with 2% of nonaffected males. Ovarian cysts are not associated with ADPKD. Pancreas and arachnoid membrane cysts are present in 5% and 8% of patients, respectively. Pancreatic cysts are almost always asymptomatic, with rare occurrences of recurrent pancreatitis and possibly chance associations of intraductal papillary mucinous tumor or carcinoma. Epididymal and prostate cysts also may occur with increased frequency. Sperm abnormalities with defective motility are common in ADPKD and rarely may be a cause of male infertility. Spinal meningeal diverticula may occur with increased frequency and rarely manifest with intracranial hypotension (orthostatic headache, diplopia, hearing loss, ataxia) caused by cerebrospinal fluid leak. The prevalence of colonic and duodenal diverticula also may be increased.

PATHOLOGY

Polycystic kidneys are diffusely cystic and enlarged (Fig. 44.8). Size varies from normal to weighing more than 4 kg. The outer and cut surfaces show numerous spherical cysts of varying size, which are distributed evenly between cortex and medulla. The collecting system typically is distorted. The epithelium lining the cysts is characterized by hyperplastic changes, including flat nonpolypoid hyperplasia, polypoid hyperplasia, and microscopic adenomas (Fig. 44.9), as well as increased rates of cell proliferation and apoptosis. Despite the frequency of hyperplastic lesions and microscopic adenomas, the incidence of renal cell carcinoma is not increased.

Cysts arise from all segments of the nephron and collecting ducts. As they grow, cysts dissociate from the parent tubule and eventually become isolated, fluid-filled sacs. There is no agreement on whether

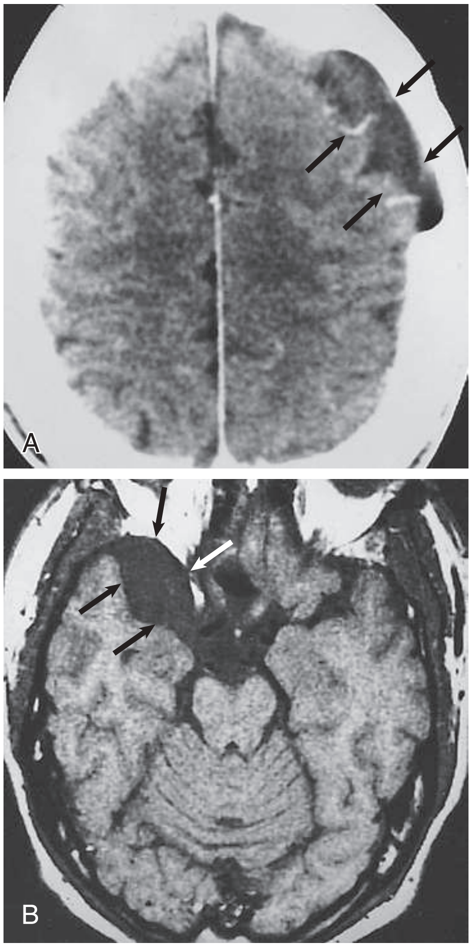

Fig. 44.7 Extrarenal manifestations of autosomal dominant polycystic kidney disease (ADPKD). Computed tomography (A) and magnetic resonance imaging (B) scans demonstrate cysts in the arachnoid membrane *(arrows)* in ADPKD.

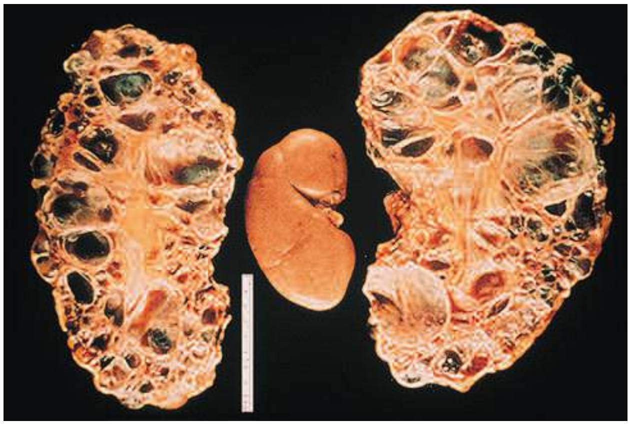

Fig. 44.8 Polycystic kidneys. Greatly enlarged polycystic kidneys from a patient with autosomal dominant polycystic disease compared with a normal kidney *(middle)*.

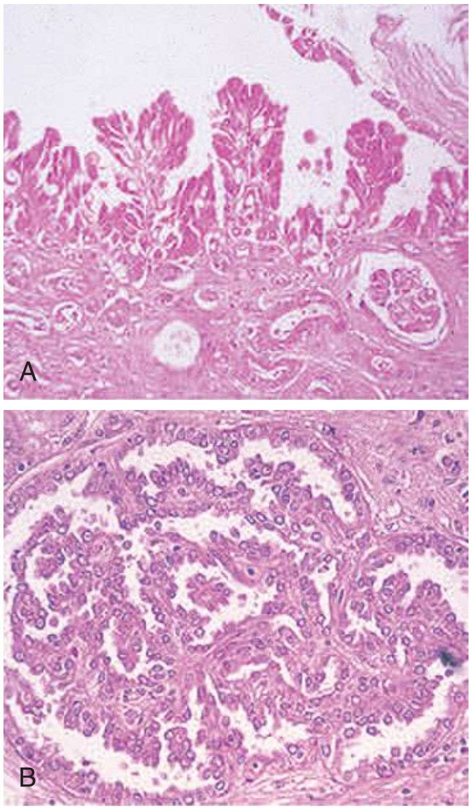

Fig. 44.9 **Renal cyst histology in autosomal dominant polycystic kidney disease (ADPKD).** (A) Papillary hyperplasia of cyst epithelium. (B) Papillary microscopic adenoma in kidney of patient with ADPKD. (Magnification ×200.)

the cysts originate preferentially from particular tubular segments. Most studies indicate that cysts are predominantly of distal nephron and collecting duct origin. Studies in advanced renal disease showing proximal tubular cysts may be confounded by the effects of obstruction and acquired renal cystic disease.

Polycystic kidneys demonstrate advanced sclerosis of preglomerular vessels, interstitial fibrosis, and tubular epithelial hyperplasia, even in patients with normal renal function or early renal failure. Sclerosis involves both afferent arterioles and interlobular arteries. Interstitial fibrosis is also prominent, even in early disease. It is associated with an interstitial infiltrate of macrophages and lymphocytes.

TREATMENT

Current therapy is directed toward the renal and extrarenal complications of ADPKD in an effort to limit morbidity and mortality. Advances in the understanding of the genetics of ADPKD and mechanisms of cyst development and growth have raised hopes for treatments specifically directed toward limiting the development and progression of the disease, and some of these treatments are now being evaluated in clinical trials (see Novel Therapies in this chapter).

Flank Pain

Causes of flank pain that may require intervention, such as infection, stone, and tumor, should be excluded. Care should be taken to avoid long-term administration of nephrotoxic agents, such as combination analgesics and nonsteroidal antiinflammatory drugs. Narcotic analgesics should be reserved for the management of acute pain. Patients with chronic kidney pain are at risk for narcotic and analgesic dependence, and a psychological evaluation and a supportive attitude by the physician are essential. Reassurance, lifestyle modification, and avoidance of aggravating activities may be helpful. Tricyclic antidepressants are helpful as in other chronic pain syndromes, with a generally well-tolerated side effect profile. Splanchnic nerve blockade with local anesthesia or corticosteroids results in pain relief prolonged beyond the duration of the local anesthetic.

When distortion of the kidneys by large cysts is deemed responsible for the pain and conservative measures fail, cyst decompression should be considered. Cyst aspiration, under ultrasound or CT guidance, is a relatively simple procedure. To prevent the reaccumulation of cyst fluid, sclerosing agents such as 95% ethanol, acidic solutions of minocycline, or sodium tetradecyl sulfate may be used. Minor complications include microhematuria, localized pain, transient fever, and systemic absorption of the alcohol. More serious complications, such as pneumothorax, perirenal hematoma, arteriovenous fistula, urinoma, and infection, are rare. Complications from aspiration of centrally located cysts are more common, and the morbidity of the procedure is proportional to the number of cysts treated.

If multiple cysts are contributing to pain, laparoscopic or surgical cyst fenestration may be of benefit. Surgical decompression is effective in 80% to 90% of patients at 1 year, and 62% to 77% have sustained pain relief for more than 2 years (Fig. 44.10A). Surgical intervention does not accelerate the decline in renal function, as once thought, but does not appear to preserve declining renal function either (see Fig. 44.10B). Laparoscopic fenestration is as effective as open surgical fenestration in short-term follow-up in patients with limited disease, and there is a shorter, less complicated recovery period compared with open surgery. Previous abdominal surgery with possible adhesion formation is a relative contraindication to the procedure.

Other interventions are available for the management of pain in ADPKD whose roles have not been fully defined. Laparoscopic renal denervation has been used in combination with cyst fenestration and may be considered, particularly in polycystic kidneys without large cysts. Thoracoscopic sympatho-splanchnicectomy is effective in some patients but has significant morbidity. Catheter-based renal denervation has been reported to be successful in a few patients, but a prospective protocolized evaluation of this approach is needed. Laparoscopic and retroperitoneoscopic nephrectomy and arterial embolization have been used to treat symptomatic polycystic kidneys in patients with ADPKD who have ESRD.

Cyst Hemorrhage

Episodes of cyst hemorrhage are self-limited, and patients respond well to conservative management with bed rest, analgesics, and increased fluid intake to prevent obstructing clots. Rarely, bleeding is more severe, with extensive subcapsular or retroperitoneal hematoma causing significant decrease in hematocrit and hemodynamic instability. This requires hospitalization and transfusion. The antifibrinolytic agent tranexamic acid has been successfully used in some patients, but no controlled studies have been performed.[30] The dose should be reduced in the presence of renal impairment. Potential adverse effects of tranexamic acid therapy include glomerular thrombosis and ureteral obstruction from clots. In patients with unusually severe or persistent hemorrhage, segmental arterial embolization can be successful. If not, surgery may be required to control bleeding.

Urinary Tract and Cyst Infection

Because most renal cyst infections begin as cystitis, prompt treatment of symptomatic cystitis and asymptomatic bacteriuria is indicated to prevent retrograde seeding of the renal parenchyma. Antibiotics that require glomerular filtration, such as highly polar aminoglycosides, are

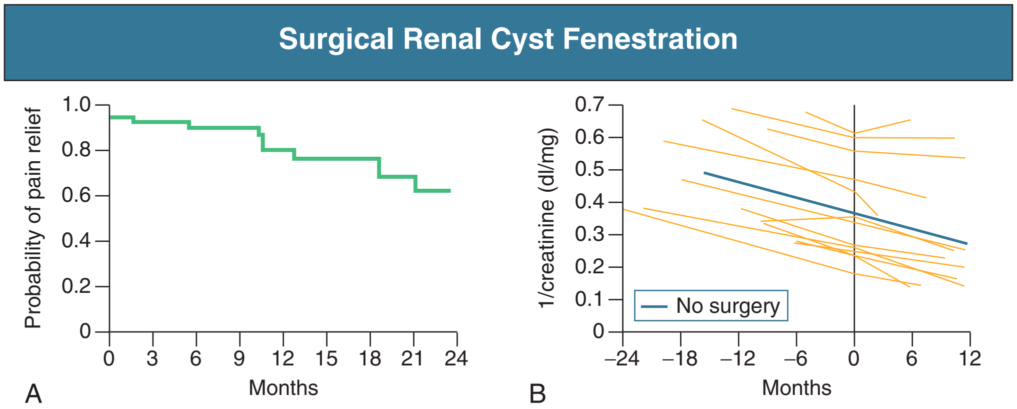

Fig. 44.10 Surgical cyst fenestration for symptomatic autosomal dominant polycystic kidney disease. (A) Effects on relief of pain. (B) Rate of decline of renal function. *Orange lines* indicate the course of renal function in individual patients who underwent cyst fenestration at month 0.

not effective for upper UTI in severe renal impairment. Cyst infection is often difficult to treat despite prolonged therapy with an antibiotic to which the organism is susceptible. Treatment failure occurs if antibiotics do not penetrate the cyst epithelium and achieve therapeutic concentrations within the cysts. Lipophilic agents have been shown to penetrate cysts reliably and have an acid dissociation constant (pK_a) that allows favorable electrochemical gradients into acidic cyst fluid. Therapeutic agents of choice include trimethoprim-sulfamethoxazole and fluoroquinolones, both of which have favorable intracystic therapeutic concentration gradients at physiologic pH in gradient and nongradient cysts.

If fever persists after 1 to 2 weeks of appropriate antimicrobial therapy, infected cysts should be drained percutaneously or surgically. In the case of end-stage polycystic kidneys, nephrectomy should be considered. If fever recurs after stopping antibiotics, complicating features such as obstruction, perinephric abscess, and stone should be excluded. If no such complicating features are identified, the antibiotic course should be extended and may require several months to fully eradicate infection.

Nephrolithiasis

Treatment of nephrolithiasis in patients with ADPKD is the same as that in patients without ADPKD (see Chapter 57). Potassium citrate is the treatment of choice in the three stone-forming conditions associated with ADPKD: uric acid lithiasis, hypocitraturic calcium oxalate nephrolithiasis, and distal acidification defects. Extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy are reported to be 82% and 80% successful, respectively, without increased complications compared with patients without ADPKD.[1] Flexible ureterorenoscopy with laser fragmentation also has been used safely and effectively and cannot cause traumatic nephron loss.[1]

Hypertension

Control of hypertension is essential because uncontrolled hypertension accelerates the decline in renal function and aggravates extrarenal complications. Antihypertensive agents of choice and optimal BP targets in ADPKD have not been established. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) increase renal blood flow in ADPKD, have a favorable side effect profile, and may have renoprotective properties that go beyond BP control. The HALT PKD study, a recent double-blind, placebo-controlled randomized clinical trial (RCT), examined the role of RAS blockade in both early and advanced ADPKD.[31,32] Monotherapy with ACE inhibitors gave good BP control in the majority of patients. In early ADPKD (15 to 49 years of age, GFR >60 ml/min/1.73 m^2), rigorous BP control (target range 95 to 110/60 to 75 mm Hg) was associated with slower increase in total kidney volume, faster eGFR decline during the first 4 months of treatment followed by a slower eGFR decline thereafter without an overall eGFR effect, a lesser increase in renal vascular resistance, and a greater decline in left ventricular mass index, after a follow-up of 8 years.[33] Patients with more severe ADPKD determined by age-adjusted kidney volume were more likely to benefit from rigorous BP control.[33] Dual RAS blockade with lisinopril and telmisartan had no beneficial effect compared with lisinopril alone in these patients, nor in more advanced ADPKD (18 to 64 years of age with GFR between 25 and 60 ml/min/1.73 m^2). The HALT PKD study therefore supports the use of an ACE inhibitor or ARB as the antihypertensive medication of choice in most patients with ADPKD and a rigorous BP target (95 to 110/60 to 75 mm Hg) in young patients with ADPKD with normal renal function and without other significant comorbidities.

Progressive Renal Failure

General strategies to delay progression of CKD are discussed in Chapter 79. Hypertension plays an important role in the progression of ADPKD to ESRD. In addition to the HALT PKD clinical trials, long-term follow-up of participants in the Modification of Diet in Renal Disease (MDRD) study suggested that individuals with ADPKD randomized to a low BP target (mean arterial pressure [MAP] <92 mm Hg) experienced significantly less ESRD and combined ESRD/death than those randomized to the usual BP target (MAP <107 mm Hg).[1]

Preclinical studies, and evidence suggesting increased vasopressin effect on the kidney and cAMP levels are involved in cyst progression, have led to the ingestion of supplemental water sufficient to achieve a urinary osmolality below 250 mOsm/kg H_2O (~3 liters in most patients) being recommended for patients with ADPKD with an eGFR greater than 30 ml/min, although there are no RCTs to support this approach.[34] Exclusions would include severe protein or sodium restriction, volume contraction, or reduced effective intravascular volume, taking diuretics or drugs enhancing the release of arginine vasopressin (AVP), or presenting abnormal voiding or urologic problems. Serum sodium concentration should be monitored.

Patients with ADPKD have reduced morbidity and mortality on dialysis compared with patients with ESRD from other causes. Women appear to do better than men. The good outcome in ADPKD may result from higher endogenous erythropoietin production, better maintenance of hemoglobin, or lower comorbidity. Rarely, hemodialysis can be

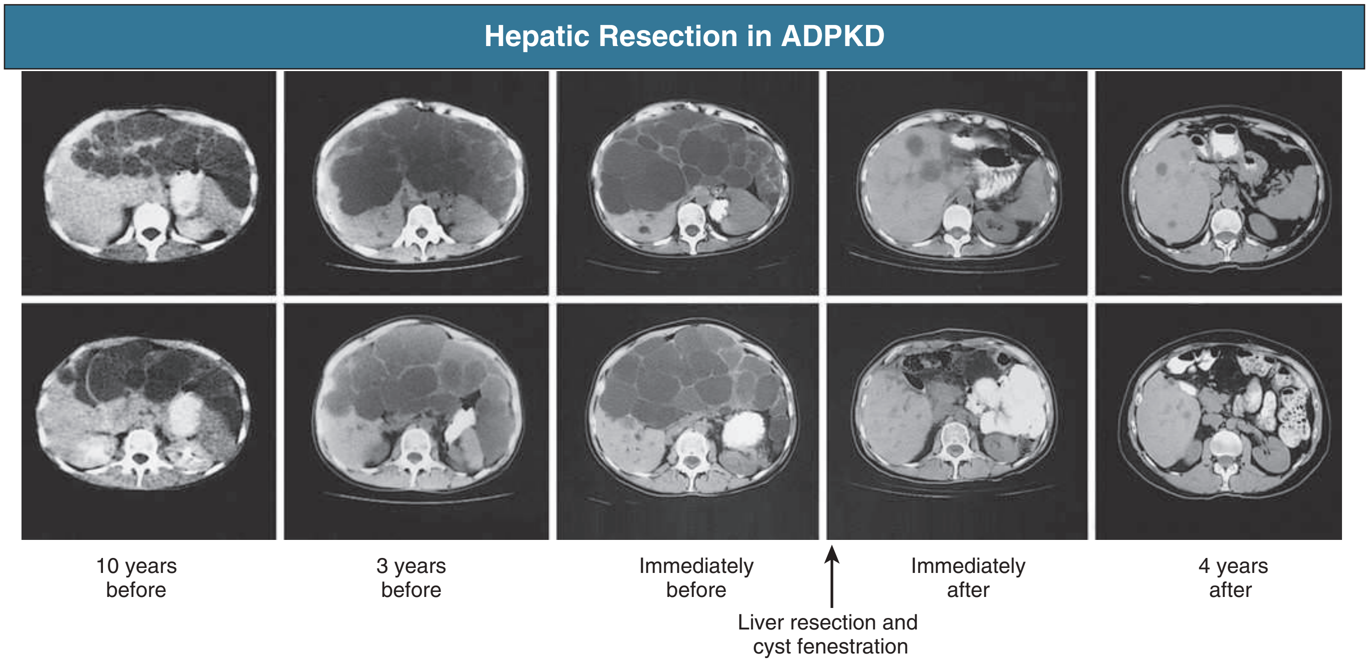

Fig. 44.11 **Hepatic resection in autosomal dominant polycystic kidney disease.** Computed tomography scans of the abdomen 10 years before *(column 1),* 3 years before *(column 2),* immediately before *(column 3),* immediately after *(column 4),* and 4 years after *(column 5)* liver resection and cyst fenestration, demonstrating long-term, sustained reduction in liver size after the procedure.

complicated by intradialytic hypotension if there is IVC compression by a medially located renal cyst. Despite renal size, peritoneal dialysis can usually be performed in ADPKD, although there is increased risk for inguinal and umbilical hernias, which require surgical repair.

Polycystic Liver Disease

Usually asymptomatic, PLD requires no treatment. When symptomatic, therapy is directed toward reducing cyst volume and hepatic size. Noninvasive measures include avoiding excessive use of ethanol, other hepatotoxins, and possibly cAMP agonists (e.g., caffeine), which have been shown to stimulate cyst fluid secretion *in vitro*. Histamine-2 blockers and somatostatin have been suggested to reduce secretion of secretin and secretory activity of cyst walls. Estrogens are likely to contribute to cyst growth, but the use of OCs and postmenopausal ERT are contraindicated only if the liver is significantly enlarged and the risk for further hepatic cyst growth outweighs the benefits of estrogen therapy. Rarely, symptomatic PLD may require invasive measures to reduce cyst volume and hepatic size. Options include percutaneous cyst aspiration and sclerosis, laparoscopic fenestration, and open surgical fenestration. Cyst aspiration is the procedure of choice if symptoms are caused by one or a few dominant cysts or by cysts that are easily accessible to percutaneous intervention. To prevent the reaccumulation of cyst fluid, sclerosis with minocycline, 95% ethanol, or sodium tetradecyl sulfate is often successful. Laparoscopic fenestration can be considered for large cysts that are more likely to recur after ethanol sclerosis, or if several cysts are present that would require multiple percutaneous passes to be treated adequately. Partial hepatectomy with cyst fenestration is an option because PLD often spares a part of the liver with adequate preservation of hepatic parenchyma and liver function[35] (Fig. 44.11). In the rare case in which no segments are spared, liver transplantation may be necessary.

When a hepatic cyst infection is suspected, any cyst with unusual appearance on an imaging study should be aspirated for diagnostic purposes. The best management is percutaneous cyst drainage in combination with antibiotic therapy. Long-term oral antibiotic suppression or prophylaxis should be reserved for relapsing or recurrent cases. Antibiotics of choice are trimethoprim-sulfamethoxazole and the fluoroquinolones, which are effective against the typical infecting organisms and concentrate in the biliary tree and cysts.

Intracranial Aneurysm

Ruptured or symptomatic intracranial aneurysm requires surgical clipping of the neck of the aneurysm. Asymptomatic aneurysms measuring less than 5 mm, diagnosed by presymptomatic screening, can be observed with repeated magnetic resonance angiography at 6 months, then annually and less frequently after stability of the aneurysm has been established. If the size increases, surgery is indicated. Definitive management of aneurysms between 6 and 9 mm remains controversial. Surgical intervention is usually indicated for all unruptured aneurysms 10 mm in diameter or larger. For patients with high surgical risk or technically difficult lesions, endovascular treatment with detachable platinum coils may be indicated.[29]

NOVEL THERAPIES

A better understanding of the pathophysiology and the availability of animal models have facilitated the development of promising candidate drugs for clinical trials (see Fig. 44.2). Of the candidates, only tolvaptan has so far entered clinical practice in some countries outside trials.

Vasopressin Antagonists

The effect of vasopressin, through V_2 receptors, on cAMP levels in the collecting duct, the major site of cyst development in ADPKD, and the role of cAMP in cystogenesis provided the rationale for successful preclinical trials of vasopressin V_2 receptor antagonists.[2] High water intake by itself also exerted a protective effect on the development of PKD in a rat model of PKD (PCK rat), probably because of suppression of vasopressin. Genetic elimination of AVP in these rats yielded animals born with normal kidneys that remained relatively free of cysts unless an exogenous V_2 receptor agonist was administered.[36]

In a large, phase III parallel-arm RCT in patients with ADPKD with estimated creatinine clearance above 60 ml/min, a split daily dose of the V_2 receptor antagonist tolvaptan administered over 3 years slowed the increase in kidney volume and decline in kidney function and lowered the frequency of ADPKD-related adverse events (kidney pain, hematuria, UTI).[37] However, tolvaptan was associated with a higher frequency of aquaresis-related adverse events (polyuria, thirst, urinary frequency, nocturia) that led to drug discontinuation in 8.3% of tolvaptan-treated patients. In addition, clinically significant increases in liver enzymes (>2.5 times the upper limit of normal) were seen in 4.9% of tolvaptan-treated versus 1.2% of placebo-treated patients and led to discontinuation of the drug in 1.8% of patients taking tolvaptan and 0.2% of the placebo group. Moderate increases in serum sodium and uric acid levels were also seen more frequently in the patients taking tolvaptan. At present, tolvaptan is approved for the treatment of rapidly progressive ADPKD in Japan, Canada, the European Union, Switzerland, and South Korea, but not in the United States. A hierarchical decision algorithm using a sequence of risk-factor assessments has been proposed to select patients with rapidly progressive disease and therefore most likely to benefit from tolvaptan.[38] A large RCT (**R**eplicating **E**vidence of **P**reserved **R**enal Function: An **I**nvestigation of Tolvaptan **S**afety and **E**fficacy in ADPKD or REPRISE) in patients with more advanced ADPKD (eGFR 25 to 65 ml/min/1.73 m^2) will be completed in 2017. Patients taking tolvaptan should have easy access to and be able to tolerate water. Liver function should be monitored closely during therapy. Serum sodium and uric acid require monitoring.

Somatostatin Analogues

Somatostatin acting on somatostatin receptors inhibits cAMP accumulation not only in the kidney but also in the liver. Somatostatin has a half-life of approximately 3 minutes, so more stable synthetic peptides (octreotide, lanreotide, pasireotide) have been developed for clinical use, which vary in stability and receptor affinity. In preclinical studies, these drugs reduced cAMP levels and proliferation of cholangiocytes in vitro, expansion of liver cysts in three-dimensional collagen culture, and development of kidney and liver cysts and fibrosis in animal models orthologous to ARPKD and ADPKD. Three small RCTs of octreotide or lanreotide have been completed[39-41] and extended as open-label, uncontrolled studies,[42-44] with similar results. Kidney growth is halted during the first year of treatment and then resumes, possibly at a lower rate than without treatment. Liver volume decreases by 4% to 6% during the first year of treatment, and this reduction is sustained during the second year. Similar results were obtained in a larger RCT of patients (Alpha-Lipoic Acid in Diabetic Neuropathy [ALADIN]) in which a trend toward stabilization of GFR was observed after the first year.[45] Several additional studies of somatostatin analogues in patients with more advanced ADPKD are in progress. Octreotide and lanreotide are generally well tolerated. Self-resolving abdominal cramps and loose stools are common in the first few days after the injections. Other adverse effects include injection site granuloma and pain, cholelithiasis, steatorrhea, weight loss, and, rarely, hair loss.

Mammalian Target of Rapamycin (mTOR) Inhibitors

The mammalian target of rapamycin (mTOR) is activated in animal models of PKD. Patients with the contiguous *PKD1/TSC2* gene syndrome have a more severe form of PKD than those with ADPKD alone. This observation suggests a convergence of signaling pathways downstream from PC1 and the TSC proteins tuberin and hamartin that control the activity of mTOR. Studies in rodent models of PKD showed that the mTOR inhibitors sirolimus and everolimus significantly prevent cyst expansion and protect renal function. However, two large randomized trials using everolimus and sirolimus for 18 to 24 months have shown no benefit.[46,47]

Other Investigational Therapies

Pravastatin, an HMG-CoA reductase inhibitor, slowed the rate of kidney growth in a small RCT in children and young adults with ADPKD.[48] A phase II, multicenter, double-blind RCT of the Src inhibitor bosutinib reduced the rate of kidney growth, with a trend to worsen renal function (ClinicalTrials.gov NCT01233869). Clinical trials of the multikinase inhibitor KD019, metformin, pioglitazone, nicotinamide, and triptolide are ongoing (ClinicalTrials.gov) (see Fig. 44.2).

TRANSPLANTATION

Transplantation is the treatment of choice for ESRD in patients with ADPKD. There is no difference in patient or graft survival between patients with ADPKD and other ESRD populations. Living donor transplants also have graft survival no different from that of non-ADPKD populations. However, living related transplantation has only recently been widely practiced in the ADPKD population. In 1999, 30% of kidney transplants for patients with ADPKD were from living donors in the United States, compared with 12% in 1990.

Complications after transplantation are no greater in the ADPKD population than in the general population, and specific complications directly related to ADPKD are rare. Cyst infection is not increased after transplantation, and there is no significant increase in the incidence of symptomatic mitral valve prolapse or hepatic cyst infection. One study showed an increased rate of diverticulosis and bowel perforation in ADPKD. Whether ADPKD increases the risk for development of new-onset diabetes mellitus after transplantation is controversial.

Although practiced routinely in the past, pretransplantation nephrectomy has fallen out of favor. By 1 and 3 years after renal transplantation, kidney volumes decrease by 37.7% and 40.6% whereas liver volumes increase by 8.6% and 21.4%, respectively.[49] Indications for nephrectomy include a history of infected cysts, frequent bleeding, severe hypertension, and massive renal enlargement with extension into the pelvis. There is no evidence of an increased risk for development of renal cell carcinoma in native ADPKD kidneys after transplantation. When nephrectomy is indicated, hand-assisted laparoscopic nephrectomy is associated with less intraoperative blood loss, less postoperative pain, and faster recovery compared with open nephrectomy and is increasingly being used.

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SELF-ASSESSMENT QUESTIONS

1. Age of end-stage renal disease (ESRD) onset in the patient with autosomal dominant polycystic kidney disease (ADPKD) depends on:
   - **A.** Mutated gene (*PKD1* vs. *PKD2*)
   - **B.** Type of mutation
   - **C.** Modifier genes
   - **D.** Environmental factors
   - **E.** All of the above
2. Which of the following statements about ADPKD and intracranial aneurysm is true?
   - **A.** All ADPKD patients should be screened for intracranial aneurysms.
   - **B.** Most intracranial aneurysms rupture.
   - **C.** The risk for rupture of an intracranial aneurysm depends on its size and location.
   - **D.** Magnetic resonance angiography to screen for intracranial aneurysms is contraindicated in advanced chronic kidney disease (CKD) because it requires administration of gadolinium.
   - **E.** None of the above.
3. Which of the following is the most common risk factor for nephrolithiasis in ADPKD?
   - **A.** Low urine citrate
   - **B.** Hypercalciuria
   - **C.** Hyperuricosuria
   - **D.** Hyperoxaluria
   - **E.** Renal tubular acidosis
4. Which of the following statements about ADPKD and hypertension is true?
   - **A.** Angiotensin-converting enzyme (ACE) inhibitors have been shown to be superior to β-blockers to treat hypertension and protect renal function in patients with ADPKD.
   - **B.** Rigorous blood pressure (BP) control has been shown to be superior to standard BP control in prospective studies to protect renal function in patients with ADPKD and CKD stage 3.
   - **C.** Both A and B are true.
   - **D.** Both A and B are false.

45

Other Cystic Kidney Diseases

Lisa M. Guay-Woodford

Numerous single-gene disorders share renal cysts as a common feature (Box 45.1).[1] These disorders may be inherited or acquired; their manifestations may be confined to the kidney or expressed systemically. They may manifest at a wide range of ages, from the perinatal period to old age (Fig. 45.1). The renal cysts may be single or multiple, and the associated renal morbidity may range from clinical insignificance to progressive parenchymal destruction with resultant renal insufficiency.

The clinical context often helps distinguish these renal cystic disorders from one another. Echogenic, enlarged kidneys in a neonate or infant should raise suspicion about autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD, see Chapter 44), tuberous sclerosis complex (TSC), or one of the many congenital syndromes associated with renal cystic disease. Renal impairment in an adolescent suggests ARPKD or nephronophthisis as possible causes. The finding of a solitary cyst in a child of 5 years of age may indicate a calyceal diverticulum, whereas this finding in a 50-year-old person is most compatible with a simple renal cyst. Renal stones occur in ADPKD and medullary sponge kidney (MSK). For those disorders with systemic manifestations, such as ADPKD, TSC, and von Hippel–Lindau (VHL) disease, the associated extrarenal features may provide other important differential diagnostic clues.

For an increasing number of the single-gene disorders, genetic testing is available in expert laboratories around the world. Genetic testing resources are listed at Gene Tests (http://www.genetests.org) and the NIH Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr).

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Definition

ARPKD is a severe, typically early-onset form of cystic disease that primarily involves the kidneys and biliary tract. Affected patients have a spectrum of clinical phenotypes that depend in part on the age at presentation.

Etiology and Pathogenesis

Genetic Basis

All typical forms of ARPKD are caused by mutations in a single gene, *PKHD1,* that encodes multiple alternatively spliced isoforms predicted to form both membrane-bound and secreted proteins. The largest protein product of *PKHD1,* the fibrocystin/polyductin complex (FPC), contains one membrane-spanning domain and an intracellular C-terminal tail. FPC localizes, at least in part, to the primary cilium and the centrosome in renal epithelial cells. The basic defects observed in ARPKD suggest that FPC mediates the terminal differentiation of the collecting duct and biliary tract. However, the exact function of the numerous isoforms has not been defined and the widely varying clinical spectrum of ARPKD may depend in part on the nature and number of splice variants that are disrupted by specific *PKHD1* mutations.

Pathogenesis

ARPKD typically begins *in utero*, and the renal cystic lesion appears to be superimposed on a normal developmental sequence. The tubular abnormality involves nonobstructive, fusiform and/or saccular dilatation of the renal collecting ducts. In the liver, defective remodeling of the ductal plate *in utero* results in persistence of primitive bile duct configurations and progressive portal fibrosis evolves.[2] The remainder of the liver parenchyma develops normally. The defect in ductal plate remodeling is accompanied by abnormalities in the branching of the portal vein. The resulting histopathologic pattern is referred to as *congenital hepatic fibrosis*.

ARPKD is one of a number of renal cystic diseases associated with congenital hepatic fibrosis, prompting these disorders to be described as hepatorenal fibrocystic diseases.[3] The primary cilium appears to play a central role in the pathogenesis of ARPKD and other hepatorenal fibrocystic diseases, so the broader term *ciliopathies* is used for these disorders, in which dysfunction of the cilia-centrosome complex appears to underpin the development of a wide array of phenotypes, including renal cystic disease.[2]

Epidemiology

The estimated incidence of ARPKD is 1 per 20,000 live births. It occurs more frequently in Whites than in other ethnic populations.

Clinical Manifestations

The clinical spectrum of ARPKD is variable. The majority of cases are identified either *in utero* or at birth. The most severely affected fetuses have enlarged echogenic kidneys and oligohydramnios as a result of poor fetal urine output. These fetuses develop the Potter phenotype, with pulmonary hypoplasia, a characteristic facies, and deformities of the spine and limbs. At birth, these neonates often have a critical degree of pulmonary hypoplasia that is incompatible with survival. The estimated perinatal mortality is about 30%. Renal function, though frequently compromised, is rarely a cause of neonatal death.

For those who survive the first month of life, the reported mean 5-year patient survival rate is 85% to 90%. Morbidity and mortality results from severe systemic hypertension, renal impairment, and portal hypertension secondary to portal-tract hyperplasia and fibrosis.[4] Hypertension usually develops in the first few months and ultimately affects 70% to 80% of patients. Individuals with ARPKD have defects in both

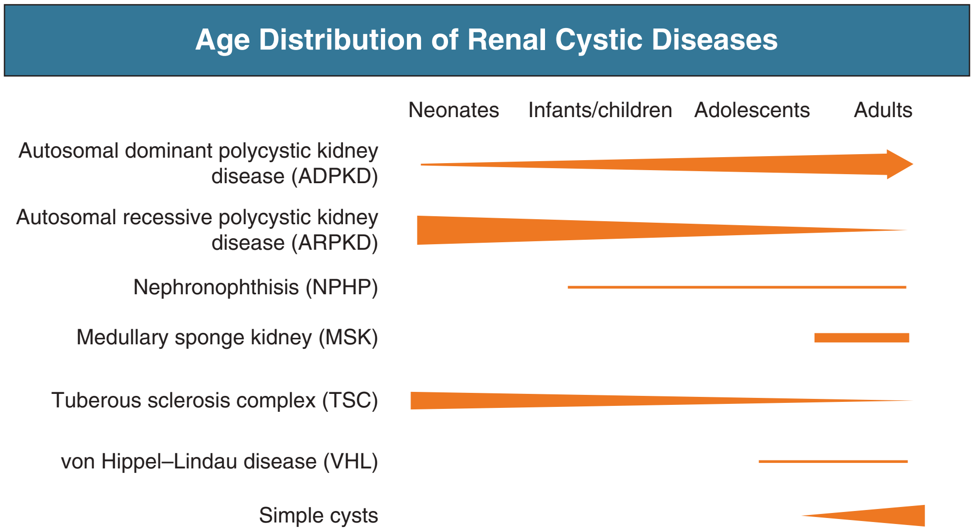

Fig. 45.1 Age distribution of patients with renal cystic disorders.

urinary diluting capacity and concentrating capacity. Newborns can have hyponatremia, presumably resulting from defects in free water excretion.[4] Although net acid excretion may be reduced, metabolic acidosis is not a significant clinical feature. Retrospective studies have noted an increased incidence of pyuria on urinalysis, as well as culture-confirmed urinary tract infection (UTI).

In the first 6 months of life, infants with ARPKD may have a transient improvement in glomerular filtration rate (GFR) as a result of renal maturation. Subsequently, a progressive but variable decline in renal function occurs, with patients presenting in the first month of life progressing more rapidly to end-stage renal disease (ESRD) than those presenting at more than 1 month of age.[5] With advances in effective therapy for ESRD, prolonged survival is common, and for many patients the hepatic complications become the predominant clinical issue.

On average, those infants with serum creatinine values greater than 2.2 mg/dl (200 μmol/l) progress to ESRD within 5 years, but this is highly variable. In longitudinal studies, the probability of renal survival without ESRD is approximately 85% at 1 year, approximately 70% at 10 years, approximately 65% at 15 years, and approximately 40% at 20 years.[6]

In children who present later in childhood or in adolescence, portal hypertension is frequently the predominant clinical abnormality, with hepatosplenomegaly and bleeding esophageal or gastric varices, as well as hypersplenism with consequent thrombocytopenia, anemia, and leukopenia. Hepatocellular function is usually preserved. Ascending suppurative cholangitis is a serious complication and can cause fulminant hepatic failure.[7,8]

Other associated features include growth retardation, although the mechanism is not yet defined and very rarely, intracranial aneurysms.

Pathology

Kidney

The renal involvement is invariably bilateral and largely symmetric. The histopathology varies depending on the age of presentation and extent of cystic involvement (Fig. 45.2A and B).

In the affected neonate, the kidneys can be 10 times normal size, but retain the typical kidney contour. Dilated, fusiform collecting ducts extend radially through the cortex. On histopathologic sections, the dilated medullary collecting ducts are often cut tangentially or transversely, resulting in a more spheroid appearance. Up to 90% of the collecting ducts are involved. Associated interstitial fibrosis is minimal in neonates and infants but increases with progressive disease.

In patients diagnosed later in childhood, the kidney size and extent of cystic involvement tend to be more limited. Cysts can expand up to 2 cm in diameter and become more spherical. Progressive interstitial fibrosis is probably responsible for secondary tubular obstruction. In older children, medullary ductal ectasia is the predominant finding.

Cysts are lined with a single layer of nondescript cuboidal epithelium. The glomeruli and nephron segments proximal to the collecting ducts are initially structurally normal, but are often crowded between ectatic collecting ducts or displaced into subcapsular wedges. The presence of cartilage or other dysplastic elements indicates a diagnosis other than ARPKD, such as cystic dysplasia.

Liver

The liver lesion in ARPKD is characterized by ductal plate malformation. The liver can be either normal in size or somewhat enlarged. Bile ducts are dilated (biliary ectasia), and marked cystic dilatation of the entire intrahepatic biliary system (Caroli syndrome) is well described.[7] In neonatal ARPKD, the bile ducts are increased in number, tortuous in configuration, and often located around the periphery of the portal tract. In older children, the biliary ectasia is accompanied by increasing portal tract fibrosis and hypoplasia of the small portal vein branches (see Fig. 45.2C). The hepatic parenchyma may be intersected by delicate fibrous septa that link the portal tracts, but the hepatocytes themselves are seldom affected.

Diagnosis

Imaging

A number of other hepatorenal fibrocystic diseases can resemble, or “phenocopy,” ARPKD (Table 45.1). Although most of these disorders are characterized by large, echogenic kidneys in the fetus and neonate, these usually can be distinguished by ultrasound. ARPKD kidneys *in utero* are hyperechogenic and display *decreased* corticomedullary differentiation due to the hyperechogenic medulla (Fig. 45.3A). With high-resolution ultrasound, the radial array of dilated collecting ducts may be imaged. In comparison, ADPKD kidneys *in utero* tend to be moderately enlarged with a hyperechogenic cortex and relatively hypoechogenic medulla causing *increased* corticomedullary differentiation.

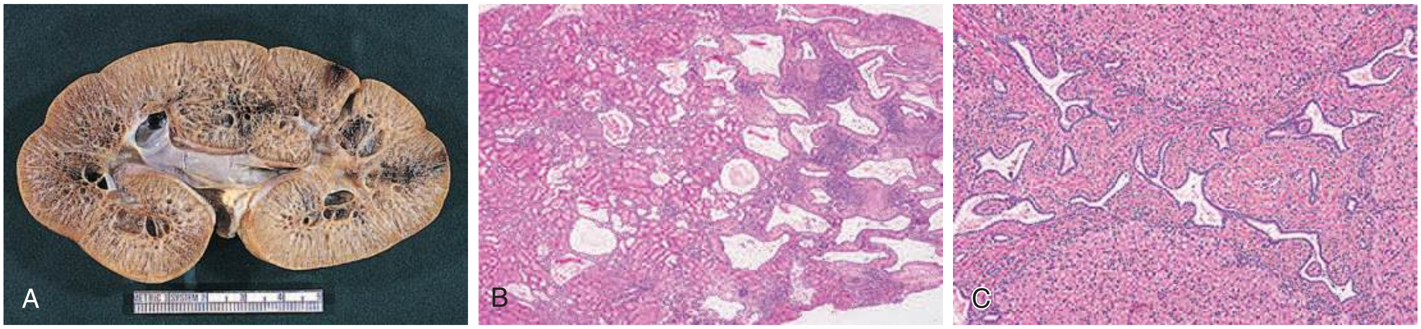

Fig. 45.2 Pathologic features of autosomal recessive polycystic kidney disease. (A) Cut section of autosomal recessive polycystic kidney disease (ARPKD) kidney from 1-year-old child shows discrete medullary cysts and dilated collecting ducts. (B) Light microscopy shows later onset ARPKD kidney with prominent medullary ductal ectasia (hematoxylin-eosin [HE] stain; magnification, ×10). (C) Light microscopy of congenital hepatic fibrosis shows extensive fibrosis of the portal area with ectatic, tortuous bile ducts and hypoplasia of the portal vein (HE stain, ×40).

Kidney size typically peaks at 1 to 2 years of age, then gradually declines relative to the child's body size, and stabilizes by 4 to 5 years. With age, there is increased medullary echogenicity with scattered small cysts, measuring less than 2 cm in diameter. These cysts and progressive fibrosis can alter the usual kidney contour, causing ARPKD in some older children to be mistaken for ADPKD. Contrast-enhanced computed tomography (CT) can be useful in delineating the renal architecture (Fig. 45.3B). Bilateral pelvicaliectasis and renal calcifications have been reported in 25% and 50% of patients with ARPKD, respectively. In adults with medullary ectasia alone, the cystic lesion may be confused with MSK.

The liver may be either normal in size or enlarged. It is usually less echogenic than the kidneys. Prominent intrahepatic bile duct dilatation suggests associated Caroli syndrome. With age, the portal fibrosis tends to progress and, in older children, ultrasound typically shows hepatosplenomegaly and a patchy increase in hepatic echogenicity.[7,8]

Genetic Testing

With the identification of *PKHD1* as the principal disease gene, genetic testing is available as a clinical diagnostic tool. The mutation detection rate is 80% to 87%. Current diagnostic approaches include gene-specific analysis and multigene testing panels using next-generation sequencing.[9] Genetic testing is primarily applied in the context of prenatal testing and preimplantation genetic diagnosis. Although patients with two truncating mutations are said to have a higher risk for perinatal death, the demonstration of a large homozygous deletion in an 8-year-old boy confounds this proposed association.[4] Patients with ARPKD have a high frequency of unique, missense changes in *PKHD1,* which can complicate the unequivocal interpretation of gene-based testing. Moreover, about 20% of ARPKD siblings have discordant clinical phenotypes. Taken together, these data complicate genetic counseling, and caution must be exercised in predicting the clinical outcome of future affected children.[9]

Treatment

The survival of neonates with ARPKD has improved significantly in the last two decades because of advances in mechanical ventilation for neonates and other supportive measures. Aggressive interventions such as unilateral or bilateral nephrectomies and continuous hemofiltration have been advocated in neonatal management, but prospective, controlled studies have yet to be performed.[4]

For those children who survive the perinatal period, blood pressure (BP) control is a major clinical issue. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), adrenergic antagonists, and loop diuretics are effective antihypertensive agents. The management of children with ARPKD and declining GFR should follow the standard guidelines established for chronic kidney disease in children.

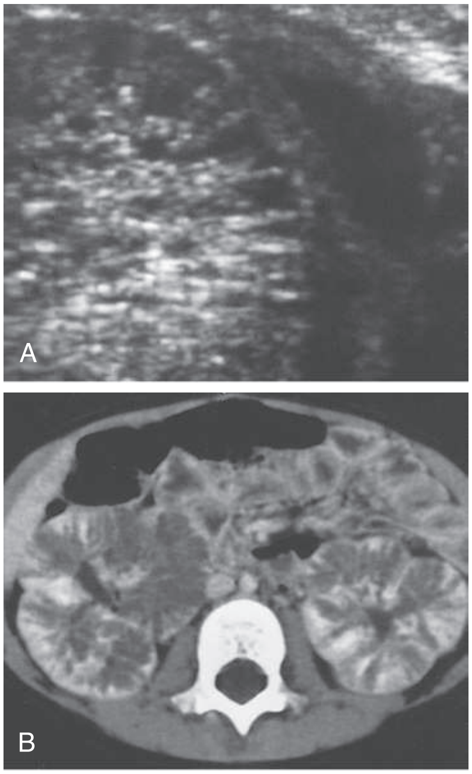

Fig. 45.3 Radiologic findings associated with autosomal recessive polycystic kidney disease. (A) Autosomal recessive polycystic kidney disease (ARPKD) in a neonate. High-resolution ultrasound reveals radially arrayed dilated collecting ducts. (B) ARPKD in symptomatic 4-year-old girl. Contrast-enhanced CT shows striated nephrogram and prolonged corticomedullary differentiation.

Given the relative urinary concentrating defect, children with ARPKD should be monitored for dehydration during intercurrent illnesses associated with fever, tachypnea, nausea, vomiting, or diarrhea. In those infants with severe polyuria, thiazide diuretics may be used to decrease

TABLE 45.1 Features of Renal Cystic Disease in Children

Clinical Characteristics	**ARPKD**	**NPHP**	**Meckel-Gruber***	**GCKD[†]**	**ADPKD**	**TSC**
Clinical onset (years)	Perinatal	NPHP2/3: 0-5 NPHP: 10-18	Perinatal Infancy	Infancy Older children	Infancy[‡] older children	Infancy[‡] Older children
Enlarged kidneys	Yes	NPHP2: Yes NPHP3: Some cases NPHP: No	Yes	variable	occurs	occurs
Renal pathology	Multiple cysts	NPHP2: Multiple cysts NPHP: Few cysts at C-M junction	Multiple cysts	Multiple cortical cysts	Multiple cysts	Few to multiple cysts; angiomyolipoma
Cyst infection	Uncommon	No	Uncommon	No	Occurs	Uncommon
Blood pressure	Normal/ increased	NPHP2: Increased NPHP: Normal	Normal	Normal/ increased	Normal/ increased	Normal/ increased
Renal function	Normal/impaired	Normal/impaired	Normal/impaired	Normal	Normal	Normal
Nephrocalcinosis/ nephrolithiasis	Nephrocalcinosis up to 25%	No	No	No	Nephrolithiases occur	No
Congenital hepatic fibrosis	Yes	Rare	Yes	No	10%-15% infantile ADPKD	No
Pancreas lesions	No	No	No	MODY5	No	No
CNS involvement	No	(Joubert)[§]	Encephalocele; mental retardation	No	No	Seizures, intellectual disability
Genetics						
Disease gene	*PKHD1*	*NPHP1-NPHP20*	*MKS1-MKS12*	*PKD1* *HNF1B*	*PKD1* *PKD2*	*TSC1* *TSC2*
Genetic testing	Yes	Most	Most	Yes	Yes	Yes

*Meckel-Gruber syndrome (MKS) is a severe, often lethal, autosomal recessive disorder characterized by bilateral renal cystic dysplasia, biliary ductal dysgenesis, bilateral postaxial polydactyly, and variable CNS malformations. The triad of renal cystic disease, occipital encephalocele, and polydactyly is most common. Genes disrupted in MKS have also been identified in patients with NPHP and Joubert syndrome, suggesting a phenotypic spectrum.

[†] GCKD: Glomerulocystic kidney disease can occur as the infantile manifestation of autosomal dominant polycystic kidney disease (ADPKD). Familial hypoplastic GCKD, resulting from mutations in *HNF1B*, the gene encoding hepatocyte nuclear factor (HNF-1β), can be associated with maturity-onset diabetes of the young, type 5 (MODY5).

[‡] A contiguous germ-line deletion of both the *PKD1* and *TSC2* genes (the PKDTS contiguous gene syndrome) occurs in a small group of patients with features of tuberous sclerosis complex (TSC), as well as massive renal cystic disease reminiscent of ADPKD, severe hypertension, and a progressive decline in renal function with the onset of end-stage renal disease in the second or third decade of life.

[§] Joubert syndrome is a genetically heterogeneous, autosomal recessive disorder characterized by developmental defects in the cerebellum (cerebellar vermis aplasia) and the eye (coloboma), as well as retinitis pigmentosa, congenital hypotonia, and either ocular motor apraxia or irregularities in breathing patterns during the neonatal period. The disease can be associated with NPHP, and mutations in several *NPHP* genes have been described in patients with Joubert syndrome.

Testing is available for most *NPHP* and *MKS* genes.

C-M, corticomedullary junction; *CNS,* central nervous system, *NPHP,* nephronophthisis; *PKDTS,* infantile severe polycystic kidney disease with tuberous sclerosis.

distal nephron solute and water delivery. Acid-base balance should be closely monitored, and supplemental bicarbonate therapy initiated as needed.

Close monitoring for portal hypertension is warranted in all patients with ARPKD. There is no correlation between the severity of the kidney and liver disease.[8] Recent studies suggest that the platelet count combined with serial abdominal ultrasound (assessing liver and splenic size) and Doppler flow studies provide good surrogate markers for the portal hypertension severity.[8] Medical management may include sclerotherapy or variceal banding.[7] Surgical approaches such as portocaval or splenorenal shunting may be indicated in some patients. Although hypersplenism is fairly common, splenectomy is seldom warranted. Unexplained fever with or without elevated transaminase levels suggests bacterial cholangitis and requires meticulous evaluation to make the diagnosis and guide aggressive antibiotic therapy.

Effective management of systemic and portal hypertension, coupled with successful renal replacement therapy, has allowed long-term patient survival. Therefore the prognosis in ARPKD, particularly for children who survive the first month of life, is far less bleak than popularly thought and aggressive medical therapy is warranted.

Although current treatment of ARPKD is entirely supportive, preclinical studies suggest future benefit from new, targeted therapies.[10]

Transplantation

A prolonged period of dialysis in childhood has been associated with both cognitive and educational impairment.[11] Therefore renal transplantation is the treatment of choice for ESRD in patients with ARPKD. ARPKD is a recessive disorder, and therefore either parent may be a suitable kidney donor. However, the identification of subtle renal and liver abnormalities on ultrasound in ARPKD *parents*[12] mandates more extensive post-transplant follow-up. Native nephrectomies may be warranted in patients with massively enlarged kidneys to allow allograft placement.

In some patients, combined kidney-liver transplantation may be appropriate.[4] Indications include the combination of renal failure and either recurrent cholangitis or significant complications of portal hypertension, such as recurrent variceal bleeding, refractory ascites, and the hepatopulmonary syndrome. In addition, liver transplantation may be a consideration for patients with a single episode of cholangitis in the context of Caroli syndrome.[7]

NEPHRONOPHTHISIS: AUTOSOMAL DOMINANT TUBULOINTERSTITIAL KIDNEY DISEASE

Definitions

Nephronophthisis (NPHP) and autosomal dominant tubulointerstitial kidney disease (ADTKD) (formerly known as *medullary cystic kidney disease*) share a triad of histopathologic features: tubular basement membrane irregularities, tubular atrophy with cyst formation, and interstitial cell infiltration with fibrosis. These histopathologically similar disorders differ in their mode of transmission, age of onset, and genetic defects. NPHP is an autosomal recessive disorder that manifests in childhood, whereas ADTKD occurs in adults. NPHP is more common than ADTKD and has been reported both as an isolated renal disease and in association with a wide range of systemic manifestations, including retinitis pigmentosa, congenital hepatic fibrosis, oculomotor apraxia, and skeletal anomalies.

Nephronophthisis

NPHP is an autosomal recessive tubulointerstitial nephropathy and one of the most frequently inherited causes of ESRD in children and adolescents.[13] The term *nephronophthisis* derives from Greek, meaning "progressive loss of nephrons."

Genetic Basis

Multiple disease-causing genes have been identified. Defects in *NPHP1* account for 21% of NPHP with large, homozygous deletions detected in 80% of affected family members and in 65% of sporadic cases. Mutations in each of the remaining NPHP genes cause no more than 4% of NPHP-related disease.[14] Clinical disease expression seems to be exacerbated by oligogenic inheritance, that is, patients carrying two mutations in a single *NPHP* gene, as well as a single-copy mutation in an additional *NPHP* gene. In addition, multiple allelism, or distinct mutations in a single gene, appears to explain the continuum of multiorgan phenotypic abnormalities observed in NPHP-related disorders, which include Meckel syndrome, Joubert syndrome, and Bardet-Biedl syndrome.[15]

Most of the protein products of the NPHP-associated genes are expressed in the cilia- centrosome complex,[2] and NPHP is considered a ciliopathy.

Clinical Manifestations

Renal Disease. Three distinct forms of NPHP (infantile, juvenile, and adolescent) were initially described, based on the age of onset of ESRD. In the infantile form, ESRD occurs before 5 years of age, whereas in juvenile NPHP (the most common form), ESRD occurs at a mean age of 13 years. However, recent studies have demonstrated that there is no clear genotype-phenotype correlation for this spectrum of presentations, and these disorders should be referred to with the single designation NPHP.

Decreased urinary concentrating capacity is invariable in NPHP and usually precedes the decline in renal function, with typical onset between 4 and 6 years of age. Polyuria and polydipsia are common. Salt wasting develops in most patients with renal impairment, and sodium supplementation is often required until the onset of ESRD. One third of patients become anemic before the onset of renal impairment, and this has been attributed to impaired regulation of erythropoietin production by peritubular fibroblasts. Growth retardation (out of proportion to the degree of renal impairment) is common.

Slowly progressive decline in renal function is typical of NPHP. Although symptoms can begin after the age of 2 years, they may progress insidiously, so that 15% of affected patients present with ESRD. There is no specific treatment. The disease is not known to recur in renal allografts.

Children with the infantile variant develop symptoms in the first few months of life and rapidly progress to ESRD, usually before the age of 2 years, but invariably by 5 years of age. Severe hypertension is common in this disorder.[16]

Unlike patients with polycystic kidney disease (PKD) or MSK, those with NPHP rarely develop flank pain, hematuria, hypertension, UTI, or renal calculi.

Associated Extrarenal Abnormalities. Extrarenal abnormalities have been described in approximately 15% of patients with NPHP,[13] the most frequent of which is retinal dystrophy due to tapetoretinal degeneration (Senior-Loken syndrome). Severely affected patients present with coarse nystagmus, early blindness, and a flat electroretinogram (Leber amaurosis); those with moderate retinal dystrophy typically have mild visual impairment and retinitis pigmentosa. Other extrarenal anomalies include oculomotor apraxia (Cogan syndrome), cerebellar vermis aplasia (Joubert syndrome), and cone-shaped epiphyses of the bones. Congenital hepatic fibrosis occurs on occasion in patients with NPHP, but the associated bile duct proliferation is mild and qualitatively different from that found in ARPKD.

Pathology

In classic NPHP, the kidneys are moderately contracted, with parenchymal atrophy causing a loss of corticomedullary demarcation. Histopathologic findings include tubular atrophy with thickened tubular basement membrane, diffuse and severe interstitial fibrosis, and cysts of variable size distributed in an irregular pattern at the corticomedullary junction and in the outer medulla. However, up to 25% of NPHP kidneys have no grossly visible cysts.

In the typical NPHP renal lesion, clusters of atrophic tubules alternate either with groups of viable tubules showing dilation or with marked compensatory hypertrophy. Multilayered thickening of tubular basement membranes is a prominent histopathologic feature (Fig. 45.4). This pattern is not unique, but the abrupt transition from one type of tubular profile to another suggests NPHP. Moderate interstitial fibrosis, usually without a significant inflammatory cell infiltrate, is interspersed among the atrophic tubules. Spherical, thin-walled cysts lined with a simple cuboidal epithelium may be evident at the corticomedullary junction, in the medulla, and even in the papillae. Microdissection studies indicate that these cysts arise from the loop of Henle, distal convoluted tubules, and collecting ducts. Glomeruli may be normal, although some may be completely sclerosed, others show periglomerular fibrosis, and still others have dilatation of Bowman space suggestive of glomerulocystic kidney disease.[17]

In comparison, the infantile form has features of both classic NPHP (such as tubular cell atrophy, interstitial fibrosis, and tubular cysts) and PKD, including enlarged kidneys and widespread cystic involvement.

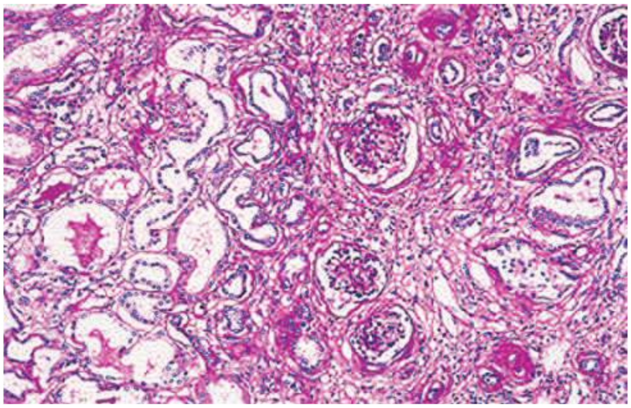

Fig. 45.4 Renal pathology in nephronophthisis. Light microscopy shows tubulointerstitial nephropathy. Atrophic tubules with irregularly thickened basement membranes are surrounded by interstitial fibrosis. Dilated tubules are evident at the corticomedullary junction. (HE stain, ×40.)

Diagnosis

In a child with NPHP and renal impairment, ultrasound typically reveals normal-sized or small kidneys with increased echogenicity and loss of corticomedullary differentiation. On occasion, cysts can be detected at the corticomedullary junction or in the medulla. Thin-section CT scanning may be more sensitive than ultrasound in detecting these cysts.

The pathologic findings in NPHP are not unique; hence in the early stages of the disease, neither renal imaging nor histopathology can confirm the clinical diagnosis. Molecular testing can be useful; newer strategies using multigene panels and next-generation sequencing technologies allow high-throughput mutation detection for known *NPHP* genes, but to date defects in these genes explain disease in only up to 40% of patients with NPHP-related disorders.[14,15]

Treatment

Current treatment of NPHP is entirely supportive. However, preclinical studies suggest that targeted therapies may have benefit for these patients. For example, treatment with a vasopressin receptor 2 antagonist remarkably attenuated renal cystic disease progression in a mouse model of *NPHP*-related disease.[10] Other investigators have proposed that therapeutic strategies should target the renal fibrosis rather than cystic disease in NPHP and note that low-dose paclitaxel has shown promising results in rodent models of renal fibrosis.[18]

Autosomal Dominant Tubulointerstitial Kidney Disease

The term *autosomal dominant tubulointerstitial kidney diseases* (ADTKD) has been proposed for the set of disorders previously described as medullary cystic kidney disease, *UMOD*-related kidney disease, familial juvenile hyperuricemic nephropathy (HNFJ1; MIM 162000), and familial glomerulocystic disease with hyperuricemia (MIM 609886).[19] ADTKD is less common than NPHP, and the renal pathologic findings are indistinguishable, although the progressive tubulointerstitial fibrosis resulting in ESRD is slower in ADTKD. Some patients have phenotypically unaffected parents, but an affected second- or third-degree relative, suggesting disease is poorly recognized in affected family members and/or there is variable penetrance.

ADTKD manifests in adults with familial renal disease characterized by bland urinalysis (i.e., little or no proteinuria or hematuria) and slowly progressive renal failure. There may be hyperuricemia or gout. Ultrasound shows normal or small kidneys, sometimes with medullary cysts.

Disease-causing mutations in four genes: *MUC1*, *UMOD*, *REN,* and *HNF1B,* are responsible for most cases.[19] Hyperuricemia is a key feature of *UMOD*-related disease.

Uremia typically occurs after 60 years of age in ADTKD-*MUC1* (MCKD1, MIM 174000), but disease progression is highly variable. In ADTKD-*UMOD* (MCKD2, MIM 603860), progression to ESRD occurs between the fourth and seventh decades of life.

MEDULLARY SPONGE KIDNEY

Definition

MSK is characterized by dilated medullary and papillary collecting ducts that give the renal medulla a spongy appearance. It is associated with nephrocalcinosis, recurrent calcium nephrolithiasis, abnormalities in renal tubular acidification and urinary concentration, bone mineralization defects, and an increased risk for UTI.[20]

Etiology and Pathogenesis

Histopathologic observations of embryonal tissue in the affected papillae, coexistence of renal tubular defects, and evidence of defects in the genes encoding the *RET* proto-oncogene and the glial cell line–derived neurotrophic factor (GDNF)[21] suggest that MSK results from a developmental defect in the ureteral bud–metanephric mesenchyme interaction. In addition, MSK occurs more frequently in individuals with other developmental anomalies and/or tumors, such as congenital hemihypertrophy, Beckwith-Wiedemann syndrome, congenital anomalies of the kidney and urinary tract syndrome, and Wilms tumor.[22]

MSK is usually a sporadic disorder, but familial clustering with autosomal dominant inheritance[23] and evidence for genetic alteration in the RET-GDNF axis suggest a genetic basis for MSK in at least a subset of patients.

Epidemiology

In the general population, the frequency of MSK may be underestimated because some affected individuals remain entirely asymptomatic. Up to 20% of patients with nephrolithiasis have at least a mild degree of MSK, but excretory urography in unselected patients indicates a disease frequency of approximately 1 in 5000 individuals.

Clinical Manifestations

MSK is asymptomatic unless complicated by nephrolithiasis, hematuria, or infection. Symptoms typically begin between the fourth and fifth decade of life, but adolescent presentations have been reported. Stones or granular debris in patients with MSK are composed of either pure apatite (calcium phosphate) or a mixture of apatite and calcium oxalate. Several factors appear to contribute to stone formation, including urinary stasis within the ectatic ducts, hypercalciuria, and hypocitraturia. Hyperparathyroidism also has been reported.

Hematuria, unrelated to either coexisting stones or infection, may be recurrent. The bleeding is usually asymptomatic, unless gross hematuria cause clot-related colic. UTI may occur in association with nephrolithiasis or as an independent event. In patients with stones, infections are more likely to occur in females than in males.

Decreased renal concentrating ability and impaired urinary acidification are common clinical features. In most patients, the acidification defect is not associated with overt systemic acidosis but bone mineralization defects are well described.[22]

Pathology

The pathologic changes are confined to the renal medullary and intrapapillary collecting ducts. Multiple spherical or oval cysts measuring 1 to 8 mm may be detected in one or more papillae. These cysts may be

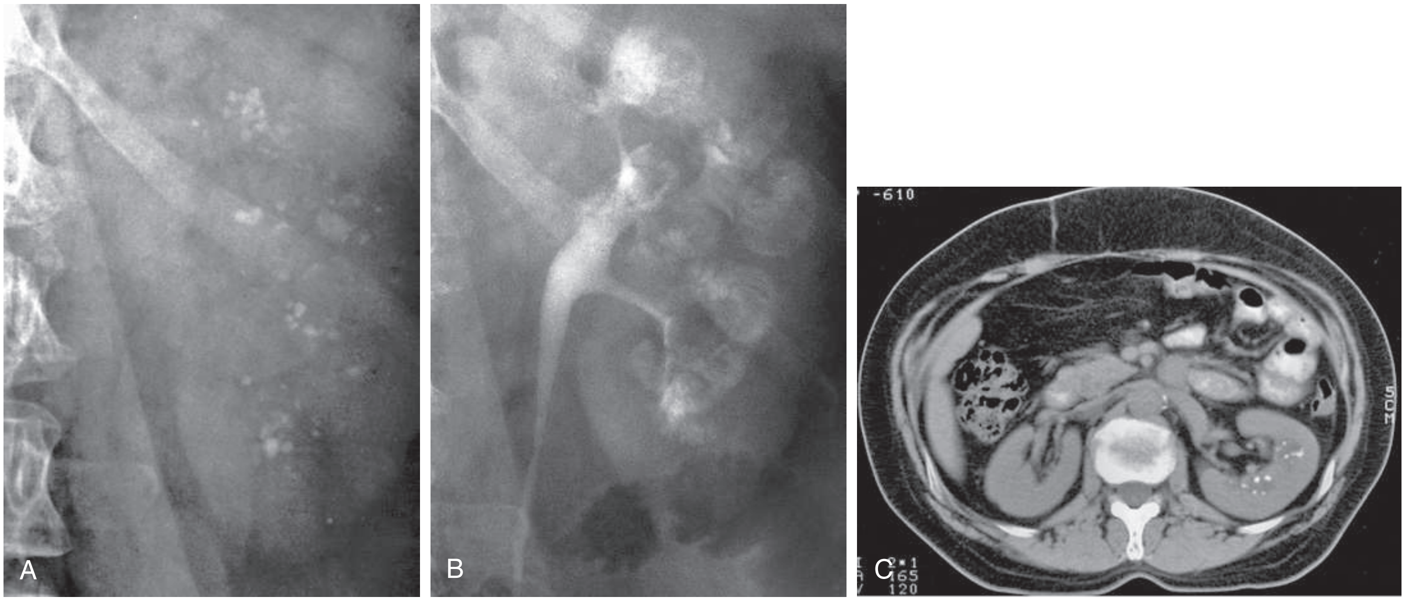

Fig. 45.5 **Radiologic findings associated with medullary sponge kidney.** (A) Initial film shows medullary nephrolithiases. (B) Ten-minute film from excretory urography shows clusters of rounded densities in the papillae among discrete linear opacities (paintbrush appearance). (C) Nonenhanced CT reveals densely echogenic foci in the medulla.

isolated or may communicate with the collecting system. The cysts are frequently bilateral and often contain spherical concretions composed of apatite. The affected pyramids and associated calyces are usually enlarged, and nephromegaly can result when many pyramids are involved. The renal cortex, medullary rays, calyces, and pelvis appear normal, unless complications (e.g., pyelonephritis or urinary tract obstruction) are superimposed.

Diagnosis

Abdominal plain radiographs often reveal radio-opaque concretions in the medulla (Fig. 45.5A). Historically, the diagnosis was established by excretory urography (see Fig. 45.5B). Retention of contrast media by the ectatic collecting ducts appears either as spherical cysts or more commonly as diffuse linear striations. The latter imparts a characteristic blush-like pattern to the papillae, the so-called bouquet of flowers or paintbrush appearance. Medullary nephrocalcinosis is a common but not invariant finding. Urography has been almost completely replaced by nonenhanced CT, which may help distinguish MSK from papillary necrosis or even ADPKD (see Fig. 45.5C).

Treatment

Asymptomatic patients with MSK require no therapy. Hematuria in the absence of stones or infection requires no intervention. If the tubular ectasia is unilateral and segmental, partial nephrectomy may alleviate recurrent nephrolithiasis and UTI. However, for the majority of patients who have bilateral disease, medical management is sufficient.

Hypercalcuria and hypocitrituria are the predominant factors contributing to MSK-related nephrolithiasis. The mainstays of treatment are potassium citrate and high fluid intake. Patients with persistent hypercalcuria and/or recurrent stone formers may benefit from thiazide diuretics. If thiazides are poorly tolerated or contraindicated, inorganic phosphate therapy may be useful. To avoid struvite stone formation, oral phosphates should *not* be used in patients with previous UTIs caused by urease-producing organisms. Patients who recurrently form and pass stones may require lithotripsy or surgical intervention (see Chapter 59).

UTIs should be treated with standard antibiotic regimens, and, for some patients, prolonged therapy may be warranted. Urease-producing organisms, such as coagulase-negative *Staphylococcus,* are particularly problematic as urinary pathogens in MSK. Positive urine cultures, even with relatively insignificant colony counts, must be vigorously pursued.

With proper management of the clinical complications, the long-term prognosis is excellent. Progression to renal impairment is unusual.

TUBEROUS SCLEROSIS COMPLEX

Definition

TSC is an autosomal dominant, tumor-suppressor gene syndrome in which benign focal malformations, called *hamartomas*, develop in multiple organ systems, including the kidneys, brain, heart, lungs, and skin.

Etiology and Pathogenesis

TSC results from inactivating mutations in one of two genes, *TSC1* on chromosome 9q32-q34 and *TSC2* on chromosome 16p13, adjacent to the *PKD1* gene. Large deletions involving both *PKD1* and *TSC2* results in the PKD1/TSC2 (infantile severe polycystic kidney disease with tuberous sclerosis [PKDTS]) contiguous gene deletion syndrome.

The focal development of hamartomas and the variability of disease expression even within families suggest that *TSC1* and *TSC2* function as tumor suppressor genes. The tumor suppressor gene paradigm proposes that two successive mutations are necessary to inactivate a target gene and cause tumor formation. The first mutation, inherited and therefore present in all cells, is necessary but not sufficient to produce tumors. A second mutation occurs after fertilization and is required to induce tumor transformation. The inactivating germ-line mutations identified in *TSC1* and *TSC2,* as well as the loss of heterozygosity detected in *TSC2*-associated and *TSC1*-associated hamartomas support the hypothesis that both *TSC1* and *TSC2* function as tumor suppressor genes.

The *TSC2* gene product tuberin interacts with hamartin, the product of the *TSC1* gene. The hamartin/tuberin (TSC1/TSC2) complex

BOX 45.1 Clinical Diagnostic Criteria for Tuberous Sclerosis Complex*

Major

- Facial angiofibromas or forehead plaque
- Nontraumatic ungual or periungual fibroma
- Hypomelanotic macules (>3)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber(s)
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma(s) (≥1)
- Lymphangioleiomyomatosis
- Renal angiomyolipoma

Minor

- Multiple, random dental pits
- Hamartomatous gastrointestinal or rectal polyps
- Bone cysts
- White matter radial migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts

From reference 31.

*Two major features or one major feature with two minor features indicate definite TSC, one major feature and one minor feature indicate probable TSC, and one major feature or two minor features indicates possible TSC.

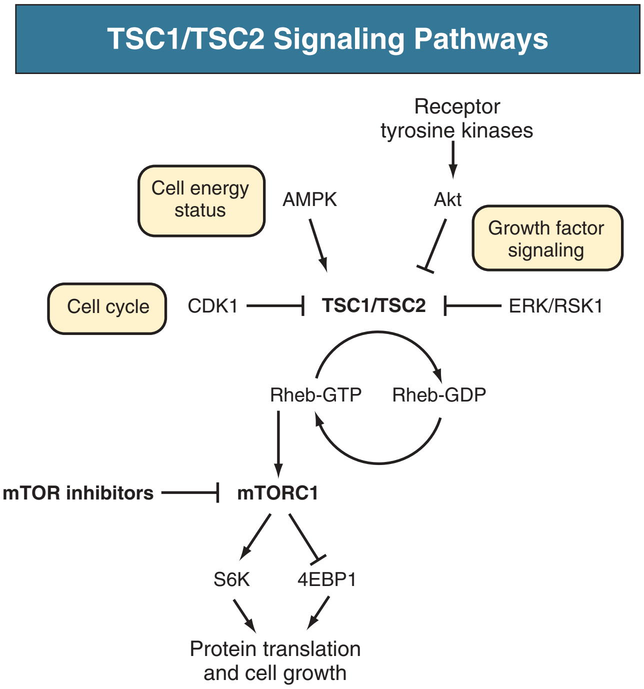

Fig. 45.6 The TSC1/TSC2 signaling pathways. Hamartin *(TSC1)* and tuberin *(TSC2)* integrate signals from extracellular growth factor binding (via *Akt* and *ERK/RSK1*), the intracellular energy status (via *AMPK*) and the cell cycle (via *CDK1*) to direct signaling pathways that regulate cellular proliferation, differentiation, and migration. Tuberin contains a guanosine triphosphatase (GTPase)-activating protein (GAP) domain in its carboxy terminus, and when it forms a complex with hamartin (TSC1/TSC2 complex) the small GTPase *Rheb* is converted from its active *GTP*-bound state to an inactive GDP-bound state. Rheb is an activator of the *mTORC1* kinase, which regulates a number of processes linked to protein synthesis and cell growth (via the ribosomal S6 kinases and the eukaryotic initiation factor 4E–binding protein (4E-BP1). mTORC1 is activated physiologically in response to growth factor signaling, which causes phosphorylation of tuberin, dissociation of the TSC1/TSC2 complex, and increased levels of Rheb-GTP. Inactivation of the TSC1/TSC2 complex through mutations in *TSC1* or *TSC2* leads to inappropriate activation of mTORC1. (From reference 24.)

functions in multiple cellular pathways, primarily by inhibiting the kinase activity of the mammalian target of rapamycin (mTOR), which functions in a protein complex (mTORC1) to regulate nutrient uptake, cell-cycle progression, cell growth, and protein translation[24] (Fig. 45.6). The *PKD1* gene product, polycystin1, plays a key role in regulating mTORC1 activity by complexing with tuberin and mTOR, thereby inhibiting the mTOR pathway.[25] In normal adult kidney, mTOR is inactive. With loss of function of either polycystin-1 or tuberin, mTOR activity is upregulated, contributing to dysregulated cell growth and cystogenesis. In addition, hamartin appears to function via TORC1-independent pathways to regulate the structural integrity of the primary cilium, suggesting that ciliary dysfunction is an additional mechanism in TSC pathogenesis.[26]

Epidemiology

TSC affects 1 in 6800 to 15,000 individuals.[27] The disease penetrance is quite variable. About 70% of patients with TSC are sporadic cases with no family history, and the disease apparently results from new mutational events. In sporadic cases, mutations in *TSC2* are approximately five times more common than mutations in *TSC1*, whereas the ratio is 1 : 1 in familial cases. *TSC1*-related disease is milder, apparently because of a reduced rate of "second hits."

Clinicopathologic Manifestations

The clinical features of *TSC1*- and *TSC2*-linked disease are similar, although *TSC2*-linked disease tends to be more severe. The most common clinical manifestations include seizures, intellectual disability and/or autism, skin lesions, interstitial lung disease, and tumors in the brain, retina, kidney, and heart. In affected individuals over 5 years of age, the most common skin lesions are facial angiofibromas (Fig. 45.7), hypomelanotic macules, and ungual fibromas.

Kidney involvement occurs frequently in TSC, with renal lesions that include angiomyolipomas (AMLs; 85%), cysts (30% to 47%), and renal cell carcinoma (RCC) (2% to 3%).[24,28] Other renal neoplasms, interstitial fibrosis with focal segmental glomerulosclerosis (FSGS), glomerular microhamartomas, and peripelvic and perirenal lymphangiomatous cysts also have been reported. Renal involvement in TSC often progresses insidiously, but can result in considerable morbidity, including retroperitoneal hemorrhage, renal impairment (~1%), and death. Renal complications are the most frequent cause of death in TSC.[24]

Renal Angiomyolipomas

AMLs are benign renal hamartomas composed of abnormal, thick-walled vessels and varying amounts of smooth muscle–like cells and adipose tissue (Fig. 45.8A and B). These are the most common renal lesions in patients with TSC, evident in approximately 80% of TSC patients by age 10 years.[24] Whereas solitary AMLs are found in the general population, particularly among older women, TSC-associated AMLs are multiple and bilateral, rarely occurring before 5 years of age, but increasing in frequency and size with age.[24] They can become locally invasive, extending into the perirenal fat or more rarely, the collecting system, renal vein, and even the inferior vena cava and right atrium.

Clinical manifestations occur secondary to hemorrhage (intratumoral or retroperitoneal) or mass effects (abdominal or flank masses and tenderness, hypertension, renal impairment). Women tend to have more numerous and larger AML than men. Pregnancy appears to increase the risk for rupture and hemorrhage.

Renal Cystic Disease

Renal cysts occur less frequently than AML in patients with TSC. However, like AML, renal cysts tend to increase in size and number over time. The concurrence of cysts and AMLs, easily detected by CT, is strongly suggestive of TSC.

The cysts in TSC can develop in any nephron segment. When limited in number and size, TSC-related cysts are predominantly cortical. In some cases, glomerular cysts predominate.[17] The cystic lining epithelia appear to be unique to TSC, with large and acidophilic epithelia containing large hyperchromatic nuclei with occasional mitotic figures (see Fig. 45.8C). Associated papillary hyperplasia and adenomas are common.

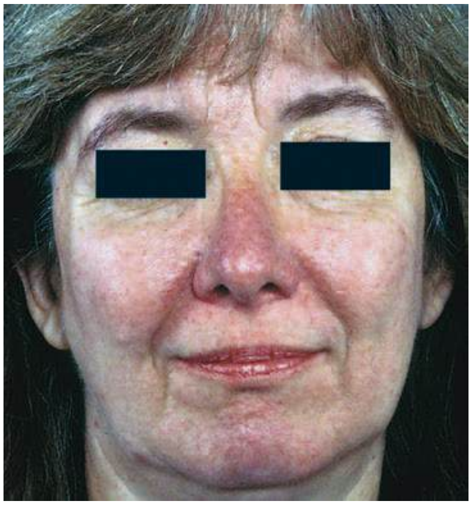

Fig. 45.7 **Facial angiofibromas in tuberous sclerosis complex.** The angiofibromas are small red bumps giving a facial rash in a butterfly distribution and on the chin.

A small subset of affected infants can present with massive renal cystic disease, severe hypertension, and a progressive decline in renal function with the onset of ESRD in the second or third decade of life. The majority of these patients have a contiguous germ-line deletion involving both the *TSC2* and *PKD1* genes, the PKDTS contiguous gene syndrome.[29] Early detection, strict BP control, and prompt therapy for the associated infantile spasms may favorably affect the overall prognosis.

Renal Neoplasms

Benign epithelial tumors, such as papillary adenomas and oncocytomas, are common in patients with TSC and can be multifocal. However, malignant transformation is rare, with a 2% to 3% lifetime risk for developing RCC. TSC-associated RCCs have a unique constellation of clinicopathologic features, including female predominance, younger age at diagnosis, association with AML, multiplicity, and slow progression.[30] Three distinct histopathologic patterns predominant, with papillary RCC being most common, followed by hybrid oncocytic/chromophobe tumor, and RCC with granular eosinophilic morphology. Although TSC-associated RCCs tend to have an indolent clinical course, the prognosis compared with sporadic RCC in the general population is unknown.

Diagnosis

TSC is a pleiotropic disease in which the size, number, and location of the lesions can be variable, even among affected individuals within the same family. Major and minor criteria have been developed to guide diagnosis (Box 45.2). Two major features or one major and two minor features are required to make the diagnosis of TSC. Imaging is the mainstay for diagnosis of TSC-associated renal lesions.[31] The presence of small cysts and fat-containing AMLs is strongly suggestive of TSC. Although the median age at presentation for both renal cysts and AML is 10 years, these lesions have been detected in infancy.[32]

Renal imaging is advised for monitoring disease progression in patients with TSC.[28] Ultrasound has historically been the preferred modality; it has high sensitivity in detecting the fat-rich AMLs and renal cysts, but is relatively insensitive for detecting fat-poor lesions. Current recommendations are to perform abdominal CT (Fig. 45.9) or magnetic resonance imaging (MRI) every 1 to 3 years for life to assess AML progression and renal cystic disease. On occasion, the distinction between an AML and RCC cannot be reliably established by imaging and biopsy is indicated.

TSC-associated renal cysts can radiologically mimic simple cysts and, when numerous, ADPKD. In the absence of AML, TSC-related renal

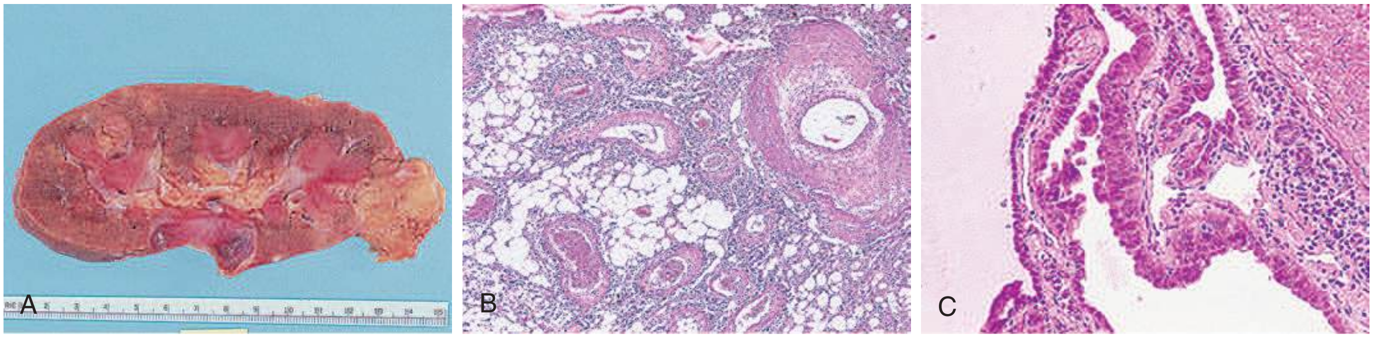

Fig. 45.8 **Renal pathology in tuberous sclerosis complex (TSC).** (A) Cut section shows multiple renal angiomyolipomas. (B) Light microscopy shows angiomyolipoma containing adipose tissue and spindle smooth muscle–like cells interspersed between abnormal vessels with thickened walls (HE stain, ×16). (C) Light microscopy shows TSC cysts lined with distinctive epithelia consisting of large, acidophilic cells with hyperchromatic nuclei (HE stain, ×65).

BOX 45.2 Renal Cystic Disorders

Nongenetic

Developmental

- Medullary sponge kidney[*]
- Renal cystic dysplasia
  - Multicystic dysplasia
  - Cystic dysplasia associated with lower urinary tract obstruction
  - Diffuse cystic dysplasia: Syndromal and nonsyndromal

Acquired

- Simple cysts
- Solitary multilocular cysts
- Hypokalemic cystic disease
- Acquired cystic disease (in advanced renal failure)

Genetic[†]

Autosomal Dominant

- Autosomal dominant polycystic kidney disease
- Autosomal dominant tubulointerstitial kidney disease
- Tuberous sclerosis complex
- von Hippel–Lindau syndrome

Autosomal Recessive

- Autosomal recessive polycystic kidney disease
- Nephronophthisis
- Meckel-Gruber syndrome

X-Linked

- Orofaciodigital syndrome type I

[*] MSK is generally considered to be a sporadic disorder, but recent studies provide evidence for familial clustering, involving autosomal dominant inheritance with reduced disease penetrance and variability in disease expression. (From reference 23.)

[†] Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM)

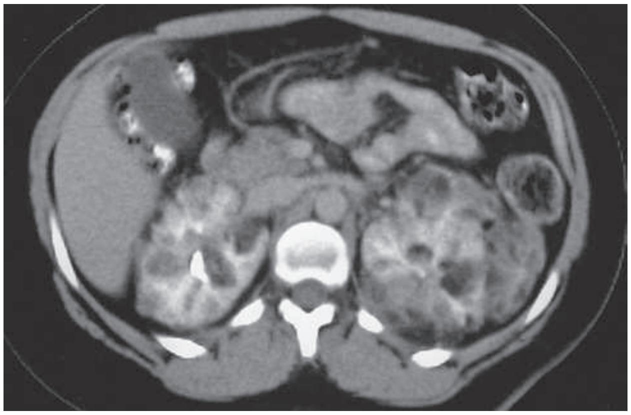

Fig. 45.9 **Radiologic findings associated with tuberous sclerosis complex.** Contrast-enhanced CT showing bilateral angiomyolipomas.

cystic disease is suggested by the limited number of cysts when compared with ADPKD and the absence of associated hepatic cysts. Although 10% of patients with TSC have hepatic AML, hepatic cysts are rare.

Gene-based diagnosis is currently available for *TSC1*- and *TSC2*-related disease, as well as to detect large-scale deletions associated with the PKDTS contiguous gene syndrome.

Treatment

Renal Angiomyolipomas

Renal AMLs are generally benign and require no treatment. Larger AMLs frequently develop micro- and macro-aneurysms, and the risk for serious hemorrhage correlates with aneurysms over 5-cm in diameter.[24] Therefore these large AMLs require preemptive treatment with either nephron-sparing surgery or embolization.[32] In addition to size and complications such as pain or hemorrhage, the inability to exclude an associated RCC should prompt intervention. When an associated malignancy cannot be excluded, nephron-sparing surgery, such as enucleation or partial nephrectomy is preferred.

The increased frequency and size of the AML in women and the reports of hemorrhagic complications during pregnancy suggest that female sex hormones may accelerate AML growth. Therefore it is prudent to caution women with multiple AMLs about the potential risks of pregnancy and estrogen administration.

Defective mTORC1 signaling is a central feature of TSC. Recent international TSC guidelines recommend mTOR inhibitors (rapalogs) as the first-line therapy for the treatment of asymptomatic, growing AMLs larger than 3 cm in diameter.[28] Sirolimus and everolimus are effective in reducing AML volume and/or postembolization response rates, with an acceptable safety profile, although they have a range of adverse events that must be borne in mind (see Chapter 101).[33]

Renal Cystic Disease

The mainstay of treatment of TSC-associated renal cystic disease is strict BP control. Surgical decompression of cystic kidneys has been suggested, but no significant beneficial effect has been established.

Renal Carcinoma

TSC-associated RCC should be suspected in enlarging, fat-poor lesions or when intratumoral calcifications are present and should be confirmed by biopsy. Because TSC-associated RCC are frequently bilateral, renal-sparing surgery should be performed whenever possible.

Renal Replacement Therapy

Chronic kidney disease, although rare in tuberous sclerosis, can occur by several different mechanisms, including AML-related parenchymal destruction, progressive renal cystic disease, interstitial fibrosis, and FSGS. A large French study reported TSC-associated ESRD to have an approximate prevalence of 0.7 cases per million. ESRD occurred in 1 per 100 patients with TSC and was more frequent in females (63%), with a mean age diagnosis of 29 years.[34] Both dialysis and renal transplantation are appropriate modes of renal replacement therapy. Given the risk for renal hemorrhage related to AML and malignant transformation, it may be advisable that patients with TSC and ESRD undergo bilateral nephrectomy before initiation of renal replacement therapy.

VON HIPPEL–LINDAU DISEASE

Definition

VHL disease is a dominantly transmitted, multisystem cancer predisposition syndrome associated with tumors of the eyes, cerebellum, spinal cord, adrenal glands, pancreas, and epididymis, as well as renal and pancreatic cysts.[35]

Etiology and Pathogenesis

VHL disease is a tumor suppressor disorder, with disease resulting from a germ-line mutation and a subsequent somatic mutation in the *VHL* gene. In approximately 80% of patients, VHL disease is familial, and disease in about 20% of cases results from de novo mutations. Moreover, *VHL* mutations have been identified in both the germ-line of patients with VHL disease and in sporadic RCC, implying that *VHL* plays an important role in the pathogenesis of RCC.[36]

The VHL protein (pVHL) plays a critical role as a negative regulator of hypoxia-inducible factors.[37] In the normal physiologic state, pVHL functions in a multiprotein complex that directs a number of proteins, most notably the α subunits of the transcription factor, hypoxia-inducible factor (HIF-α), for destruction via the ubiquination pathway. In cells that lack pVHL, HIF-α subunits are stabilized and bind to HIF-β. The heterodimer then translocates to the nucleus, leading to overexpression of HIF-target genes, which encode proteins that regulate glucose uptake, metabolism, extracellular pH, erythropoiesis, angiogenesis (vascular endothelial growth factor [VEGF] and platelet-derived growth factor B [PDGFB]), and mitogenesis (transforming growth factor β [TGFβ]). This transcriptional dysregulation promotes the pathologic growth and survival of endothelial cells, pericytes, and stromal cells and ultimately their malignant transformation.[36,37]

Clinical Manifestations

VHL disease has an incidence of 1 in 36,000 live births and has been observed in all ethnic groups.[24,35] Biallelic *VHL* inactivation leads to increased risk for central nervous system (CNS) and retinal hemangioblastomas, RCC, pheochromocytomas, pancreatic islet cell tumors, endolymphatic sac tumors, and papillary cystadenomas of the broad ligament (females) and epididymis (males). In addition, cystic changes can occur in the kidney and pancreas.

VHL-associated disease appears to cluster in two complexes (Table 45.2). In the initial stratification, patients with VHL disease can be subclassified based on a low risk (type 1) or high risk (type 2) of developing pheochromocytoma. Type 1 disease is characterized by large deletions or truncations of the *VHL* gene, which cause complete inactivation of the gene and result in high levels of HIF activity. Type 2 disease primarily involves missense mutations and is associated with partial activity of pVHL. Type 2 can be further subdivided into three subtypes: type 2A, which has a low incidence of renal lesions; type 2B, which is associated with a high risk for RCC; and type 2C, which is associated only with pheochromocytoma and no other malignancies.[37]

RCCs are typically multiple and bilateral. Although RCC may manifest with hematuria or back pain, more often detection occurs as an incidental finding on unrelated imaging studies or during a screening protocol. The mean age of symptomatic presentation is 35 to 40 years, although patients have been diagnosed in adolescence. In VHL disease, men and women are equally affected with RCC, in contrast to the male predominance in sporadic RCC. VHL disease–associated RCC metastasizes to the lymph nodes, liver, lungs, and bones and accounts for about 50% of VHL disease–related deaths.

In VHL disease, renal cysts arise from tubular cells that have undergone somatic loss of the wild-type allele. Renal cysts occur in about 60% of patients and are commonly bilateral; deterioration of renal function as a result of cystic kidney disease has been reported but is unusual.

TABLE 45.2 Classification of von Hippel–Lindau Subtypes

Subtype	Tumor Manifestations
Type 1	Hemangioblastoma (CNS, retina), renal cell carcinoma, low risk for pheochromocytoma
Type 2A	Hemangioblastoma (CNS, retina), pheochromocytoma, low risk for renal cell carcinoma
Type 2B	Hemangioblastoma (CNS, retina), renal cell carcinoma, pheochromocytoma
Type 2C	Predominantly pheochromocytoma Very limited risk for hemangioblastoma and renal cell carcinoma

From reference 38.
CNS, Central nervous system.

Pathology

RCC is one of the most common tumors in VHL disease, with a lifetime risk of approximately 70% for patients with VHL disease.[35] VHL disease–associated RCCs are mostly of the clear cell type and usually bilateral and multifocal in distribution. Detailed microscopic examination of VHL disease–associated renal cystic lesions often reveals small foci of carcinoma. VHL disease–associated RCCs tend to have low-grade histology and a better 10-year survival rate than sporadic RCC. More advanced RCCs do metastasize, and metastatic disease is a major cause of death in patients with VHL disease.

Diagnosis

The minimum clinical criteria for the diagnosis of VHL disease in an at-risk individual include the presence of a single retinal or cerebellar hemangioblastoma, RCC, or pheochromocytoma.[35] Up to 50% of affected individuals with familial VHL disease may manifest only one feature of the syndrome. In presumed sporadic cases (20% of patients), the clinical diagnosis requires two tumors (such as two hemangioblastomas or a hemangioblastoma and a characteristic visceral tumor).

Molecular analysis of the *VHL* gene is indicated in patients with known or suspected VHL disease or in at-risk children from families with VHL, given that unsuspected, untreated tumors can cause significant morbidity.[36] Presymptomatic genotyping can be useful in determining the phenotypic classification of VHL disease and used to direct monitoring for a specific subset of tumors. In addition, genotyping can be useful in distinguishing whether a pheochromocytoma has occurred in the context of a VHL type 2 mutation, is found in multiple endocrine neoplasia (MEN) type 2, or is nonsyndromic.[38]

In patients with type 2 VHL disease, annual assessment of BP, measurement of urinary catecholamine metabolites, as well as abdominal ultrasound imaging should be initiated at the age of 2 years. Abdominal MRI and iodine-131 metaiodobenzyl-guanidine (MIBG) scans are indicated if abnormalities are detected. By the age of 16 years, all patients with VHL disease should have annual MRI scans of the abdomen. Ultrasound is a useful alternative imaging modality in pregnant women. Annual assessment should be lifelong. Early detection of renal disease and a multidisciplinary approach to follow-up can substantially improve survival.[35]

Differential Diagnosis

The differential diagnosis of VHL disease–associated renal lesions includes several conditions, most notably ADPKD and TSC (Table 45.3). As with VHL, ADPKD affects both sexes with a similar mean age at presentation. However in VHL disease, kidney involvement is characterized by a few bilateral cysts, RCC, normal kidney size, normal BP, and usually normal renal function. Renal cyst infection, a frequent finding in ADPKD, is uncommon in VHL disease, and RCC is an infrequent complication of ADPKD. Cysts in the liver are frequent in ADPKD and rare in VHL disease. Pancreatic cysts are rare in ADPKD, but can be numerous and scattered through the pancreas in VHL disease (Fig. 45.10A). The CNS in ADPKD is affected by arterial aneurysms, whereas hemangioblastomas are the predominant CNS manifestation in VHL disease (see Fig. 45.10B).

TSC should be considered in the differential diagnosis of multiple renal tumors. In both TSC and VHL disease, multiple renal cysts occur.

TABLE 45.3 **Features of Renal Cystic Disease in Adults**

Clinical Characteristics	Simple Cysts	ADPKD	MSK	VHL	TSC	Acquired Cystic Disease
Clinical onset (y)	>40	30-40	20-40	30-40	10-30	Chronic renal failure
Cysts	Single/multiple	Multiple	Multiple	Few, bilateral	Multiple	Multiple
Cyst infection	Uncommon	Common	Common	Uncommon	Uncommon	Uncommon
Tumors	No	Rare	No	RCC, often bilateral	Angiomyolipoma/RCC	Common
Blood pressure	Normal/ increased	Increased	Normal	Normal/increased	Normal/ increased	Normal/ increased
Renal function	Normal	Normal/ impaired	Normal	Normal	Normal/ impaired	Impaired/ESRD
Nephrolithiasis	No	Common	Common	No	No	No
Liver cysts	No	Common	No	Rare	No	No
Pancreas cysts	No	Few	No	Multiple	No	No
CNS involvement	No	Aneurysms	No	Hemangioblastomas	Seizures, intellectual disability	No
Skin lesions	No	No	No	No	See Fig. 45.9	No
Genetics						
Disease gene	No	*PKD1* *PKD2*	No	*VHL*	*TSC1* *TSC2*	No
Genetic testing*	No	Yes	No	Yes	Yes	No

*Genetic testing: Listed at the NIH Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr).
ADPKD, Autosomal dominant polycystic kidney disease; *CNS,* central nervous system; *ESRD,* end-stage renal disease; *MSK,* medullary sponge kidney; *RCC,* renal cell carcinoma; *TSC,* tuberous sclerosis complex; *VHL,* von Hippel–Lindau disease.

However, the TSC-associated renal tumor is usually an AML and extrarenal lesions readily distinguish VHL disease and TSC.

Treatment

Surgery continues to be the mainstay of treatment for RCC in patients with VHL disease. Optimal management requires surgical intervention before renal vein invasion and distant metastases occur because metastatic lesions respond poorly to chemotherapy and radiation. Nephron-sparing surgery is the procedure of choice when possible (see Chapter 59). Repeated surgical intervention may be required as tumors continue to develop. Laparoscopic surgery may have a role in the future management of these patients.

Bilateral nephrectomy and renal transplantation may be an acceptable alternative to repeated nephron-sparing surgery in patients with VHL disease–associated RCC. It remains to be determined whether post-transplant immunosuppression enhances the growth of the retinal and CNS hemangioblastomas and other lesions found in patients with VHL disease.

Drugs that inhibit the pVHL-HIF-VEGF pathway, such as the multiple tyrosine kinase inhibitors, sunitinib, sorafenib, and pazopanib, and the monoclonal anti-VEGF antibody bevacizumab, have a proven role for sporadic RCC and may be therapeutically useful in VHL-related hemangioblastomas and RCC.[37] A number of clinical trials are currently in progress (www.clinicaltrials.gov).

SIMPLE CYSTS

Introduction and Definition

Simple renal cysts are the most commonly acquired renal cystic lesion and occur twice as frequently in men as in women. Simple cysts are vusually unilateral and may be either solitary or multiple. They occur rarely in children but become increasingly common with age.[39] In a seminal ultrasound study, unilateral cysts were detected in 1.7% of patients 30 to 49 years of age, 11% of patients 50 to 70 years of age, and 22% to 30% of patients over age 70 years.[40] This age-related increase in cyst incidence has been corroborated by MRI studies.

Etiology and Pathogenesis

Simple renal cysts likely originate from the distal convoluted tubule or collecting ducts and may arise from renal tubular diverticula, but the pathogenic mechanisms are unknown. Focal tubular obstruction and renal parenchymal ischemia have both been suggested as etiologic processes. Less likely is the possibility that simple cysts arise from calyceal diverticuli, because simple cysts are often found in the renal cortex and their frequency increases with age.

Age, smoking, renal dysfunction, and hypertension[41] have been implicated as risk factors for simple cysts. However, these associations may be coincidental, given that the studies were largely retrospective, the cohorts had variable reasons for diagnostic referral, and the observations were not optimally controlled for patient age.[42]

Clinical Manifestations

Simple cysts are typically asymptomatic. However, increasing evidence supports a relationship between simple renal cysts and hypertension,[41] which may be associated with increased renalase levels.[43] In addition, red blood cell abnormalities (elevated red blood mass, hematocrit, and hemoglobin) are well described in patients simple renal cysts.[44] Patients also can present with hematuria, flank pain, evidence of infection, or obstruction of the collecting system. Clinical symptoms are more common with neoplasms than simple cysts, and should therefore prompt evaluation for cyst-associated malignancy.[42]

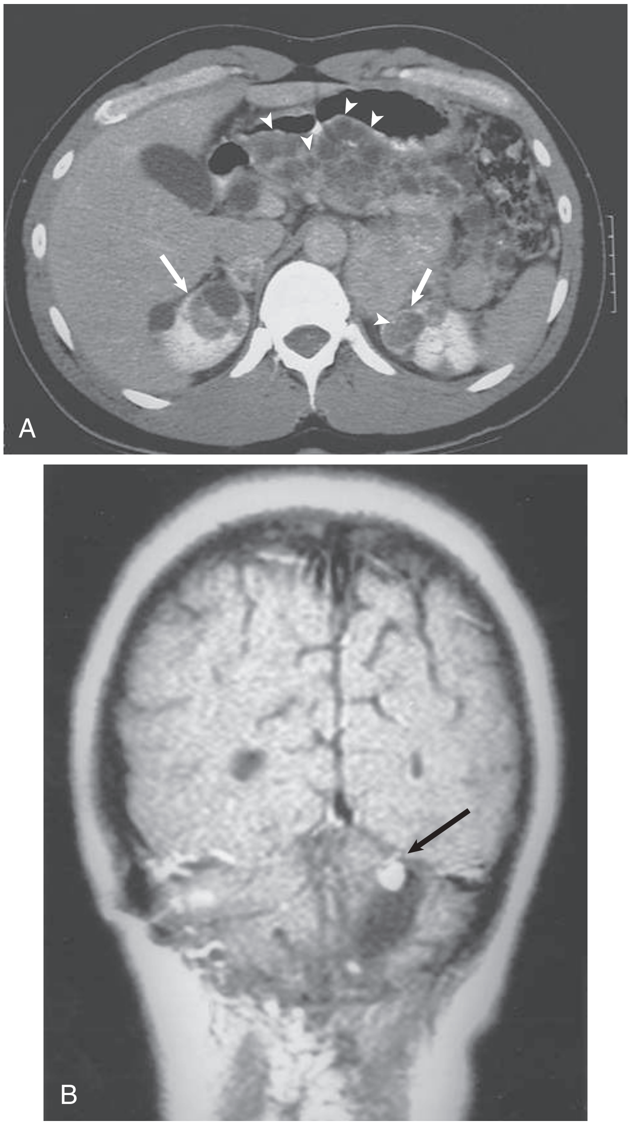

Fig. 45.10 **Radiologic findings associated with von Hippel–Lindau syndrome.** (A) Noncontrast CT shows massive cystic involvement of the pancreas *(arrowheads)* and bilateral renal cysts *(arrows)*. (B) Contrast-enhanced MRI shows a right cerebellar hemangioblastoma with a small enhancing mass *(arrow)*.

Pathology

Whether unilateral or bilateral, simple cysts are usually spherical and unilocular. They may be solitary or multiple. On average, simple cysts measure 0.5 to 1.0 cm diameter, but 3- to 4-cm cysts are not uncommon. Simple cysts can occur in the cortex, where they can protrude from the cortical surface (exophytic cysts), the corticomedullary junction, or the medulla. By definition, they do not communicate with the renal pelvis. The cyst walls are typically thin and transparent, lined with a single layer of flattened epithelium. Cyst fluid is essentially an ultrafiltrate of plasma. In the wake of infection, cyst walls can become thickened, fibrotic, and even calcified.

Diagnosis

Simple cysts are most often detected as incidental findings during abdominal imaging studies. On occasion, they are discovered during radiologic evaluation of palpable abdominal masses, pyelonephritis, or hematuria after abdominal trauma.

The critical clinical challenge is to distinguish single or multiple simple cysts from cysts associated with ADPKD, other cystic diseases, or RCC. This distinction usually can be made on the basis of patient age, family history, and renal imaging patterns (see Table 45.3).[42,45]

The ultrasound features of simple cysts include smooth walls, lack of septae, and lack of intracystic debris. If the ultrasound pattern is indeterminate, CT scanning should be performed. Benign cysts have homogeneous attenuation, no contrast enhancement, thin and smooth cyst walls, and no associated calcifications, unless prior infection has occurred.

A classification system for renal cysts based on their appearance and enhancement on CT, described by Israel and Bosniak[45] is widely used and informs management (see Table 59.5).

Treatment

Simple cysts associated with pain or renin-dependent hypertension can be managed with percutaneous aspiration under radiologic guidance and instillation of a sclerosing agent into the cyst cavity.[46] Laparoscopic or retroperitoneoscopic cyst unroofing (marsupialization) may be more appropriate for large cysts containing volumes in excess of 100 ml. Cyst infection with Enterobactericeae, staphylococci, and *Proteus* has been reported, and operative or percutaneous drainage is often required in addition to antibiotic treatment.

SOLITARY MULTILOCULAR CYSTS

Solitary multilocular cysts are generally benign neoplasms that arise from the metanephric blastema. These solitary cysts also have been designated multilocular cystic nephroma, benign cystic nephroma, and papillary cystadenoma. By definition, the cystic structures are unilateral, solitary, and multilocular. The cystic locules do not communicate with each other or with the renal pelvis. These locules are lined with a simple epithelium and the interlocular septa do not contain differentiated renal epithelia structures.

There is a spectrum of multilocular cysts; at one end is cystic nephroma (CN) and at the other end is cystic partially differentiated nephroblastoma (CPDN), in which the septa contain foci of blastemal cells. It is not clear whether a multilocular cyst represents a congenital abnormality in nephrogenesis, a hamartoma, a partially or completely differentiated Wilms tumor, or a benign variant of Wilms tumor.

There is a bimodal age distribution,[47] with approximately half the cases occurring in children younger than 4 years of age and half the cases detected in adults. The childhood cases (mostly CPDN) are usually found in boys, whereas multilocular cysts presenting in adulthood (mostly CN) occur more commonly in women. An abdominal or flank mass is the most common clinical feature, because these cysts are typically quite large and often replace an entire pole. Associated hematuria, calculi, urinary tract obstruction, and infection occur in rare instances. Diagnosis can be made either by ultrasound or CT (Fig. 45.11).

Almost all multilocular cysts are Bosniak class III (see Table 59.5) complex renal cysts suspicious for malignancy.[45] CPDN in children may contain blastema and incompletely differentiated metanephric tissue, but usually has a benign course. In adults, associated foci of RCC or sarcoma must be excluded. For both diagnostic accuracy and treatment, partial nephron-sparing surgery is usually required. The typical prognosis of solitary multilocular cysts is excellent.

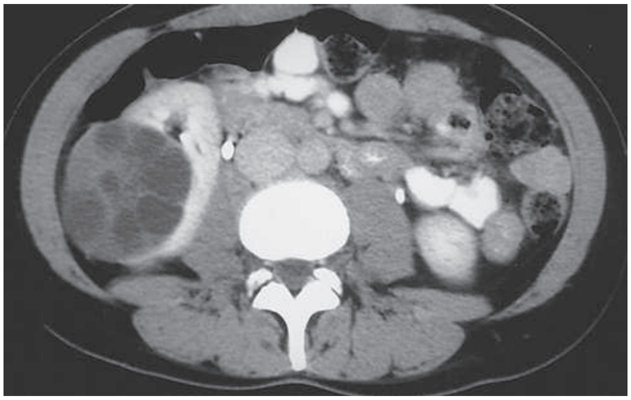

Fig. 45.11 **Solitary multilocular cyst.** Contrast-enhanced CT shows a solitary, septated, and well-circumscribed renal cystic lesion in the right kidney.

RENAL LYMPHANGIOMATOSIS

Renal lymphangiomatosis is a rare, generally benign disorder characterized by developmental malformation of renal lymphatic channels. Synonyms include hilar, pericalyceal, paracalyceal, peripelvic, or parapelvic lymphangiectasis.

The cystic phenotype is widely variable, and the underlying pathogenesis is unclear. Dilatation may involve a single lymphatic channel or multiple channels. The lymphangiectasis may be unilateral or bilateral, may be limited to the hilar region, or may extend into the renal parenchyma to the corticomedullary junction. On occasion, renal lymphangiomatosis may be very extensive and simulate either ADPKD or ARPKD.[48] The distinguishing features include cyst lining by lymphatic endothelium and cyst fluid containing lymphatic constituents such as albumin and lipid.

The characteristic ultrasound or CT findings include multiple, bilateral small peripelvic cysts that splay the renal hilum, as well as capsular cysts in the perirenal space, both separated by thin septations. Renal lymphangiomas are most often asymptomatic and require no treatment. However, the condition may be exacerbated by pregnancy, resulting in large perinephric lymph collections and ascites that can require percutaneous drainage.

GLOMERULOCYSTIC KIDNEY DISEASE

Glomerular cysts occur in three different clinical contexts: (1) isolated glomerulocystic kidney disease (GCKD); (2) glomerulocystic kidneys associated with heritable malformation syndromes, such as TSC, Meckel syndrome, ADTKD2, orofaciodigital syndrome type I, trisomies 9, 13, and 18, the short-rib polydactyly syndromes, and Zellweger cerebrohepatorenal syndrome; and (3) glomerular cystic changes in dysplastic kidneys.[17]

Isolated GCKD can occur as a sporadic condition, a familial disorder, or the infantile manifestation of ADPKD. Pathologically, the kidney architecture is normal, with no dysplastic elements in the cortex and no evidence of urinary tract obstruction. Cystic dilatation predominantly involves the Bowman space and the initial proximal tubule; it is defined as a two- or threefold dilatation of the Bowman space compared with the normal glomerular dimension. Glomerular cysts can be distributed from the subcapsular zone to the inner cortex. The typical ultrasound pattern in GCKD involves increased echogenicity of the renal cortex with minute cysts, smaller than those evident in ADPKD. Young infants with either familial or sporadic forms of GCKD also may have renal medullary dysplasia and biliary dysgenesis.[17]

Heritable GCKD is usually transmitted as an autosomal dominant trait often occurring as the infantile expression of ADPKD. In these infants, the kidneys are bilaterally enlarged and diffusely cystic. In non-ADPKD–associated GCKD families, the kidneys are typically normal in size, although on occasion enlarged kidneys are observed. Finally, several sporadic cases of nonsyndromal GCKD have been described, suggesting either spontaneous mutations or a recessively transmitted disorder.[17]

Familial hypoplastic GCKD (MIM 137920) appears to be a distinct form of GCKD in which the kidneys are smaller than normal and often associated with medullo-calyceal abnormalities. This multisystem disease is pleiotropic among affected family members with variable associations of hypoplastic GCKD, gynecologic abnormalities, maturity-onset diabetes of the young, type V (MODY5), and hypomagnesemia and results from mutations in HNF1B, the gene encoding hepatocyte nuclear factor 1-β.[49]

ACQUIRED CYSTIC DISEASE

Hypokalemic Cystic Disease

Renal cysts are often seen in association with chronic hypokalemia secondary to primary hyperaldosteronism or other renal potassium-wasting disorders. Nearly 50% of patients with idiopathic adrenal hyperplasia and 60% of patients with adrenal tumors are reported to have renal medullary cysts, which typically regress after adrenalectomy.

Hilar Cysts

Hilar cysts are spherical accumulations of clear, fat droplet–containing fluid within the renal sinus. These cystic structures are not lined by epithelia. They are most commonly seen in debilitated patients and may represent atrophy of the renal sinus fat.

Perinephric Pseudocysts

Perinephric pseudocysts are also unlined cavities. They typically occur under the renal capsule or in the perirenal fascia as a result of urine extravasation from traumatic or spontaneous rupture of a renal cyst, or as the posterior extension of a pancreatic pseudocyst. Surgical intervention is indicated for associated urinary tract obstruction. Otherwise, treatment is directed to the underlying cause.

Acquired Cystic Disease in Renal Failure

Acquired cystic disease is a significant complication of prolonged renal failure (see Table 45.3), occurring as the result of progressive structural end-stage kidney remodeling and may be associated with RCC. Acquired renal cystic disease is discussed further in Chapter 88.

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SELF-ASSESSMENT QUESTIONS

1. Extrarenal complications of autosomal recessive polycystic kidney disease (ARPKD) can include which of the following?
   A. Congenital hepatic fibrosis
   B. Caroli syndrome
   C. Growth retardation
   D. Intracranial aneurysms
   E. All the above
2. Which renal cystic disease is distinguished by small, contracted kidneys?
   A. Autosomal recessive polycystic kidney disease (ARPKD)
   B. Nephronophthisis (NPHP)
   C. Medullary sponge kidney (MSK)
   D. Von Hippel–Lindau (VHL) disease
   E. None of the above
3. Which phenotypic feature most accurately distinguishes tuberous sclerosis complex (TSC) from von Hippel–Lindau disease?
   A. Systemic hypertension
   B. Renal cysts
   C. Renal angiomyolipomas
   D. Renal cell carcinoma
   E. Liver cysts
4. Gene-based testing is a clinically informative tool for which of the following disorders?
   A. ARPKD
   B. NPHP
   C. MSK
   D. VHL disease
   E. All the above
5. Medullary sponge kidney (MSK) is a single-gene disorder in a subset of patients.
   A. True
   B. False

46

Alport Syndrome and Other Familial Glomerular Syndromes

Michelle N. Rheault, Clifford E. Kashtan

ALPORT SYNDROME

Definition

Alport syndrome (AS) is a generalized, inherited disorder of basement membranes caused by mutations affecting specific proteins of the type IV (basement membrane) collagen family. The major features of AS are hematuria, progressive nephritis with proteinuria and declining renal function, sensorineural deafness, and ocular abnormalities. AS is a rare disease, affecting approximately 1 in 50,000 people and is seen in all ethnicities and races. AS accounts for approximately 0.5% of adults and 1.7% of children with end-stage renal disease (ESRD) in the United States.[1]

Etiology and Pathogenesis

Type IV Collagen

Type IV collagen is a major constituent of basement membranes. The type IV collagen family of proteins comprises six isomeric chains, designated α1(IV) to α6(IV). Each of these chains has a major collagenous domain of about 1400 residues containing the repetitive triplet sequence glycine (Gly)–X–Y, in which X and Y represent a variety of other amino acids; a C-terminal noncollagenous (NC1) domain of about 230 residues; and a noncollagenous N-terminal sequence of 15 to 20 residues.

Each type IV collagen molecule is a heterotrimer composed of three α chains. Formation of these heterotrimers is initiated by C-terminal NC1 domain interactions, accompanied by folding of the collagenous domains into triple helices. There are at least three types of type IV collagen heterotrimer: α1(IV)$_2$–α2(IV), α3(IV)–α4(IV)–α5(IV), and α5(IV)$_2$–α6(IV). Type IV collagen triple helices form open, nonfibrillar networks that associate with laminin assemblies through interactions mediated by nidogen to form basement membranes.

The six type IV collagen genes are arranged in pairs on three chromosomes (Fig. 46.1). The 5′ ends of each gene pair are adjacent to each other, separated by sequences of varying length that contain motifs involved in transcriptional regulation.[2]

In basement membranes there is a ubiquitous network comprising the α1(IV) and α2(IV) chains; and other networks, restricted in distribution, composed of α3(IV), α4(IV), and α5(IV) chains, or α5(IV) and α6(IV) chains. Glomerular basement membrane (GBM) contains separate α1–α2(IV) and α3–α4–α5(IV) networks, whereas epidermal basement membranes (EBMs) contain separate networks of α1–α2(IV) chains and α5–α6(IV) chains. The α3α4α5(IV) network is also expressed in the Bowman capsule and distal tubule in the kidney, alveolar basement membranes, and basement membranes of the testis, eye, and ear.[3] A network of α1, α2, α5, and α6(IV) chains has been described in smooth muscle basement membranes.[3] These various networks likely have different physical and functional characteristics and interact differently with other matrix components and adjacent cells. α1–α2(IV) chains are also found in mesangial matrix.

Genetics

There are three forms of AS: an X-linked form resulting from mutations at the *COL4A5* locus, primarily affecting the α5(IV) chain; an autosomal recessive form arising from mutations at the *COL4A3* locus or the *COL4A4* locus, affecting the α3(IV) and α4(IV) chains, respectively; and an autosomal dominant form from heterozygous mutations in *COL4A3* or *COL4A4* (Table 46.1). Approximately 80% of AS was previously thought to be inherited in an X-linked manner, with 15% autosomal recessive and 5% autosomal dominant inheritance patterns observed. With the advent of next-generation sequencing, it is clear that autosomal dominant Alport syndrome (ADAS) is more common than previously recognized, accounting for approximately 20% to 30% of affected families.[4]

X-Linked Alport syndrome. X-linked Alport syndrome (XLAS) is the predominant form of the disease. Several hundred *COL4A5* mutations have been described, mostly missense mutations, splice-site mutations, and deletions of fewer than 10 base pairs.[5,6] A common missense mutation involves replacement of a glycine residue in the collagenous domain of the α5(IV) chain by another amino acid. Such mutations are thought to interfere with the normal folding of the α5(IV) chain into triple helices with other α(IV) chains.

Untreated male patients with *COL4A5* mutations consistently progress to ESRD during the second or third decade of life, and most have deafness.[7] Genotype has a strong correlation with kidney disease progression in males with XLAS. In males with a large deletion, nonsense mutation, or a small mutation changing the mRNA reading frame, the risk for developing ESRD before age 30 is 90%. Splice-site mutations and missense mutations have a less severe renal phenotype with 70% and 50% reaching ESRD by age 30 years, respectively.[7] Women with XLAS have a wide variability in disease severity, and there is no genotype-phenotype correlation.[8] The severity of disease in a female heterozygous for a *COL4A5* mutation probably depends primarily on the relative activities of the mutant and normal X chromosomes in renal, cochlear, and ocular tissues due to X-inactivation.[9]

Autosomal recessive Alport syndrome. Autosomal recessive Alport syndrome (ARAS) arises from mutations affecting both alleles of *COL4A3* or *COL4A4*.[10] ARAS should be suspected when an individual with typical clinicopathologic features of the disease lacks a family history, especially when a young female has severe disease, such as deafness, nephrotic syndrome, or impaired renal function. However, sporadic cases of AS may represent *de novo* mutations at the *COL4A5* locus or a germ-line

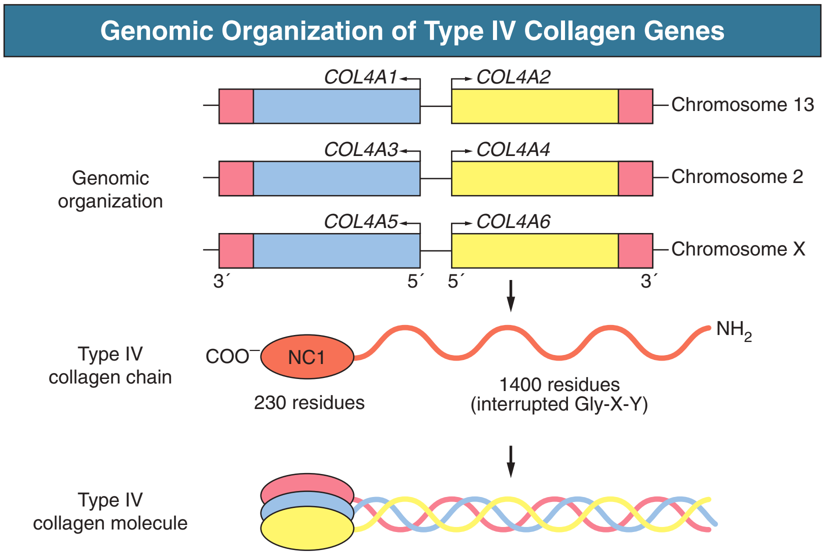


Fig. 46.1 Genomic organization of type IV collagen genes. Each type IV collagen chain is synthesized from one of the pairs of type IV collagen genes. Each type IV collagen molecule is a heterotrimer of three type IV collagen chains (see also Fig. 46.4).

TABLE 46.1 **Molecular Genetics of Alport Syndrome**

Inheritance	Affected Locus	Gene Product
X-linked (XLAS)	*COL4A5*	α5(IV)
X-linked + leiomyomatosis	*COL4A5* + *COL4A6*	α5(IV) + α6(IV)
Autosomal recessive (ARAS)	*COL4A3* *COL4A4*	α3(IV) α4(IV)
Autosomal dominant (ADAS)	*COL4A3* *COL4A4*	α3(IV) α4(IV)

COL4A5 mutation in the proband's mother. Most patients with ARAS develop ESRD and deafness before age 30 years, regardless of gender.[10]

Autosomal dominant Alport syndrome. Heterozygous mutations in *COL4A3* or *COL4A4* typically result in asymptomatic hematuria. In some families, however, these mutations also may be associated with progressive nephropathy, that is, ADAS. Patients with ADAS tend to have a slower course to ESRD than those with XLAS or ARAS.[11,12]

Type IV Collagen in Alport Basement Membranes

The GBMs and tubular basement membranes of males with XLAS usually fail to express the α3(IV), α4(IV), and α5(IV) chains but do express the α1(IV) and α2(IV) chains (Fig. 46.2). Women with XLAS frequently exhibit mosaic expression of the α3(IV), α4(IV), and α5(IV) chains in GBM, whereas expression of the α1(IV) and α2(IV) chains is preserved. Most males with XLAS show no EBM expression of α5(IV), whereas female heterozygotes frequently display mosaicism (Fig. 46.3). Lens capsules of some males with XLAS do not express the α3(IV), α4(IV), or α5(IV) chains, whereas expression of these chains appears normal in other patients.

In most patients with ARAS, GBM shows no expression of the α3(IV), α4(IV), or α5(IV) chains, but α5(IV) and α6(IV) are expressed in the Bowman capsule, distal thin basement membrane (TBM), and EBM (Fig. 46.4). Therefore XLAS and ARAS may be differentiated by immunohistochemical analysis. Basement membrane expression of type IV collagen α chains appears to be normal in patients with ADAS.

These observations indicate that a mutation affecting one of the chains involved in the α3–α4–α5(IV) network can prevent GBM expression not only of that chain but also of the other two chains as well; evidence suggests that this reflects post-translational events. Some mutant chains are unable to participate in the formation of trimers; as a result, the normal chains that are prevented from forming trimers undergo degradation. Other mutations may allow formation of abnormal trimers that are degraded before deposition in basement membranes can occur (Fig. 46.5).

Ultrastructural studies of Alport cochleae suggest that the hearing deficit may be attributable to a defect in adherence of the organ of Corti to the basilar membrane.[13]

Clinical Manifestations

Renal Defects

Hematuria is the cardinal finding of AS. Affected males have persistent microhematuria. Many also have episodic macrohematuria during upper respiratory tract infections, usually during the first two decades of life. Hematuria has been discovered in the first year of life in affected boys, in whom it is probably present from birth. Boys who are free of hematuria during the first 10 years of life are unlikely to be affected.

More than 90% of females with XLAS have persistent or intermittent microhematuria, but about 5% of obligate heterozygotes never manifest hematuria.[8] Hematuria is persistent in both males and females with ARAS. About 50% of carriers of *COL4A3* or *COL4A4* mutations have hematuria.

Proteinuria is usually absent early in life but develops eventually in all males with XLAS and in males and females with ARAS. Proteinuria increases progressively with age and may result in nephrotic syndrome. Proteinuria develops eventually in at least 75% of heterozygous females.[8] Hypertension also increases in incidence and severity with age and is more likely in affected males than affected females with XLAS, but there are no gender differences in the hypertension frequency in ARAS.

ESRD develops in all affected males with XLAS, at a rate determined primarily by the nature of the underlying *COL4A5* mutation.[7] Thus the rate of progression is fairly constant among affected males within a particular family, but there is significant interkindred variability.

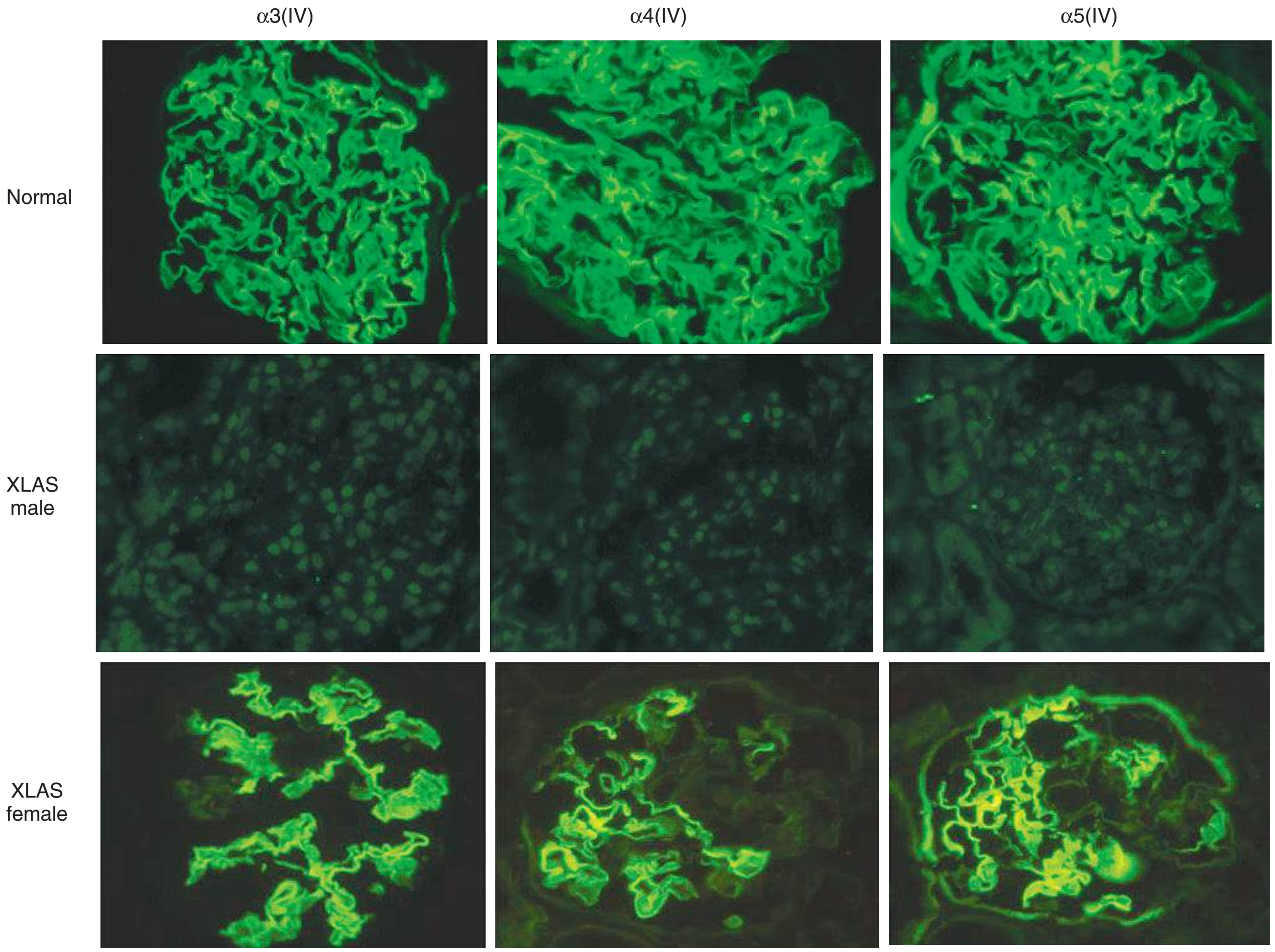


Fig. 46.2 **Immunohistochemistry of glomerular basement membrane (GBM) in X-linked Alport syndrome (XLAS).** In a normal individual *(top row)*, GBM stains strongly for the α3(IV), α4(IV), and α5(IV) chains of type IV collagen. Staining of GBM of an affected male is negative for each of these chains *(middle row)*, whereas an affected female shows mosaic immunoreactivity *(bottom row)*.

Significant intrakindred variability in the rate of progression to ESRD has been reported in some families with missense *COL4A5* mutations.

Progression to ESRD in females with XLAS was considered an unusual event until a 2003 European study of several hundred females with XLAS found that 12% developed ESRD before age 40 (vs. 90% of males with XLAS), increasing to 30% by age 60 and 40% by 80.[8] A confirmatory European registry study showed a 15% prevalence of ESRD in heterozygous women.[14] The risk for ESRD is significantly increased in heterozygotes with proteinuria. The outcome of XLAS in females is presumed to depend on the relative activities of the normal and mutant X chromosomes, but other unknown factors also likely influence outcome.[9] Macrohematuria in childhood, nephrotic syndrome, and the finding of diffuse GBM thickening by electron microscopy (EM) are risk factors for chronic kidney disease (CKD) in affected females.[15] Sensorineural deafness and anterior lenticonus are also indicative of an unfavorable outcome in affected women. Both males and females with ARAS appear likely to progress to ESRD during the second or third decade of life.[10]

Cochlear Defects

Deafness is frequently but not universally associated with the Alport renal lesion, occurring in about 90% of males and 25% to 30% of females with XLAS.[7,8] In some families with Alport nephropathy and apparently normal hearing, deafness may occur late and may be very slowly progressive.

Hearing loss in AS is never congenital and usually becomes apparent by late childhood to early adolescence in boys with XLAS and in both boys and girls with ARAS. Hearing loss is present in 50% of males with XLAS by approximately age 15, 75% by age 25, and 90% by age 40.[7] Hearing loss is less common in females with XLAS, with 10% of XLAS affected by 40 years of age and about 20% by age 60.[8] Hearing loss is also common in ARAS with approximately 40% to 66% of individuals affected,[10] but less common in ADAS with only 2% to 13% affected.[11,12] Hearing impairment in members of families with AS is always accompanied by evidence of renal involvement. In its early stages, the hearing deficit is detectable only by audiometry, with bilateral reduction in sensitivity to tones in the range of 2000 to 8000 Hz. In affected males, the deficit extends progressively to other frequencies, including those of conversational speech.

Ocular Defects

Ocular defects occur in 30% to 40% of males with XLAS and in about 15% of XLAS females.[7,8] *Anterior lenticonus,* a cone-shaped distortion of the anterior surface of the lens, is virtually pathognomonic of AS, occurs in about 15% of males with XLAS, and is almost entirely restricted to AS families with progression to ESRD before age 30 years and

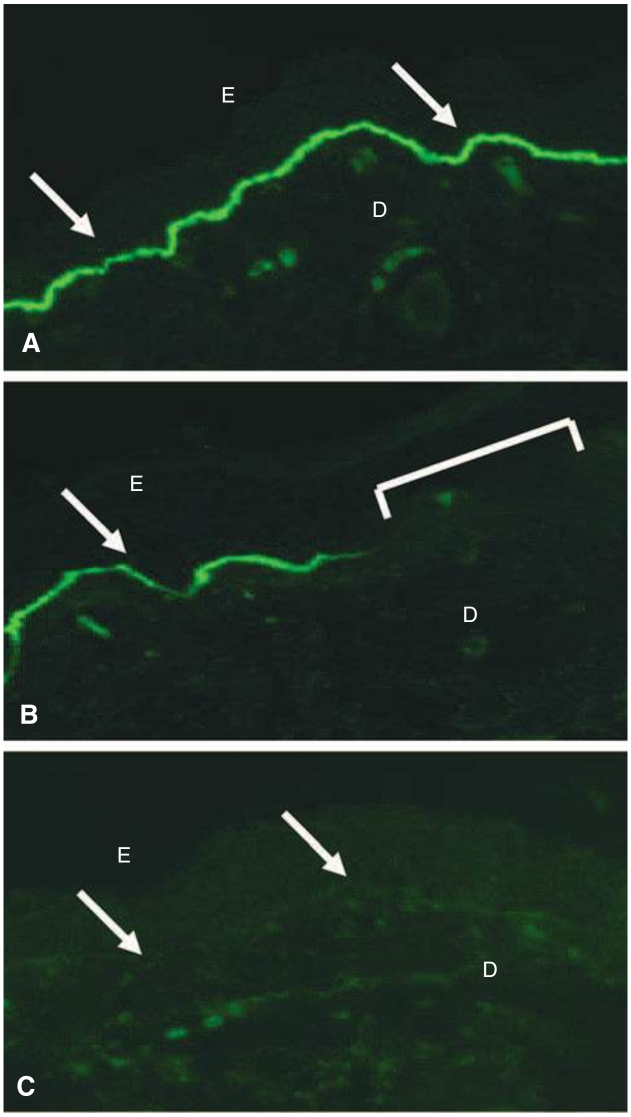


Fig. 46.3 **Immunohistochemistry of epidermal basement membrane (EBM) in X-linked Alport syndrome.** (A) In a normal male, EBM shows strong staining for α5(IV) at the dermoepidermal junction *(arrows)* between dermis *(D)* and epidermis *(E).* (B) In an affected female, EBM shows mosaic staining *(arrow);* the *white bracket* identifies a length of EBM negative for α5(IV). (C) In affected males, staining of EBM *(arrows)* for α5(IV) is absent.

deafness.[7] Anterior lenticonus is absent at birth, usually appearing during the second to third decade of life after the onset of CKD and is bilateral in 75% of patients (Fig. 46.6A). The spectrum and frequencies of ocular lesions appear to be similar in XLAS and ARAS.[16] Ocular lesions are almost never observed in ADAS.[11,12]

Another common ocular manifestation of AS is a maculopathy, with whitish or yellowish flecks or granulations in a perimacular distribution. This is present in 50% to 60% of men with XLAS, in men and women with ARAS, and in approximately 15% of women with XLAS[16] (see Fig. 46.6B). The maculopathy does not appear to be associated with any visual abnormalities.

Corneal endothelial vesicles (posterior polymorphous dystrophy) have been observed in AS and may indicate defects in the Descemet membrane, the basement membrane underlying the corneal endothelium. Recurrent corneal erosion in AS has been attributed to alterations of the corneal EBM.

Leiomyomatosis

The association of AS with leiomyomatosis of the esophagus and tracheobronchial tree has been reported in about 30 families.[6] Affected females typically also have genital leiomyomas, with clitoral hypertrophy and variable involvement of the labia majora and uterus. Bilateral posterior subcapsular cataracts also occur frequently in affected individuals. Symptoms usually appear in late childhood and include dysphagia, postprandial vomiting, retrosternal or epigastric pain, recurrent bronchitis, dyspnea, cough, and stridor. This syndrome typically arises from a contiguous gene deletion on the X-chromosome involving exon 1 of *COL4A5,* the common promoter region that regulates gene expression of *COL4A5* and *COL4A6,* and the first 2 exons of the adjacent *COL4A6* gene.[17] The genotype-phenotype relationship in this disorder is uncertain because deletions in this region may occur without associated leiomyomas, and conversely some families with XLAS and leiomyomas do not have deletions involving the common promoter region and *COL4A6.*[18]

Hematologic Defects

An autosomal dominant syndrome of hereditary nephritis, deafness, and megathrombocytopenia called *Epstein syndrome* has been described in a small number of families. Families with Fechtner syndrome exhibit these features as well as leukocyte inclusions (May-Hegglin anomaly). Both Epstein and Fechtner syndrome arise from mutations in nonmuscle myosin heavy-chain IIA (*MYH9*).[19] Although in some patients ultrastructural changes in GBM resemble those of AS, basement membranes of these patients do not have abnormal expression of type IV collagen α chains. Therefore Epstein and Fechtner syndromes are best considered distinct forms of hereditary nephritis rather than variants of AS.

Arterial Abnormalities

Aneurysmal dilation of the thoracic and abdominal aorta and smaller arterial vessels has been described in a small number of males with AS.[20]

Renal Pathology

There are no pathognomonic lesions by light microscopy or immunofluorescence in AS. In affected males, biopsies obtained before 5 years of age typically show no light microscopy changes. Mesangial hypercellularity and matrix expansion are typically observed in older children and adolescents. Glomeruli of affected males eventually show focal segmental glomerulosclerosis (FSGS), and interstitial fibrosis and tubular atrophy are often found in affected boys older than 10 years.[21] Light microscopy findings in affected females correlate with proteinuria and kidney function; an affected female of any age who has isolated microhematuria is likely to have little or no abnormality by light microscopy. Indirect immunofluorescence of type IV collagen α-chain expression in renal or skin basement membranes can be diagnostic (see earlier discussion).

EM frequently reveals diagnostic abnormalities. In most patients with AS there is variable thickening, thinning, basket weaving, and lamellation of the GBM (Fig. 46.7). The thick segments measure up to 1200 nm in depth, usually have irregular outer and inner contours, and are found more frequently in males than in females. The lamina densa is transformed into a heterogeneous network of membranous strands, which enclose clear electron-lucent areas that may contain round granules of variable density measuring 20 to 90 nm in diameter. There are variable degrees of epithelial foot process fusion.

Not all Alport kindreds demonstrate these characteristic ultrastructural features. Thick, thin, normal, and nonspecifically altered GBMs have all been described. Affected young males, heterozygous females at any age, and, on occasion, affected adult males may have diffusely attenuated GBM measuring as little as 100 nm or less in thickness rather than

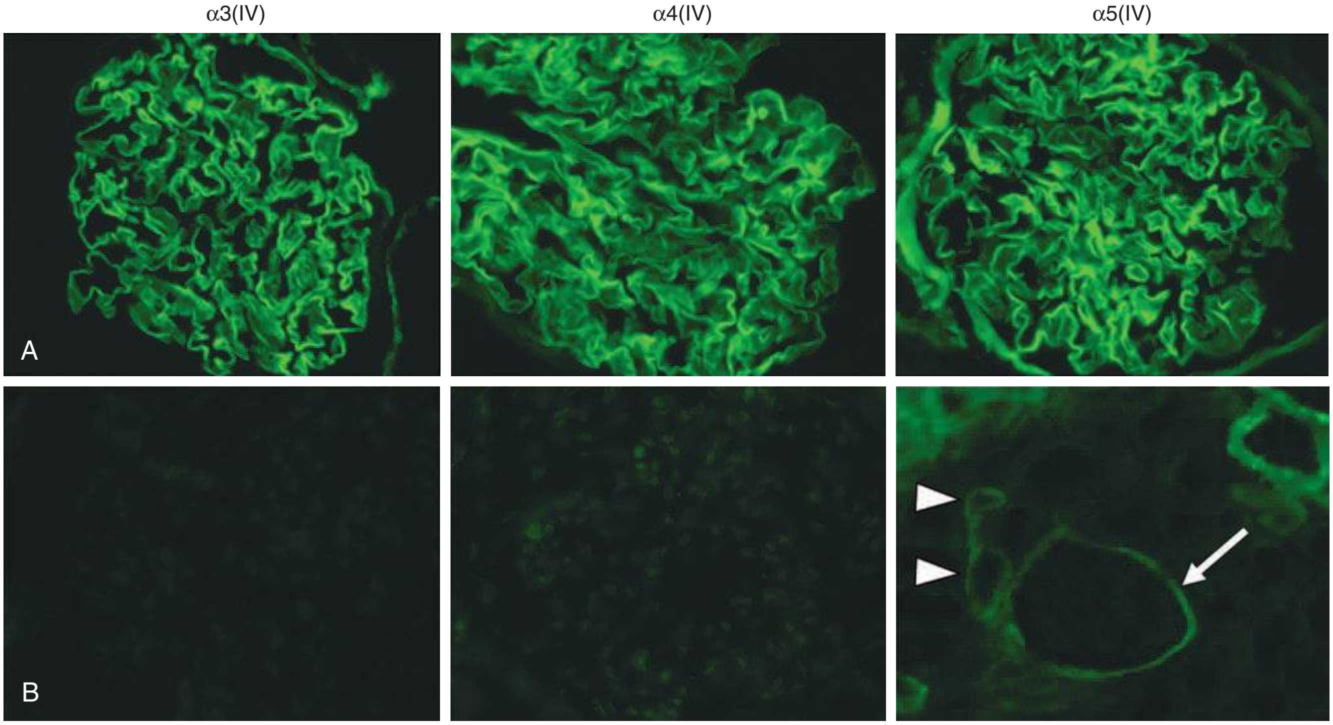


Fig. 46.4 Immunohistochemistry of kidney in patient with autosomal recessive Alport syndrome. (A) Normal glomerular basement membrane (GBM) and Bowman capsule staining for α3(IV), α4(IV), and α5(IV). (B) Patient shows no GBM staining, but α5(IV) is present in the Bowman capsule *(arrow)* and distal tubular basement membranes *(arrowheads)*.

the pathognomonic lesion. Although diffuse attenuation of GBM has been considered the hallmark of thin basement membrane nephropathy (TBMN), some patients with this abnormality are members of kindreds with a history of progression to renal failure. Therefore the significance of an ultrastructural finding of thin GBM must be considered in the context of the family history, basement membrane expression of type IV collagen α chains, and, if available, molecular genetic information. There are a number of families reported with features of hereditary FSGS with or without the classic AS basement membrane lesion associated with mutations in *COL4A3* or *COL4A4*.[22] These findings highlight the utility of detailed genetic evaluation to avoid misdiagnosis.

Diagnosis and Differential Diagnosis

Fig. 46.8 summarizes the evaluation of patients with hematuria and a positive family history. AS should be included in the initial differential diagnosis of patients with persistent microhematuria after excluding structural abnormalities of the kidneys or urinary tract (see Chapter 59). The presence on EM of diffuse thickening and multilamellation of the GBM predicts a progressive nephropathy, regardless of family history. However, in a patient with a negative family history, EM cannot differentiate de novo XLAS from ARAS. In some patients, the biopsy findings may be ambiguous, particularly in females and young patients of either gender. Furthermore, families with progressive nephritis and *COL4A5* mutations in association with GBM thinning have been described, indicating that the classic Alport GBM lesion is not present in all Alport kindreds.

If an undiagnosed patient has hematuria and multiple relatives with hematuria, who should undergo renal biopsy? The natural history of the AS renal lesion suggests that older, male individuals are more likely to exhibit diagnostic ultrastructural GBM abnormalities. In families with a firm diagnosis of AS established, evaluation of individuals with newly recognized hematuria can be limited to ultrasound of the kidneys and urinary tract to exclude coincidental tumor or structural anomalies of the urinary tract.

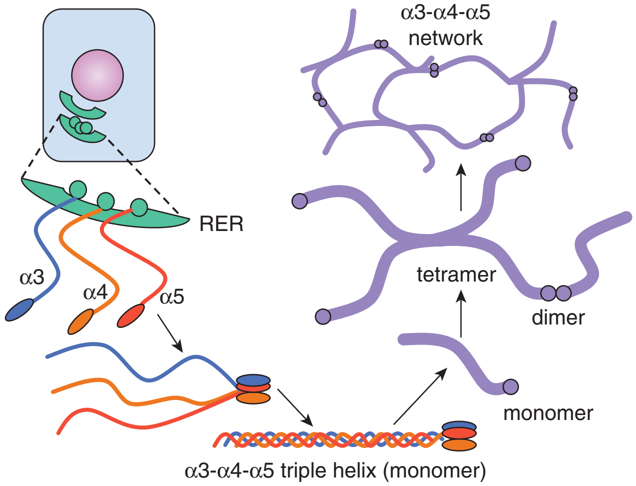
Absence of the α3, α4, and α5 chains of type IV collagen from GBM and distal TBM is unique to AS (Table 46.2). Expression of α5(IV) in the EBM detected by immunofluorescence may be informative, but apparently normal expression of type IV collagen α chains in basement membranes does not exclude the diagnosis of AS. Although mosaic expression of α5(IV) is diagnostic of the carrier state in heterozygous females, a normal result does not exclude heterozygosity. A female member of an Alport kindred who does not have hematuria still may be a carrier, but is less likely to exhibit detectable mosaicism than females with hematuria.

A firm histologic diagnosis of AS cannot always be established, or it may not be possible to determine the mode of transmission, despite careful evaluation of the pedigree and application of the full range of histologic methods. In these situations, genetic analysis may provide information essential for determining prognosis and guiding genetic counseling. Genetic analysis for AS is widely available in commercial and research laboratories.

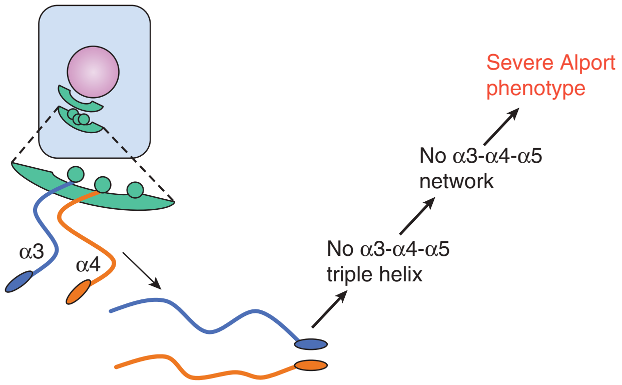
Genetic analysis using conventional Sanger sequencing identifies 80% to 90% of males with *COL4A5* mutations. Next-generation sequencing allows for simultaneous evaluation of *COL4A3, COL4A4,* and *COL4A5*.[23] Identification of a specific genotype can provide some prognostic information about the risk for kidney disease progression and risk for associated hearing loss and eye findings in an individual patient.[7] Once a new diagnosis of AS is made, all potentially affected family members including females should be screened for hematuria to identify those who may be at risk for progressive kidney disease, and targeted mutation analysis can be offered if requested by at-risk individuals.[24]

Glomerular diseases that typically occur sporadically may on occasion be heritable and should be considered in the differential diagnosis.

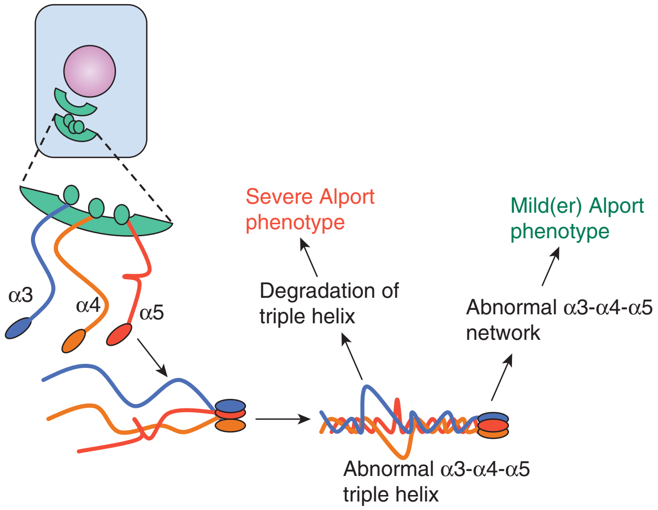
Assembly of Type IV Collagen Heterotrimers in Health and in Alport Syndrome


α3-α4-α5
network
RER
tetramer
dimer
α3
α4
α5
monomer
α3-α4-α5 triple helix (monomer)

Normal


Severe Alport
phenotype
No α3-α4-α5
network
No α3-α4-α5
triple helix
α3
α4

Effect of a "severe" COL4A5 mutation: deletion, frameshift, premature stop


Severe Alport
phenotype
Mild(er) Alport
phenotype
Degradation of
triple helix
Abnormal α3-α4-α5
network
α3
α4
α5
Abnormal α3-α4-α5
triple helix

Effects of a COL4A5 missense mutation

Fig. 46.5 Assembly of type IV collagen heterotrimers in health and in Alport syndrome. *RER,* Rough endoplasmic reticulum.

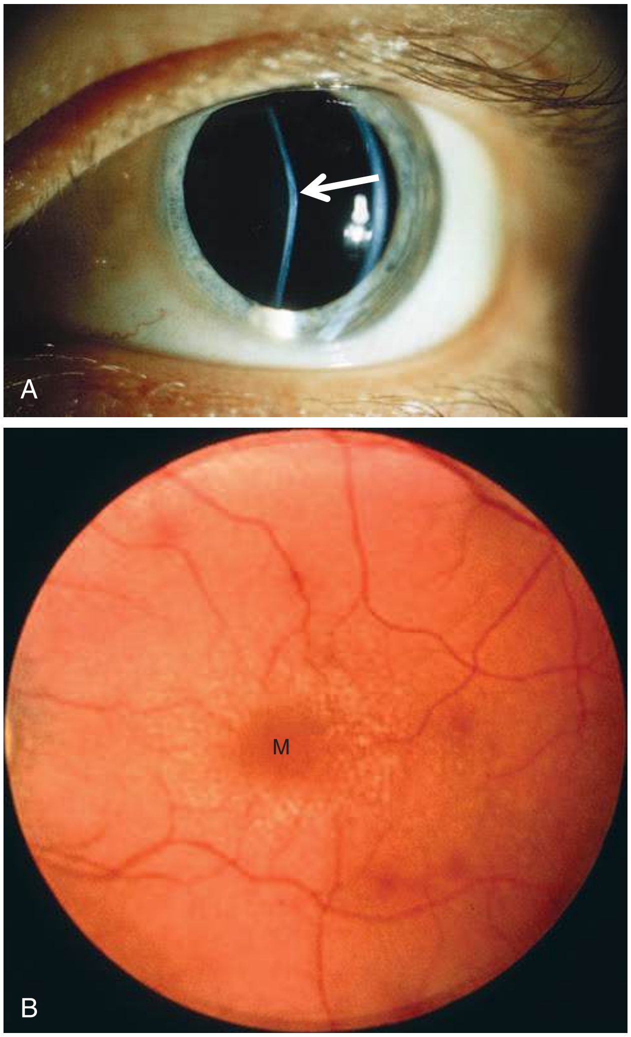


Fig. 46.6 **Ocular abnormalities in Alport syndrome.** (A) Anterior lenticonus shown by slit-lamp ophthalmoscopy. The anterior surface of the lens is cone shaped (*arrow* marks apex of the cone), rather than the normal smooth ellipse. (B) Perimacular flecks. Note the white flecks surrounding the macula *(M)*. (From Flinter FA. Disorders of the basement membrane: hereditary nephritis. In: Morgan SH, Grunfeld JP, eds. *Inherited Disorders of the Kidney*. Oxford: Oxford University Press; 1998.)

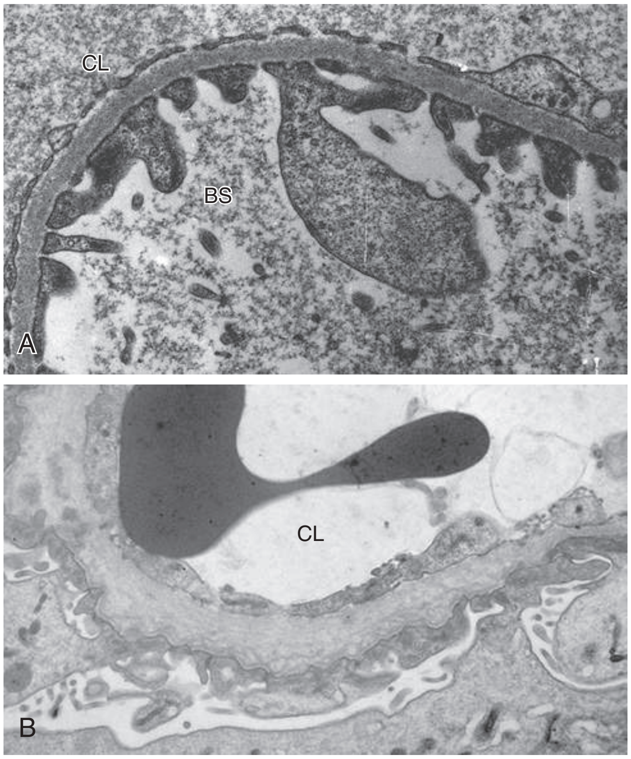


Fig. 46.7 **Renal biopsy in Alport syndrome.** (A) Normal glomerular capillary wall. *BS,* Bowman space. (B) Glomerular capillary wall from a patient with Alport syndrome, at the same magnification. *CL,* Capillary lumen. Note the thickening of the glomerular basement membrane (GBM), the splitting of the lamina densa into multiple strands, and the marked irregularity of the epithelial aspect of the GBM in the patient with Alport syndrome.

These include IgA nephropathy, FSGS, membranous nephropathy, membranoproliferative glomerulonephritis, and C3 glomerulopathy.

Natural History

Microhematuria, the first and invariable renal manifestation of AS, probably reflects GBM thinning with focal ruptures because of defective expression of the α3–α4–α5(IV) network. In its early stages, AS is clinically and often histologically indistinguishable from TBMN, which typically has a benign outcome. GBM attenuation is therefore an insufficient explanation for the divergent natural histories of the two conditions. What factors initiate and drive the progression of Alport nephropathy to ESRD? Reduction in the quantity of α3(IV), α4(IV), and α5(IV) chains in GBM (as likely occurs in TBMN) probably has consequences different from complete loss of these chains, as occurs in most males with XLAS and most patients with ARAS. The normal transition from the $\alpha1(IV)_2$–$\alpha2(IV)_1$ network of nascent glomeruli to the α3(IV)– α4(IV)– α5(IV) network of mature glomeruli fails to occur in AS, and α1(IV) and α2(IV) chains accumulate in Alport glomeruli as the disease progresses.[25,26] Alport GBM also shows overexpression of other matrix proteins normally absent from GBM or present in scant quantities, including type V collagen, type VI collagen, laminin α2 chain, and fibronectin. These alterations in GBM composition are unique to AS.[25,27] Both glomerular endothelial cells and podocytes appear to contribute to the accumulation of these proteins in Alport GBM. Recently, mesangial filopodial invasion of the GBM with deposition of ectopic laminin chains was proposed as another mechanism of matrix accumulation.[28] Alterations in glomerular extracellular matrix are accompanied by changes in glomerular cell behavior, including expression of transforming growth factor β1, integrins, and matrix metalloproteinases. Activation of fibrogenic pathways in the renal interstitium presumably represents a downstream consequence of glomerular disease.

Treatment

Current clinical practice recommendations for delaying ESRD in patients with AS focus on the early introduction of renin-angiotensin system (RAS) blockade to suppress urinary protein excretion.[24,29] The use of RAS blockade is based on experimental and clinical evidence as well as practical considerations. Angiotensin-converting enzyme (ACE) inhibition lengthens survival in mice with ARAS, doubling survival when begun before the onset of proteinuria. ACE inhibition begun after the onset of proteinuria also improves survival in Alport mice, to a lesser degree. The effect of ramipril on survival was superior to that of candesartan in a murine comparison study.

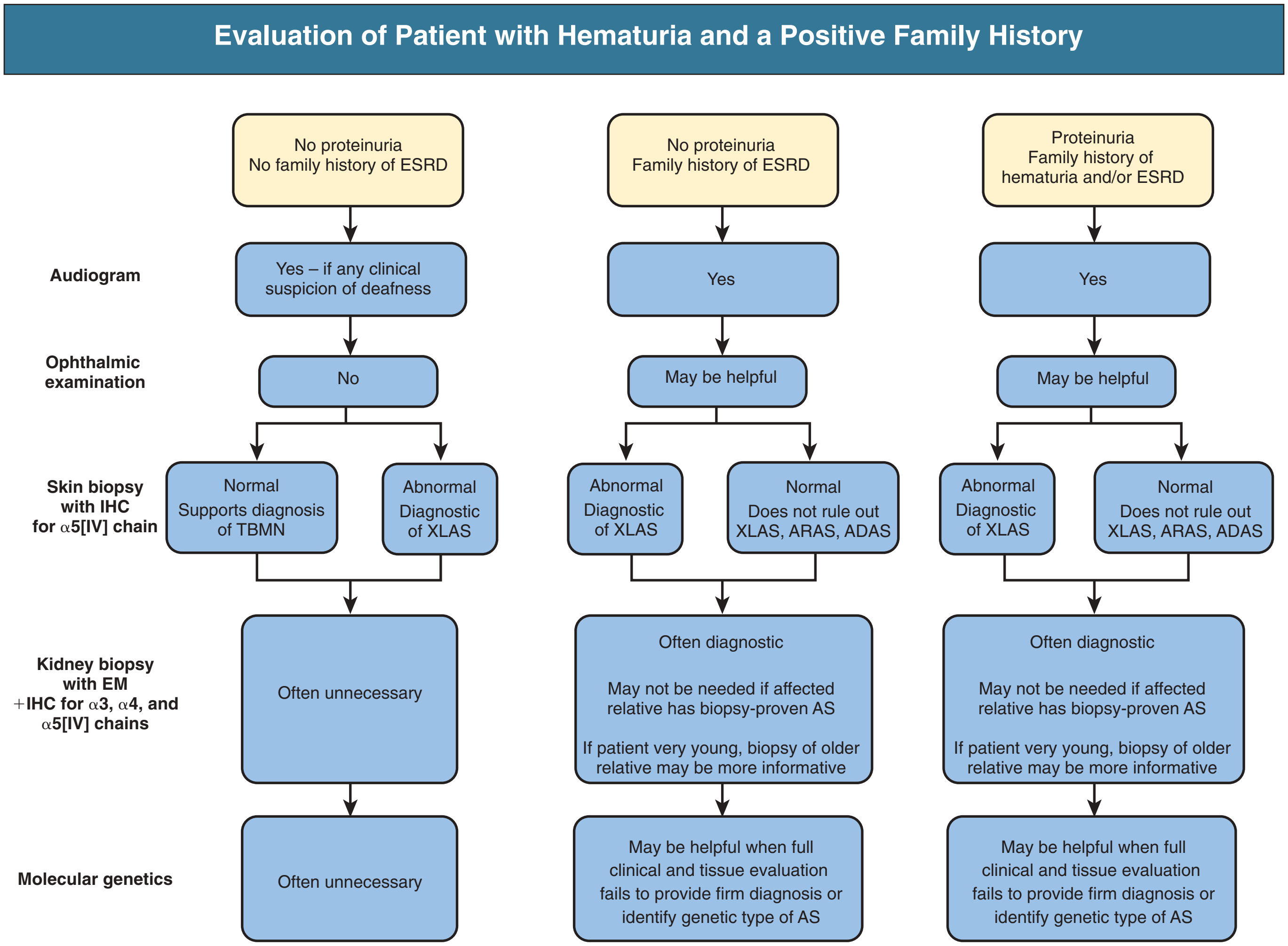

Evaluation of Patient with Hematuria and a Positive Family History
No proteinuria
No family history of ESRD
No proteinuria
Family history of ESRD
Proteinuria
Family history of hematuria and/or ESRD
Audiogram
Yes – if any clinical suspicion of deafness
Yes
Yes
Ophthalmic examination
No
May be helpful
May be helpful
Skin biopsy with IHC for α5[IV] chain
Normal
Supports diagnosis of TBMN
Abnormal
Diagnostic of XLAS
Abnormal
Diagnostic of XLAS
Normal
Does not rule out XLAS, ARAS, ADAS
Abnormal
Diagnostic of XLAS
Normal
Does not rule out XLAS, ARAS, ADAS
Kidney biopsy with EM +IHC for α3, α4, and α5[IV] chains
Often unnecessary
Often diagnostic
May not be needed if affected relative has biopsy-proven AS
If patient very young, biopsy of older relative may be more informative
Often diagnostic
May not be needed if affected relative has biopsy-proven AS
If patient very young, biopsy of older relative may be more informative
Molecular genetics
Often unnecessary
May be helpful when full clinical and tissue evaluation fails to provide firm diagnosis or identify genetic type of AS
May be helpful when full clinical and tissue evaluation fails to provide firm diagnosis or identify genetic type of AS

Fig. 46.8 Evaluation of patient with hematuria and positive family history. *ADAS,* Autosomal dominant Alport syndrome; *ARAS,* autosomal recessive Alport syndrome; *AS,* Alport syndrome; *EM,* electron microscopy; *ESRD,* end-stage renal disease; *IHC,* immunohistochemistry; *TBMN,* thin basement membrane nephropathy; *XLAS,* X-linked Alport syndrome.

Uncontrolled clinical studies in AS have shown that RAS blockade can reduce proteinuria. In a large multicenter, randomized, double-blind study comparing losartan with placebo or amlodipine in children with AS and proteinuria there was a significant reduction in proteinuria with losartan over 12 weeks.[30] A 3-year extension of this study showed comparable efficacy of enalapril and losartan in reducing proteinuria.[31] A retrospective review of treated Chinese children with AS similarly showed a decline in proteinuria with ACE inhibition that was sustained over 5 years of follow-up.[32]

Retrospective data from the European Alport Registry indicates that ACE inhibitor therapy initiated while glomerular filtration rate (GFR) is still normal delays ESRD by years.[33] This also has been shown in pairs of affected brothers discordant for ACE inhibitor therapy with a delay in ESRD of a median of 13 years in the earlier treated brother.[33] ACE inhibitors can be used safely in children with CKD, at doses that achieve suppression of urinary protein excretion.[34] RAS blockers are relatively inexpensive and widely available, so any child in the world with AS should be able to receive treatment.

Consensus recommendations for the management of AS children include (1) early screening for hematuria in at-risk children, (2) regular determination of urinary protein excretion on diagnosis, and (3) initiation of RAS blockade once overt proteinuria develops.[29] The goal of treatment is to reduce the ratio of urine protein to creatinine (uPCR) by 50% in children with a ratio of 0.2 to 1 mg/mg or to less than 0.5 mg/mg in those with uPCR greater than 2 mg/mg.[29] A randomized trial examining the effect of RAS blockade on the transitions from isolated hematuria to microalbuminuria to overt proteinuria is under way in Europe (EARLY PRO-TECT). Future clinical trials comparing RAS blockade to other therapies, alone or in combination, will be needed to identify the most effective approaches to delaying and preventing ESRD in patients with AS.

Transplantation

Renal transplantation is typically successful in patients with AS who reach ESRD with graft survival equivalent to that in patients with other diagnoses.[35] However, anti-GBM glomerulonephritis involving the renal allograft is a rare but dramatic manifestation of AS, occurring in 2% to 3% of male patients with AS who undergo transplantation and typically presents in the first year (see Chapter 24).

Are women who are heterozygous for *COL4A5* mutations suitable kidney donors? Clearly, those with proteinuria, hypertension, or reduced GFR should not donate, nor should women with hearing loss. A case

TABLE 46.2 Immunostaining for Type IV Collagen in Alport Syndrome

Type IV Collagen Group	Glomerular Basement Membranes	Bowman Capsules	Distal Tubular Basement Membrane	Epidermal Basement Membrane
Normal (Males and Females)				
α3(IV)	Present	Present	Present	Absent
α4(IV)	Present	Present	Present	Absent
α5(IV)	Present	Present	Present	Present
X-Linked (Males)*				
α3(IV)	Absent	Absent	Absent	Absent
α4(IV)	Absent	Absent	Absent	Absent
α5(IV)	Absent	Absent	Absent	Absent
X-Linked (Females)†				
α3(IV)	Mosaic			Absent
α4(IV)	Mosaic			Absent
α5(IV)	Mosaic			Mosaic
Autosomal Recessive (Males and Females)*				
α3(IV)	Absent	Absent	Absent	Absent
α4(IV)	Absent	Absent	Absent	Absent
α5(IV)	Absent	Present	Present	Present

*In some Alport kindreds, staining of basement membranes for type IV collagen chains is entirely normal. Therefore a normal result does not exclude a diagnosis of X-linked Alport syndrome.

†Some heterozygous females have normal basement membrane immunoreactivity for type IV collagen chains. Therefore a normal result does not exclude the carrier state.

series of heterozygous donors showed new-onset hypertension, proteinuria, and decline in GFR after kidney donation in most women.[36] Given the recent finding that 30% to 40% of heterozygous women may eventually develop ESRD, the risk that a heterozygous donor will ultimately develop significant renal impairment must be higher than for the usual kidney donor. However, a common clinical scenario is a mother choosing to donate to her son with AS, and the choices of the whole family should be considered.

HEREDITARY ANGIOPATHY WITH NEPHROPATHY, ANEURYSMS, AND CRAMPS (HANAC SYNDROME)

An autosomal dominant hereditary angiopathy associated with nephropathy, aneurysms, and muscle cramps (HANAC syndrome) is caused by missense mutations in the *COL4A1* gene that allow for expression of an abnormal α1(IV) chain.[37] Renal findings in affected individuals include microhematuria and macrohematuria, mild renal impairment, and renal cysts. Retinal arteriolar tortuosity and retinal hemorrhage are common in affected individuals, as are intracranial aneurysms and leukoencephalopathy. Some affected individuals have elevated serum creatine kinase and muscle cramps.

Renal biopsy in affected individuals with hematuria shows no abnormalities of GBM structure or type IV collagen expression. However, basement membranes of the Bowman capsules, tubules, and interstitial capillaries exhibited irregular thickening, splitting into multiple layers and focal interruptions.

THIN BASEMENT MEMBRANE NEPHROPATHY

Definition

Isolated glomerular hematuria may occur as a familial or sporadic condition and is often associated with an excessively thin GBM on renal biopsy. The term *thin basement membrane nephropathy* (TBMN) is used to identify both familial and sporadic isolated hematuria associated with attenuated GBM. It is likely that several disorders that differ at the molecular level are associated with GBM thinning, and in some patients it is probably a normal variant.

Similar to AS, familial TBMN is an inherited GBM disorder manifested by chronic hematuria, but it differs clinically from AS in several important respects: (1) extrarenal abnormalities are rare; (2) proteinuria, hypertension, and progression to ESRD are unusual, seen in less than 10% of affected individuals, and extremely unusual before age 40; (3) gender differences in expression of TBMN are not apparent; and (4) transmission is autosomal dominant. TBMN and early AS may be difficult to differentiate histologically because diffuse GBM attenuation is characteristic of both. However, the GBM of patients with TBMN remains attenuated and does not undergo the progressive thickening and multilamellation that occurs in AS. Although TBMN is nonprogressive, careful evaluation and follow-up of individuals with TBMN is required to monitor for progressive kidney disease.

Etiology and Pathogenesis

Although TBMN is an autosomal dominant condition, a negative family history may not be reliable because patients are frequently unaware that they have relatives with hematuria. Familial TBMN has been localized to *COL4A3* or *COL4A4* in numerous kindreds,[38] and 50% or more heterozygotes have hematuria. However, linkage to *COL4A3* and *COL4A4* has been excluded in other families with isolated hematuria, indicating that TBMN is genetically heterogeneous.[39]

Immunohistologic studies of type IV collagen in GBM of patients with TBMN show no abnormalities in the distribution of any of the six α chains. Immunohistologic evaluation of GBM type IV collagen may therefore be useful in the differentiation of TBMN from AS.

Clinical Manifestations

TBMN is the most common cause of persistent microhematuria in children and adults and is common in the general population, with an estimated prevalence of 1% to 2%.[40] Of patients referred to a nephrologist for evaluation of persistent hematuria, 20% to 25% will prove to have thin GBM on renal biopsy. Individuals with TBMN typically have persistent microhematuria that is first detected in childhood. In some patients, microhematuria is intermittent and may not be detected until adulthood. Episodic macrohematuria, often in association with upper respiratory infections, is not unusual. The hematuria of TBMN appears to be a lifelong condition.

Overt proteinuria and hypertension are unusual in TBMN but have been reported in up to 30% of adults. Some of these patients may have had AS, in which the predominant abnormality of GBM was attenuation rather than thickening and multilamellation. Other glomerular disorders, such as IgA nephropathy and FSGS, may occur concurrently with TBMN.

Pathology

Light and immunofluorescence microscopy are unremarkable in typical cases of TBMN. Most patients exhibit diffuse thinning of the whole GBM and of the lamina densa (Fig. 46.9). GBM width is age and gender dependent in normal individuals.[40] Both the lamina densa and the GBM increase rapidly in thickness between birth and 2 years of age, followed by gradual thickening into adulthood. GBM thickness in adult men (373 ± 42 nm) exceeds that in adult women (326 ± 45 nm). Each EM laboratory should establish a consistent technique for measuring GBM thickness and determine its own reference range for GBM width to make comparisons with published data meaningful. Typically, a value of 250 nm will accurately separate adults with normal GBM from those with TBMN. For children, the cut-off is in the range of 200 to 250 nm. Intraglomerular variability in GBM width is minimal in patients with TBMN.

Diagnosis and Differential Diagnosis

If the family history indicates autosomal dominant transmission of isolated hematuria without deafness or ocular abnormalities, if there is no family history of CKD, and if kidney and urinary tract imaging studies are normal, a presumptive diagnosis of TBMN often can be made without kidney biopsy (see Fig. 46.7). When family history is negative or unknown or there are coexisting features that are atypical for TBMN (e.g., proteinuria; deafness), renal biopsy may be very informative. Normal distribution of type IV collagen α chains in the kidney provides supportive but not conclusive evidence for a diagnosis of TBMN. Marked variability in GBM width within a glomerulus in a patient with persistent microhematuria should raise suspicion of AS, although focal lamina densa splitting has been described in TBMN. Genetic analysis may confirm a heterozygous mutation in *COL4A3* or *COL4A4*.

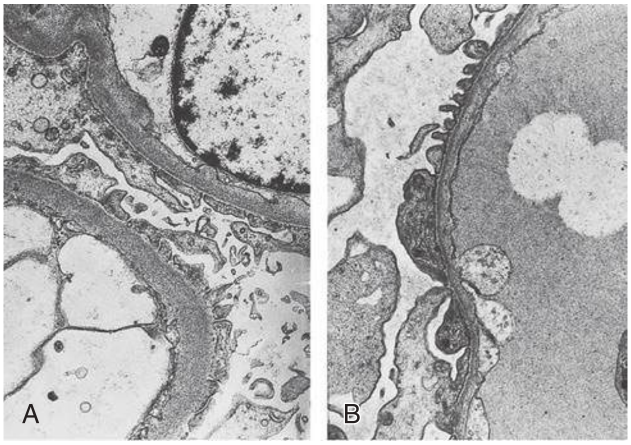


Fig. 46.9 Thin basement membrane nephropathy. Electron micrographs of renal biopsy specimens. (A) Normal glomerular capillary wall. (B) Thin basement membrane nephropathy at the same magnification. Note the diffuse and uniform attenuation of the glomerular basement membrane and the lamina densa. (From Warrell DA, Cox TM, Firth JD, Benz EJ Jr, eds. *Oxford Textbook of Medicine.* Oxford: Oxford University Press; 2003:322.)

Treatment

Patients with TBMN should be reassured but not lost to follow-up. The risk for chronic renal impairment is small (<5%) but real. Urinalysis and measurement of blood pressure and renal function are recommended every 1 to 2 years.

FABRY DISEASE (ANDERSON-FABRY DISEASE)

Definition

Fabry disease is caused by hereditary deficiency of the enzyme α-galactosidase A (α-Gal A), resulting in the intracellular accumulation of neutral glycosphingolipids with terminal α-linked galactosyl moieties (Fig. 46.10). Clinically, this leads to progressive CKD, pain crises, sweating abnormalities, vascular cutaneous lesions, and cardiac and eye abnormalities.

Etiology and Pathogenesis

More than 500 mutations causing Fabry disease have been identified in *GLA,* the gene for α-Gal A, which is located on the X chromosome. Most of the described mutations are associated with the classic Fabry phenotype, in which there is multisystem involvement. Certain missense mutations have been identified in patients with a mild phenotype limited to cardiac abnormalities.

Glycosphingolipids are normal constituents of the plasma membrane, the membranes of intracellular organelles, and circulate in association with apolipoproteins. The neutral glycosphingolipids that accumulate in Fabry disease are identical to those found in normal tissue. All tissues except red blood cells accumulate globotriaosylceramide (Gb3), with the highest concentrations found in the diseased kidney.

Clinical Manifestations and Pathology

Fabry disease is a multisystem disorder, with prominent and potentially devastating involvement of the kidneys, heart, and peripheral and central nervous systems. As expected for an X-linked disorder, severe clinical manifestations occur in hemizygous males, whereas heterozygous females have a variable but typically less severe course. In affected males, the initial features of the disease are seen in childhood and early adolescence

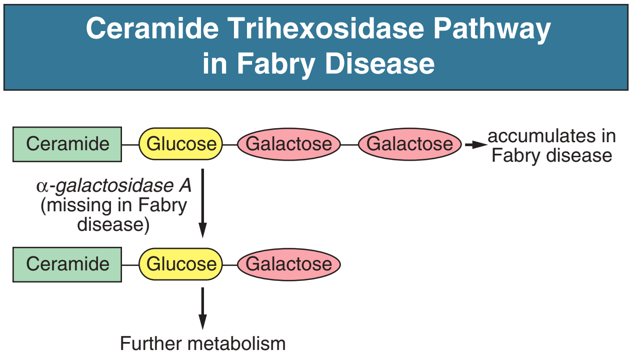

Ceramide Trihexosidase Pathway in Fabry Disease
Ceramide
Glucose
Galactose
Galactose
accumulates in Fabry disease
α-galactosidase A (missing in Fabry disease)
Ceramide
Glucose
Galactose
Further metabolism

Fig. 46.10 Ceramide trihexosidase pathway in Fabry disease. α-Galactosidase A deficiency leads to tissue accumulation of trihexosylceramide.

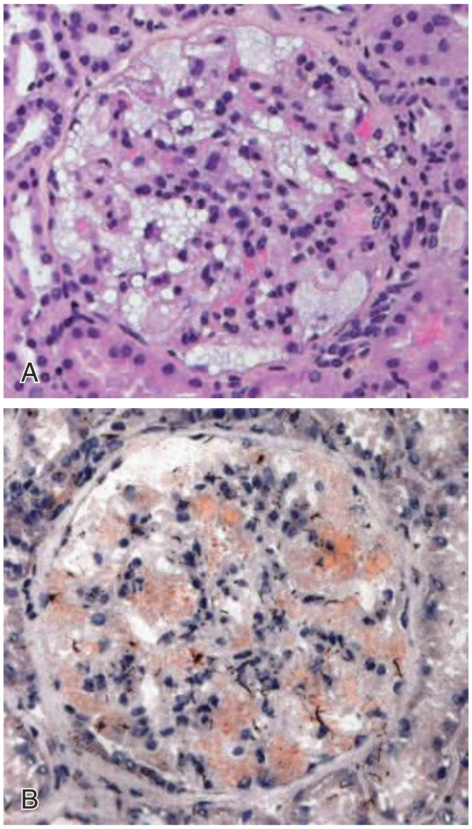


Fig. 46.11 Light microscopy of a renal biopsy specimen in Fabry disease. Glomerular epithelial cell glycosphingolipid deposition demonstrated by (A) vacuolation on hematoxylin-eosin staining (magnification ×20; (B) oil red O staining (×20). (Courtesy Dr. Paolo Menè and Dr. Antonella Stoppacciaro, University of Rome.)

and consist of paresthesias and pain in the hands and feet with episodic pain crises. The course of the disease is variable but usually leads to ESRD in the third to sixth decade. Myocardial or cerebral infarctions are typical terminal events. Severe Fabry disease in a female reflects extensive inactivation of the X chromosome carrying the normal α-Gal A allele.[41]

Renal Defects

Although the earliest manifestation of renal involvement is a concentrating defect, the nephropathy of Fabry disease typically manifests as mild to moderate proteinuria, sometimes with microhematuria, beginning in the third decade although proteinuria in childhood is reported. Nephrotic syndrome is unusual. Urinary oval fat bodies, with a Maltese cross configuration when viewed with a polarizing microscope, are a result of the large amounts of glycosphingolipid in the urine (see Chapter 4, Fig. 4.2B). Deterioration of renal function is gradual, with hypertension and ESRD developing by the fourth or fifth decade of life. Heterozygous women typically have mild renal involvement but up to 10% may develop ESRD.

Glomerular visceral epithelial cells are enlarged and packed with small, clear vacuoles that represent glycosphingolipid material (Fig. 46.11). Vacuoles also may be seen in parietal epithelial cells and the epithelial cells of the distal convoluted tubule and loop of Henle, but only rarely in mesangial cells, glomerular endothelial cells, or proximal tubular epithelial cells. There is progressive segmental and global glomerulosclerosis. Vacuoles are also observed in endothelial cells and smooth muscle cells of arterioles and arteries.

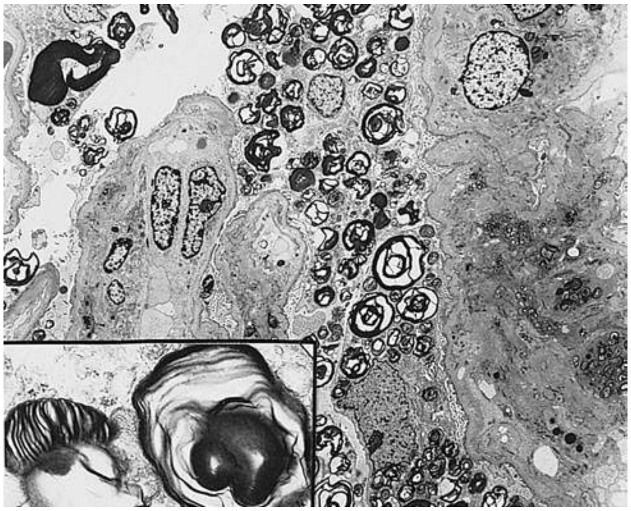


Fig. 46.12 Electron micrograph of a renal biopsy specimen in Fabry disease. Glycosphingolipid is deposited in cytoplasmic vacuoles in glomerular visceral epithelial cells. *Inset,* Cytoplasmic vacuoles contain electron-dense material in parallel arrays (zebra bodies) and in concentric whorls (myelin figures). (Courtesy Dr. J. Carlos Manivel.)

On EM, there are abundant inclusions within lysosomes, particularly within visceral epithelial cells (Fig. 46.12). The inclusions (myelin figures) are typically round, comprising concentric layers of dense material separated by clear spaces. The layers may be arranged in parallel (zebra bodies). Detachment of visceral epithelial cells from the underlying basement membrane may be observed. Inclusions are also observed in heterozygous females, although usually in smaller numbers than in affected males. Typical inclusions may be noted in excreted renal tubular cells.

The progression of Fabry nephropathy to ESRD probably reflects two parallel processes. Visceral epithelial cell dysfunction, which results in proteinuria, is followed by visceral epithelial cell detachment and necrosis, leading to capillary loop collapse and segmental sclerosis. Simultaneously, progressive impairment of arteriolar flow may develop as enlarging endothelial cells impinge on vascular lumina, resulting in ischemic glomerular damage.

Heart Defects

Glycosphingolipid accumulation in coronary artery endothelial cells and in the myocardium results in coronary artery narrowing, which may lead to angina, myocardial infarction, or congestive heart failure. Left ventricular hypertrophy (LVH) may be an early finding.[42] Arrhythmias resulting from infiltration of the conduction system and valvular lesions also may occur. Certain missense mutations affecting α-Gal A may present as isolated LVH.

Nervous System

Autonomic dysfunction is a prominent feature of Fabry disease, typically manifested by hypohidrosis, acral paresthesias and pain, and altered intestinal motility. Cerebrovascular symptoms (secondary to narrowing of the vascular lumen from accumulation of glycosphingolipid in vascular endothelial cells) tend to appear during the fourth decade and include hemiparesis, vertigo, diplopia, dysarthria, nystagmus, nausea and vomiting, headache, ataxia, and memory loss. The vertebrobasilar circulation is preferentially involved. Symptoms are often recurrent. Life-threatening intracerebral hemorrhage and infarction are not unusual. Dementia arising from glycosphingolipid accumulation in small cerebral blood vessels also has been described.

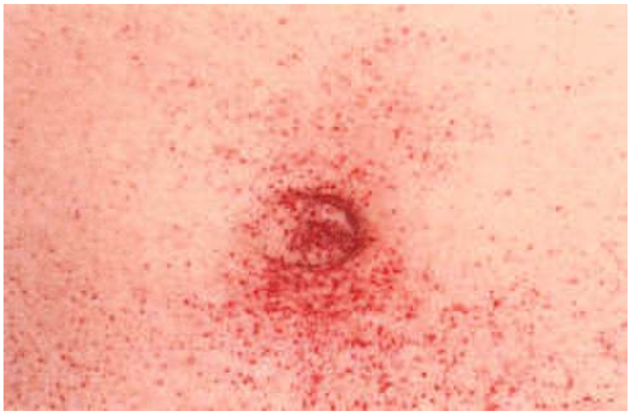


Fig. 46.13 Angiokeratoma in Fabry disease. Note the multiple periumbilical angiokeratomas. (Courtesy Dr. S. Waldek.)

Skin

Angiokeratomas usually appear during the second decade of life and can be the earliest presentation of Fabry disease, presenting as dark-red macules or papules of variable size (Fig. 46.13), originally known as *angiokeratoma corporis diffusum*. Typical locations include the lower trunk, buttocks, hips, genitalia, and upper thighs. The number of lesions varies from none up to 40 and increase in size and number.[43] On histologic examination, angiokeratomas consist of dilated small veins in the upper dermis, covered by hyperkeratotic epidermis. Telangiectasias may be noted, especially behind the ears.

Eyes

Characteristic corneal opacities are common in both men and women with Fabry disease, present in approximately 75% of affected men and women.[44] These lesions, termed *verticillata,* are identified by slit-lamp examination and are whorls of whitish discoloration that radiate from the center of the cornea. Cataracts (23% of males and 10% of females) and dilated conjunctival or retinal vessels may be observed.[44]

Lungs

Dyspnea and cough are common in men with Fabry disease, often with obstructive features on spirometry. This may be a consequence of fixed narrowing of the airways caused by glycosphingolipid accumulation.

Diagnosis

Diagnosis of affected males usually can be made clinically, with the additional information from slit-lamp eye examination to identify corneal opacities. The diagnosis should be confirmed by demonstrating decreased (<15%) or absent α-Gal A activity in serum, leukocytes, cultured skin fibroblasts, or tissue. Atypical variants may have enzyme activity up to 35% of normal. Heterozygous females may have very low (<15%) α-Gal A activity similar to that in males or may have more normal levels, making measurement of enzyme activity an insensitive way of diagnosing carriers. If enzyme levels are equivocal, alternative approaches to diagnosis include careful slit-lamp eye examination, measurement of urinary ceramide digalactoside and trihexoside, and genetic testing. Current information on laboratories offering sequencing of the α-Gal gene can be obtained at https://www.ncbi.nlm.nih.gov/gtr/conditions/C0002986/. Identification of carriers is particularly relevant when family members are being considered as living kidney donors.

Fabry disease should be considered in patients with unexplained ESRD,[45] especially if LVH is present or there is a history of stroke or nondiabetic paresthesia.

Treatment

The introduction of enzyme replacement therapy with recombinant human α-Gal A (agalsidase) has transformed the treatment of Fabry disease. Randomized clinical trials showed that agalsidase administration for 5 to 6 months resulted in reduced plasma and urine Gb3; amelioration of neuropathic pain; enhanced quality of life; clearing of Gb3 deposits from kidney, heart, and skin; and improved cerebral blood flow.[46] A multicenter longitudinal study showed that agalsidase stabilized renal function in patients with mild to moderate renal impairment at baseline and reduced left ventricular mass in those with LVH at baseline over 1 to 2 years of treatment. However, the impact of enzyme replacement therapy on long-term renal outcome is still unclear. Addition of RAS blockade to enzyme replacement can result in sustained reductions in proteinuria. In patients with ESRD, agalsidase may be infused during hemodialysis because there is little clearance of the enzyme by hemodialysis. Agalsidase therapy has been recommended for all affected males and symptomatic carrier females, but the drug is prohibitively expensive in many parts of the world.[47,48] An alternative treatment approach based on chemical "chaperones" is under investigation; however, a recent study did not show a significant treatment effect.

Renal transplantation is an effective treatment for advanced Fabry nephropathy but does not ameliorate the extrarenal manifestations. Transplanted kidneys from deceased donors or unaffected living donors may develop glycosphingolipid inclusions, but this usually is not clinically significant. Fabry heterozygotes should not become kidney donors. Coronary artery and cerebrovascular disease are the major causes of mortality in patients with Fabry disease who have undergone renal transplantation. Renal allograft recipients with Fabry disease are candidates for agalsidase treatment.

Fabry Disease in Childhood

Often it is not appreciated that the signs and symptoms of Fabry disease, particularly pain crises, acroparesthesias, angiokeratomas, and corneal opacities, typically have their onset in childhood, and thus the diagnosis is frequently delayed until well into adult life.[48] Symptomatic children with Fabry disease are potential candidates for agalsidase therapy.[48]

NAIL-PATELLA SYNDROME

Definition

Nail-patella syndrome (NPS) is an uncommon autosomal dominant condition characterized by hypoplasia or absence of the patellae, dystrophic nails, dysplasia of the elbows and iliac horns, and renal disease.

Etiology and Pathogenesis

NPS is caused by mutations in the LIM homeodomain transcription factor *LMX1B,* including missense, splicing, insertion or deletion, and nonsense alterations. In vitro studies of the transcriptional effects of mixing wild-type and mutant *LMX1B* suggest that NPS results from haploinsufficiency of *LMX1B,* rather than a dominant-negative effect. Although *LMX1B* appears to be important for normal limb and kidney development, the precise mechanisms for the renal effects of *LMX1B* mutations remain under investigation.

Clinical Manifestations

Renal Defects

Clinically apparent renal disease occurs in fewer than half of NPS patients. The nephropathy is usually benign, with an approximately 3% to 5% risk for progression to ESRD.[49,50] The clinical signs of NPS nephropathy appear in adolescence or young adulthood and typically include microhematuria and mild proteinuria, although some patients develop nephrotic syndrome and mild hypertension. The severity of the renal manifestations may differ substantially in related individuals.

Skeletal Defects

The patellae are absent or hypoplastic in more than 90% of patients with NPS, which may be associated with knee joint effusions and osteoarthritis (Fig. 46.14).[49,50] In about 80% of patients, osseous processes project posteriorly from the iliac wings (iliac horns), which is pathognomonic (Fig. 46.15). Anomalies of the elbows include aplasia, hypoplasia, and posterior processes at the distal end of the humeri.

Nails

Nail abnormalities occur in about 98% of patients and are typically bilateral and symmetric. Fingernails are affected more often than toenails. The nails may be absent or dystrophic with discoloration, koilonychia, longitudinal ridges, or triangular lunulae.[50]

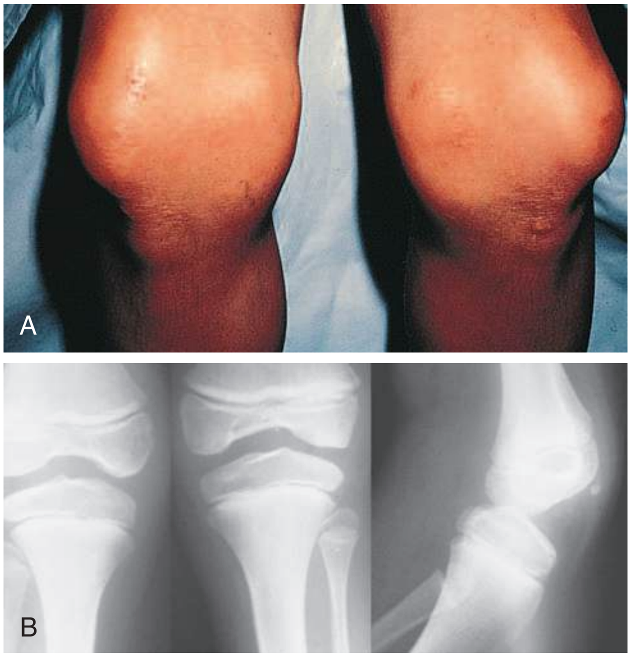


Fig. 46.14 **Nail-patella syndrome.** Clinical (A) and radiologic (B) appearance of absence of the patellae. (Courtesy Dr. R. Vernier.)

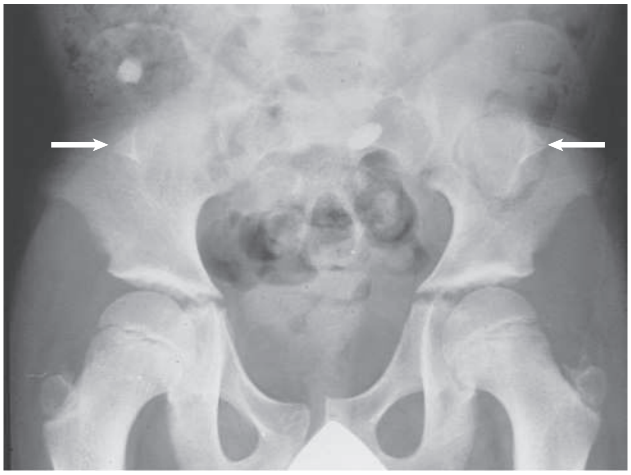


Fig. 46.15 **Nail-patella syndrome.** Iliac horns *(arrows)*. (Courtesy Dr. R. Vernier.)

Renal Pathology

Light microscopy findings in NPS are nonspecific and may demonstrate FSGS, mild mesangial hypercellularity, or no changes, in which case EM is required to make the diagnosis. EM shows multiple irregular lucencies of the GBM, giving it a moth-eaten appearance (Fig. 46.16). Such lucencies also may be observed in the mesangium. These lucent areas sometimes contain cross-banded collagen fibrils, which are more easily observed after staining with phosphotungstic acid (Fig. 46.17).

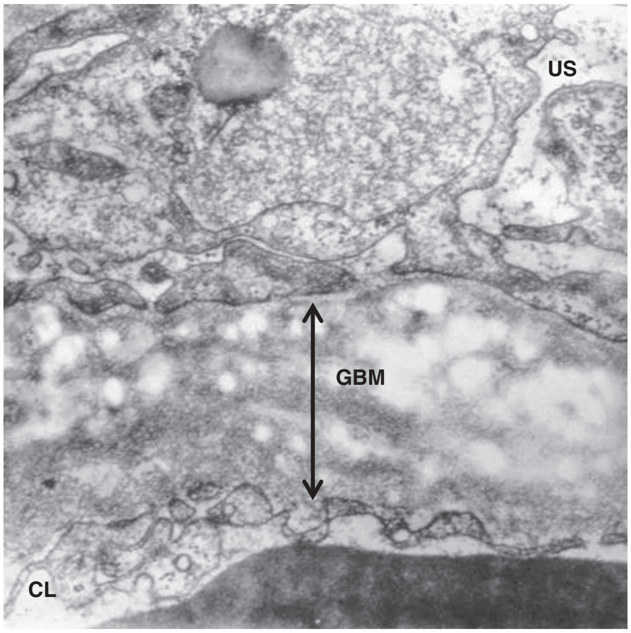


Fig. 46.16 **Electron micrograph of renal biopsy specimen in nail-patella syndrome.** The glomerular basement membrane appears moth-eaten on routine staining. *CL,* Capillary lumen; *US,* urinary space. (Courtesy Dr. R. Vernier.)

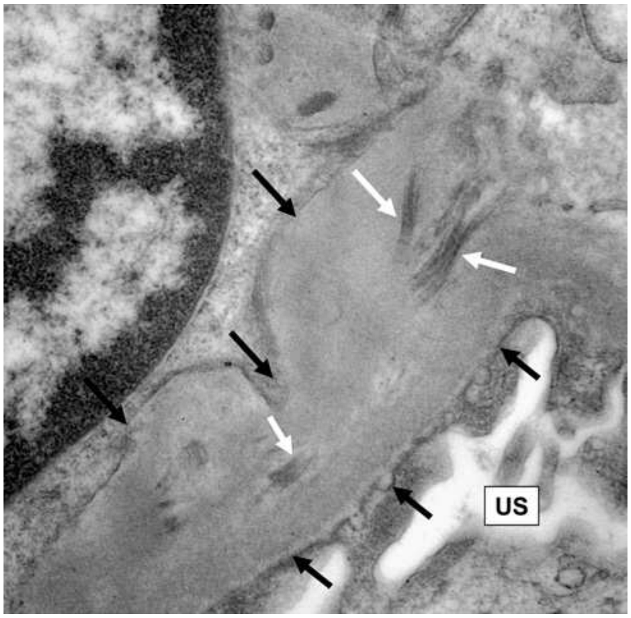


Fig. 46.17 **Electron micrograph of renal biopsy specimen in nail-patella syndrome.** *Black arrows* show margins of irregular glomerular basement membrane. Staining with phosphotungstic acid reveals fibrillar collagen *(white arrows)*. *US,* Urinary space.

The fibrils, which are type III collagen, tend to be arranged in clusters, and the surrounding GBM is often thickened. This may be observed without clinically evident renal disease, but fibrils have not been found in extraglomerular basement membranes. Cross-banded fibrils of type III collagen have been seen in GBM of patients with glomerular disease who lack nail or skeletal abnormalities, sometimes as a familial condition with autosomal recessive inheritance (collagen III glomerulopathy; see Chapter 28). It is unclear whether there is a pathogenic relationship between collagen type III glomerulopathy and NPS.

Treatment

No specific therapy is available for the nephropathy of NPS. There has been no reported recurrence in transplanted kidneys. Because NPS is an autosomal dominant disorder, careful evaluation of potential living related kidney donors for features of NPS is essential.

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SELF-ASSESSMENT QUESTIONS

1. You are seeing a 15-year-old boy with Alport syndrome. What statement about his parents is *most* likely to be true?
   A. His father has Alport syndrome.
   B. His mother has Alport syndrome.
   C. Both parents are carriers of Alport syndrome.
   D. Neither parent has Alport syndrome.
   E. None of the above
2. Which of the following ocular abnormalities have been described in patients with Alport syndrome?
   A. Anterior lenticonus
   B. Recurrent corneal erosions
   C. Perimacular flecks
   D. Posterior polymorphous dystrophy
   E. All of the above
3. Which of the following statements about hearing loss in Alport syndrome is true?
   A. Alport syndrome may be picked up by neonatal hearing screening.
   B. In males with Alport syndrome, hearing loss is usually undetectable by audiometry until adulthood.
   C. Hearing loss in Alport syndrome initially targets high frequencies above the range of conversational speech.
   D. The hearing loss of Alport syndrome is conductive.
   E. Hearing loss in Alport syndrome is typically unilateral.

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Inherited Disorders of Sodium and Water Handling

Detlef Bockenhauer

Every 24 hours, glomerular filtration yields about 150 liters of water, and 21,000 mmol of sodium (Na^+) in a healthy individual, yet only minute fractions of these quantities are excreted eventually in the urine. The precise amount excreted is tightly regulated to maintain homeostasis. Many different tubular transporters are involved in this homoeostatic process and are either directly or indirectly dependent on the electrochemical gradient for Na^+ generated by the Na^+,K^+-ATPase. In this way, Na^+ reabsorption is central not only for volume, but also for acid-base and electrolyte homeostasis. This molecular integration of homeostatic processes is reflected in the clinical picture; whereas disorders of water transport primarily cause a disturbance of serum Na^+ concentration, disorders of Na^+ transport generate specific patterns of clinical signs and symptoms related to blood pressure (BP) and electrolyte and acid-base disturbances, which help establish the underlying diagnosis.

PHYSIOLOGY OF SODIUM AND WATER REABSORPTION

Sodium Transporters and the Corresponding Inherited Disorders

In all tubular epithelial cells, a basolateral energy-requiring Na^+,K^+-ATPase ensures that intracellular Na^+ is kept at low levels and K^+ is high. Coupled with apical K^+, which travels down its concentration gradient to establish a lumen-positive electrical potential, an electrochemical gradient for Na^+ is created across the apical cell membrane, which drives Na^+ uptake from the tubular lumen into the cell via dedicated transporters and channels. Transport across the basolateral membrane to complete Na^+ reabsorption is facilitated by the Na^+,K^+-ATPase in all segments. Na^+ transport in each segment is inhibited by specific diuretics, so insight into the clinical picture of inherited disorders of Na^+ transport is gained by considering the effects of the corresponding diuretic. An overview of the transport process is given in Fig. 47.1.

In the proximal tubule (PT), an apical Na^+-hydrogen (H^+) exchange protein (NHE3) facilitates most of the Na^+ reabsorption. Because of this connection with H^+ excretion, this transport process is indirectly blocked by carbonic anhydrase inhibitors, such as acetazolamide. So far, no inherited disorder of isolated Na^+ in the PT has been reported. Instead, impaired sodium reabsorption in the PT typically occurs in the context of general PT dysfunction, which underlies renal Fanconi syndrome (see Chapter 48).

In the thick ascending limb (TAL), the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) can be blocked by loop diuretics such as furosemide. The corresponding inherited disorder is Bartter syndrome, in which the function of this transporter is either directly or indirectly impaired. Thus Bartter syndrome can be conceptualized as “inherited furosemide.”

In the distal convoluted tubule (DCT), Na^+ is reabsorbed by the Na^+-Cl^- cotransporter (NCCT), which is inhibited by thiazides. Disorders involving this transporter include Gitelman syndrome, caused by inherited loss of function of this transporter. Gitelman syndrome can therefore be conceptualized as “inherited thiazide.” The mirror image of Gitelman syndrome is pseudohypoaldosteronism type 2 (PHA2), or Gordon syndrome, in which the underlying genetic causes lead to an overactivity of NCCT.

In the collecting duct (CD), Na^+ reabsorption is facilitated by the epithelial sodium channel (ENaC) (Fig. 47.1). Amiloride and triamterene specifically block ENaC. Several inherited disorders affect transport through this channel. Inherited loss of function of ENaC is called *PHA type 1*. Because ENaC is highly regulated by the mineralocorticoid receptor (MR), there are several other disorders that affect ENaC function through dysregulation of the MR. These and other disorders that affect Na^+ transport (Table 47.1) are discussed in the following section.

Water Reabsorption

In the PT, water follows sodium chloride (NaCl, salt) passively through aquaporins, the constitutively open water transport proteins in apical and basolateral tubular cell membranes. In this way Na^+ transport is directly linked to unregulated water reabsorption. The TAL and CD are the segments critical for regulated water reabsorption. The TAL is water impermeable and thus also called the *diluting segment*, because salt transport via NKCC2 dilutes the tubular fluid. This helps establish the interstitial concentration gradient, which drives water reabsorption in the arginine vasopressin (AVP) sensitive parts of the nephron, the late DCT and CD. In this way, sodium transport is linked to regulated water reabsorption. Consequently, patients with Bartter syndrome have impaired urinary concentrating ability, which helps explain the polyuria associated with this disorder.

Final control over water reabsorption is exerted in the CD and regulated by AVP. In the absence of AVP, the apical membranes of the epithelial cells in the CD are water impermeable, resulting in water diuresis (Fig. 47.2). Binding of AVP to the AVPR2 receptor in the CD initiates a signaling cascade that results in the insertion of the water channel aquaporin 2 (AQP2) into the apical membrane, allowing water to pass through the epithelial cell layer, following the interstitial concentration gradient, resulting in antidiuresis. Inherited disorders affecting the function of AVPR2 or AQP2 cause either nephrogenic diabetes insipidus

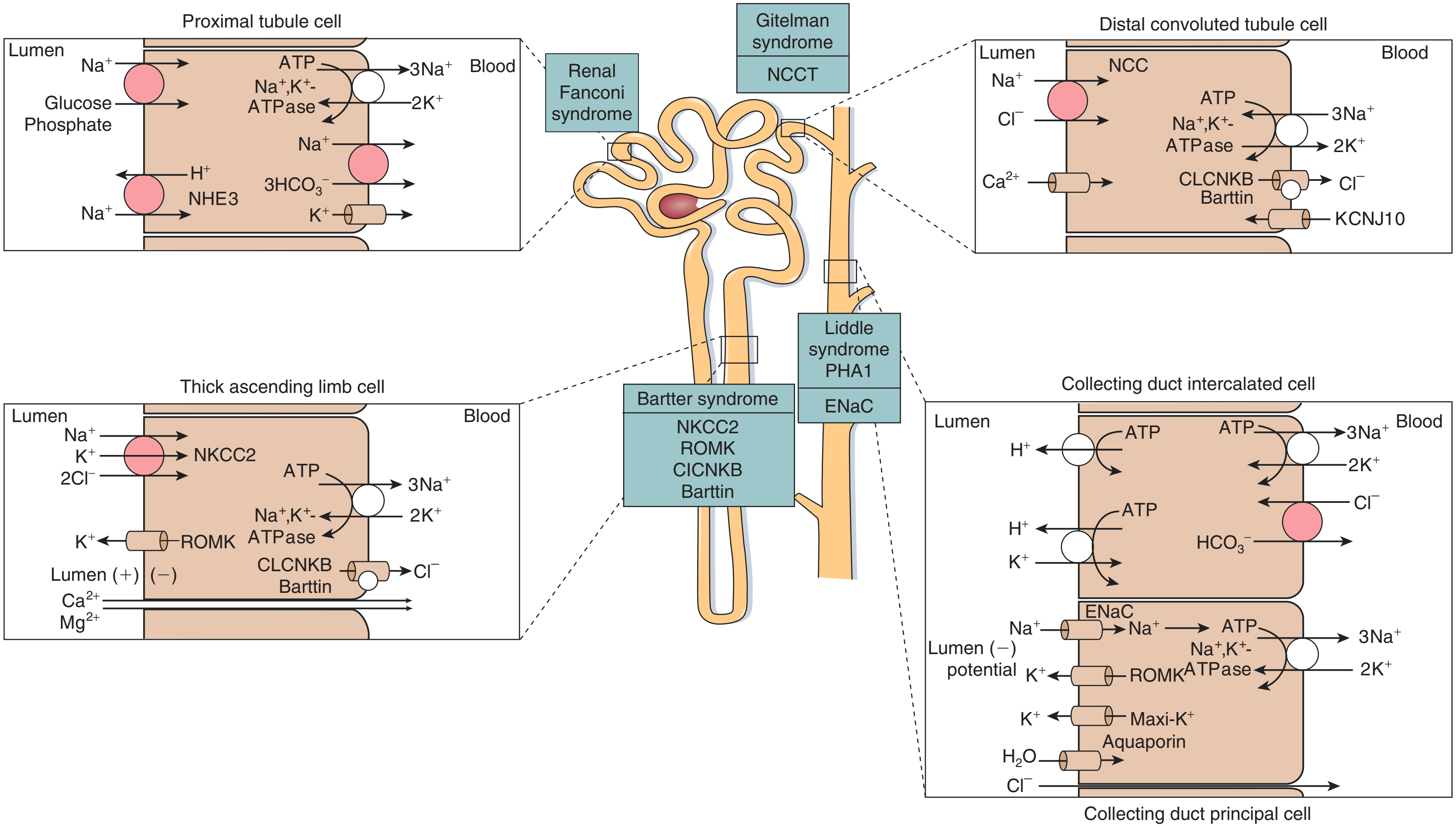
Proximal tubule cell
Lumen
Na+
Glucose
Phosphate
H+
NHE3
Na+
ATP
Na+,K+-
ATPase
3Na+
2K+
Blood
Na+
3HCO3−
K+
Renal
Fanconi
syndrome
Gitelman
syndrome
NCCT
Distal convoluted tubule cell
Lumen
Na+
Cl−
Ca2+
NCC
ATP
Na+,K+-
ATPase
3Na+
2K+
CLCNKB
Barttin
Cl−
KCNJ10
Blood
Thick ascending limb cell
Lumen
Na+
K+
2Cl−
NKCC2
ATP
Na+,K+-
ATPase
3Na+
2K+
K+
ROMK
Lumen (+)
(−)
CLCNKB
Barttin
Cl−
Ca2+
Mg2+
Blood
Bartter syndrome
NKCC2
ROMK
ClCNKB
Barttin
Liddle
syndrome
PHA1
ENaC
Collecting duct intercalated cell
Lumen
H+
ATP
ATP
3Na+
2K+
Blood
Cl−
H+
K+
ATP
HCO3−
ENaC
Na+
Na+
ATP
Na+,K+-
ATPase
3Na+
2K+
Lumen (−)
potential
K+
ROMK
K+
Maxi-K+
Aquaporin
H2O
Cl−
Collecting duct principal cell

Fig. 47.1 The molecular basis of salt handling along the nephron. The physiological mechanisms of salt handling along the nephron are discussed in more detail in Chapter 2. **Salt transport in the thick ascending limb (TAL) of the loop of Henle.** 0% to 20% of filtered Na is reabsorbed here. The furosemide-sensitive cotransporter Na-K-2Cl-ATPase (NKCC2, mutations of which cause Bartter syndrome type 1 (BS1)) provides Na^+ entry into the epithelial cell. Apical K^+ recycling through the ROMK channel (the cause of BS2) ensures the efficient functioning of NKCC2, establishing a lumen-positive transepithelial voltage that drives paracellular cation reabsorption. Chloride exits through basolateral Cl^- channels, predominantly CLCNKB (the cause of BS3). The β-subunit (barttin, cause of BS4) is necessary for normal functioning of CLCNKB. **Salt transport in the distal convoluted tubule.** 5-10% of filtered Na^+ is reabsorbed here via the thiazide-sensitive Na^+-Cl^- cotransporter (NCCT, the cause of Gitelman syndrome) on the apical side. CLCNKB is expressed here as well as in TAL; therefore mutations in this channel cause BS3 (a TAL disorder), but can phenocopy Gitelman syndrome (a DCT disorder). **Salt transport in principal cell of the collecting duct.** 2-5% of filtered Na^+ is reabsorbed here via the amiloride-sensitive epithelial Na^+ channel (ENaC). Loss-of-function mutations in ENaC cause pseudohypoaldosteronism type 1 (PHA1), gain-of-function mutations cause Liddle syndrome. Na^+ uptake is indirectly coupled to K^+ (through ROMK) and H^+ secretion (through H^+-ATPase in the neighboring intercalated cell). Aldosterone activates the mineralocorticoid receptor, increasing activity of ENaC and Na^+,K^+-ATPase, enhancing Na^+ reabsorption and K^+ and H^+ secretion, resulting in hypokalemic alkalosis. Cortisol is also a ligand for the mineralocorticoid receptor but is normally removed by oxidation by 11β-hydroxysteroid dehydrogenase to cortisone. (With permission from Hoenig MP, Zeidel ML. Homeostasis, the milieu interieur, and the wisdom of the nephron. *Clin J Am Soc Nephrol* 2014;9[7]:1272-1281.)

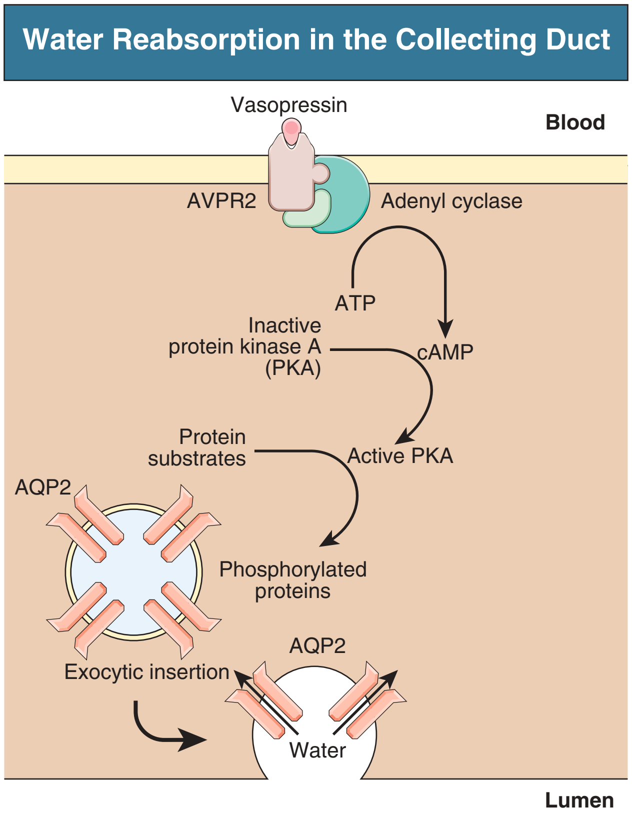

Fig. 47.2 **Water reabsorption in the collecting duct.** Activation of the basolateral arginine vasopressin type 2 receptor *(AVPR2)* initiates the signaling cascade that ultimately results in insertion of the aquaporin 2 *(AQP2)* water channel in the apical membrane, making it water permeable and thus allowing water reabsorption and urinary concentration. Loss-of-function mutations in AVPR2 cause X-linked nephrogenic diabetes insipidus, whereas gain-of-function mutations cause nephrogenic syndrome of inappropriate antidiuresis. Loss-of-function mutations in AQP2 are the cause of autosomal nephrogenic diabetes insipidus. *ATP,* Adenosine triphosphate; *cAMP,* cyclic adenosine monophosphate.

(NDI) through loss of function or nephrogenic syndrome of inappropriate antidiuresis (NSIAD) through gain of function.

DISORDERS OF SODIUM HANDLING

Based on the biochemical phenotype, four main categories can be distinguished. The causes are summarized in Fig. 47.3. Their diagnostic evaluation and management are summarized in Figs. 47.4 and 47.5.

1. Hypokalemic alkalosis and low-normal BP (Bartter syndrome, Gitelman syndrome, EAST syndrome)
2. Hypokalemic alkalosis and high BP (Liddle syndrome, apparent mineralocorticoid excess, glucocorticoid-remediable hyperaldosteronism, adrenal 17α-hydroxylase deficiency, adrenal 11β-hydroxylase deficiency)
3. Hyperkalemic acidosis and low-normal BP (PHA1, adrenal 21-hydroxylase deficiency, adrenal aldosterone synthase deficiency)
4. Hyperkalemic acidosis and high BP (Gordon syndrome)

Some of the disorders are caused by mutated renal transport proteins (e.g., Gitelman syndrome) or associated regulatory proteins (e.g., Gordon syndrome). In others, the genetic defect resides in the adrenals and the changes in adrenal mineralocorticoids and glucocorticoids create the renal phenotype. All the inherited disorders are rare with estimated incidences of around 1 in 100.000.

CONDITIONS WITH HYPOKALEMIA, METABOLIC ALKALOSIS, AND LOW-NORMAL BLOOD PRESSURE

Bartter Syndrome

Bartter syndrome is a genetically heterogeneous autosomal recessive disorder of salt reabsorption in the TAL.[1]

Pathogenesis

Currently four causative genes have been associated with Bartter syndrome: *NKCC2* for Bartter syndrome type 1 (BS1), *ROMK* (renal outer medullary potassium) for type 2 (BS2), *ClCKNB*, type 3 (BS3), and *BSND* for type 4 (BS4) (see Table 47.1 and Fig. 47.1). In addition, another disorder, familial hypocalcemic hypercalciuria, caused by activating mutations in *CaSR*, encoding the calcium-sensing receptor, can cause Bartter-like electrolyte abnormalities and is thus sometimes referred to as *Bartter type 5*,[2] but will not be discussed here. Although all the genetic defects directly or indirectly impair salt reabsorption through NKCC2, differences between the various forms of Bartter syndrome typically allow correct classification on clinical grounds. A first discriminator is the urine calcium excretion. TAL is an important segment for calcium reabsorption, which occurs passively through paracellular pathways, lined by claudins.[3] The driving force for this is generated by the combined action of NKCC2 and ROMK. Whereas transport via NKCC2 is electroneutral, potassium is recycled back into the tubular lumen via ROMK, establishing a lumen positive transepithelial potential. Consequently, calcium reabsorption in the TAL is impaired in BS1 and BS2, leading to hypercalciuria and nephrocalcinosis, whereas it is typically unaffected in BS3 and BS4. CLCKNB is also expressed in the DCT, so symptoms of BS3 can overlap with Gitelman syndrome. Hypomagnesemia is thus a common feature. Finally, Barttin is also critical for inner ear function, so affected patients have sensorineural deafness in addition to Bartter syndrome.

The initial step of tubuloglomerular feedback (TGF) occurs in the macula densa, which is part of the TAL; reduced Cl^- absorption in the macula densa initiates a signaling cascade that includes enhanced prostaglandin E2 (PGE2) production with consequent activation of renin and aldosterone.[4] Because Cl^- absorption is impaired in Bartter syndrome, these patients have impaired TGF with elevated levels of PGE2, renin, and aldosterone, and it is the latter that mediates the typical electrolyte profile of hypokalemic metabolic alkalosis.[5]

Clinical Manifestations

Bartter syndrome from mutations in NKCC2, ROMK, or Barttin usually has earlier onset than that caused by mutations of CLC-Kb, mostly during pregnancy (*antenatal* Bartter syndrome).[6,7] In contrast, the later onset form is often called *classic* Bartter syndrome, reflecting the phenotype originally described by Bartter and colleagues.[8]

The clinical features of antenatal Bartter syndrome include polyuria, hypokalemic metabolic alkalosis, and high urinary chloride excretion in a newborn with vomiting and failure to thrive and a history of polyhydramnios and premature delivery. A prenatal diagnosis of Bartter syndrome may be made by demonstration of high Cl^- concentrations in amniotic fluid, if genetic testing is not informative. BS2, secondary to ROMK mutations, can have a different phenotype in the first days of life, because ROMK is not only involved in salt reabsorption in the TAL, but also mediates potassium secretion in the CD. Consequently, patients with BS2 often present initially with hyperkalemia and hyponatremia, leading to an erroneous diagnosis of PHA1.[9] Over the course of the first few days to weeks, serum potassium levels decrease, presumably as a result of the expression of other potassium channels in the

TABLE 47.1 Inherited Single-Gene Defects of Sodium and Water Handling

Syndrome	Inheritance	Gene Localization	Gene Product
Neonatal Bartter syndrome	AR	15q	Na-K-2Cl cotransporter *NKCC2*
Neonatal Bartter syndrome	AR	11q	Renal potassium channel *ROMK*
Transient neonatal Bartter syndrome	X-linked	Xp	MAGED2
Classic Bartter syndrome	AR	1p	Renal chloride channel *ClC-Kb*
Bartter syndrome with deafness	AR	1p	β subunit of ClC-Kb *barttin*
Gitelman syndrome	AR	16q	NaCl cotransporter *NCCT*
Liddle syndrome	AD	16p	Epithelial sodium channel *ENaC*
Syndrome of apparent mineralocorticoid excess	AR	16q	11β-hydroxysteroid dehydrogenase type II
Glucocorticoid-remediable aldosteronism	AD	8q	Aldosterone synthase *CYP11B2*
Pseudohypoaldosteronism type I	AD	4p	Mineralocorticoid receptor
	AR	12p, 16p	*EnaC*
Gordon syndrome	AD	12p	WNK1
	AD	17q	WNK4
	AD	2q	CUL3
	AD/AR	5q	KLHL3
Congenital adrenal hyperplasia	AR	6p	21-hydroxylase
	AR	8q	11β-hydroxylase
	AR	10q	17α-hydroxylase
Nephrogenic diabetes insipidus	X-linked	Xq	AVP receptor 2
	AR	12q	Aquaporin 2

AD, Autosomal dominant; *AR,* autosomal recessive; *AVP,* arginine vasopressin.

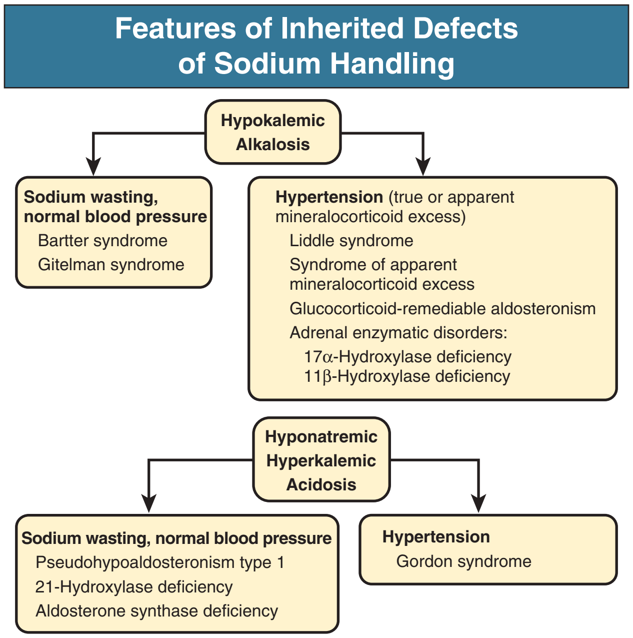
Features of Inherited Defects of Sodium Handling
Hypokalemic Alkalosis
Sodium wasting, normal blood pressure
Bartter syndrome
Gitelman syndrome
Hypertension (true or apparent mineralocorticoid excess)
Liddle syndrome
Syndrome of apparent mineralocorticoid excess
Glucocorticoid-remediable aldosteronism
Adrenal enzymatic disorders:
17α-Hydroxylase deficiency
11β-Hydroxylase deficiency
Hyponatremic Hyperkalemic Acidosis
Sodium wasting, normal blood pressure
Pseudohypoaldosteronism type 1
21-Hydroxylase deficiency
Aldosterone synthase deficiency
Hypertension
Gordon syndrome

Fig. 47.3 Features of inherited defects of sodium handling.

CD that compensate for the loss of ROMK function. Hypercalciuria and nephrocalcinosis are typical features of BS1 and BS2.[3]

Classic Bartter syndrome is typically associated with mutations in *CLCNKB* (BS3). These patients present mostly in the first decade of life with vomiting, polyuria, recurrent episodes of dehydration, and hypokalemic metabolic alkalosis. Electrolyte abnormalities are typically more severe than in antenatal Bartter syndrome.[6,7] Moreover, hypomagnesemia with renal Mg^{2+} wasting is common. This also may explain why some patients with BS3 can phenotypically mimic Gitelman syndrome.[10]

BS4 is characterized also by sensorineural deafness. Clinically, it manifests as a severe form of BS3, sometimes with extreme electrolyte abnormalities.[5] Presumably, in BS3, the closely related chloride channel CLC-Ka can compensate for the loss of CLC-Kb function in the inner ear and to some degree in the kidney. However, both channels require Barttin as a subunit, so that loss-of-function mutations in Barttin are functionally equivalent to loss of both chloride channels.[11] Patients with BS4 typically experience progressive chronic kidney disease, although a milder phenotype has been reported, presumably due to mutations with residual Barttin function.[12]

Diagnosis and Differential Diagnosis

The key features of Bartter syndrome are hypokalemic, hypochloremic alkalosis with evidence of renal Cl^- and K^+ wasting and low or normal BP. In syndromes of chronic severe hypokalemia with metabolic alkalosis, the differential diagnosis is facilitated by evaluating the BP and urinary chloride concentration.

Hypertension in the context of hypokalemic alkalosis indicates a primary activation of salt reabsorption in the CD, such as from pathologic activation of the MR (e.g., hyperaldosteronism) or the sodium channel ENaC. Bartter syndrome, however, is associated with a normal or low-normal BP. The clinical picture can be mimicked by extrarenal loss of sodium, for example, in diarrhea, vomiting, or burns and is characterized by very low Cl^- excretion in the urine, (FECl <0.5%). Congenital chloride diarrhea can be misdiagnosed as BS because the biochemical picture in the blood is identical and the large and often clear-appearing stool volume is misinterpreted as urine, especially in female babies in diapers.[13]

Analysis of urinary Ca^{2+} excretion can help distinguish between the various forms of BS and Gitelman syndrome (Table 47.2). Genotyping is recommended to confirm the final diagnosis.

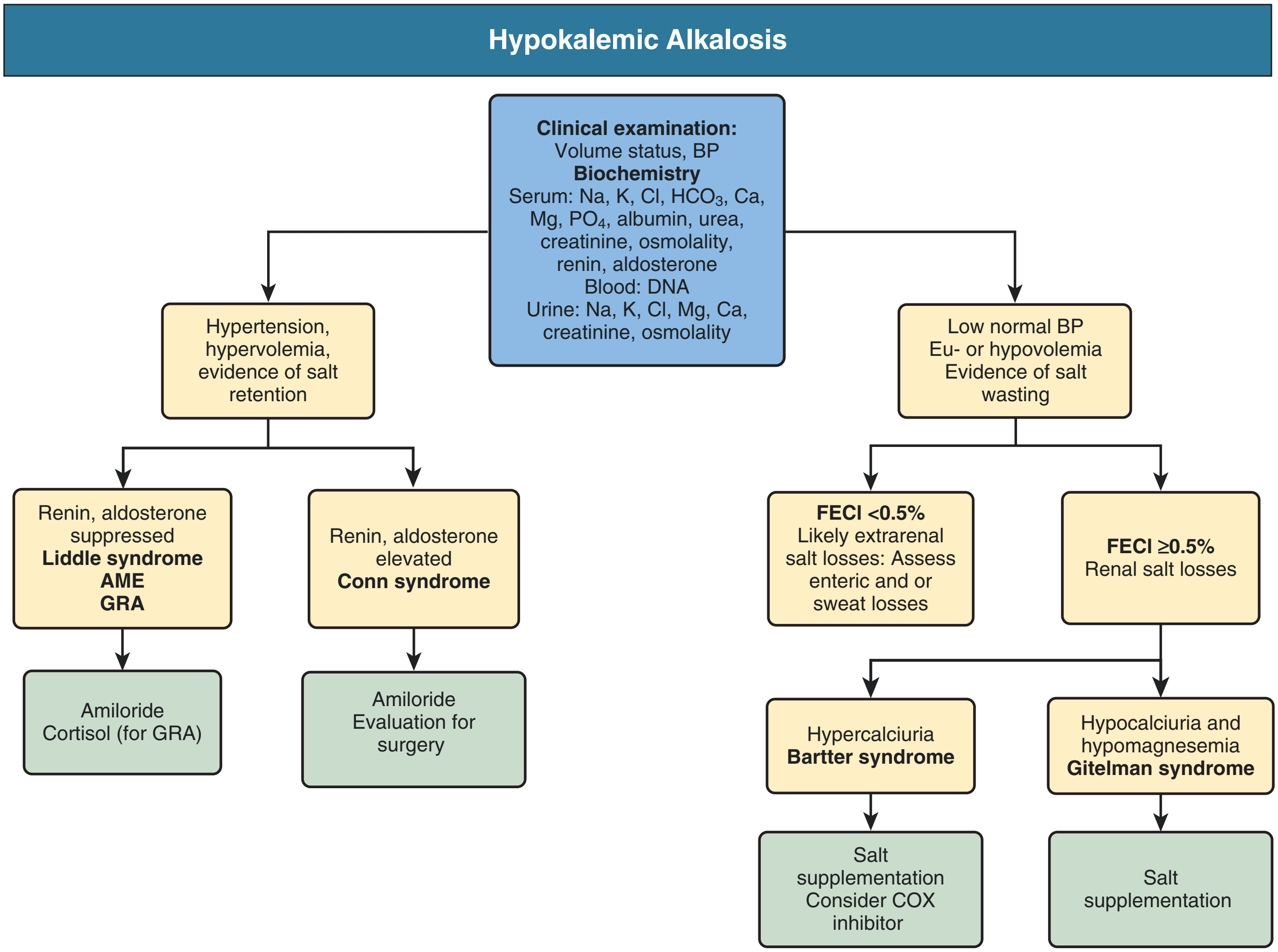
Hypokalemic Alkalosis
Clinical examination:
Volume status, BP
Biochemistry
Serum: Na, K, Cl, HCO3, Ca, Mg, PO4, albumin, urea, creatinine, osmolality, renin, aldosterone
Blood: DNA
Urine: Na, K, Cl, Mg, Ca, creatinine, osmolality
Hypertension, hypervolemia, evidence of salt retention
Low normal BP
Eu- or hypovolemia
Evidence of salt wasting
Renin, aldosterone suppressed
Liddle syndrome
AME
GRA
Renin, aldosterone elevated
Conn syndrome
FECl <0.5%
Likely extrarenal salt losses: Assess enteric and or sweat losses
FECl ≥0.5%
Renal salt losses
Amiloride
Cortisol (for GRA)
Amiloride
Evaluation for surgery
Hypercalciuria
Bartter syndrome
Hypocalciuria and hypomagnesemia
Gitelman syndrome
Salt supplementation
Consider COX inhibitor
Salt supplementation

Fig. 47.4 Diagnostic and management algorithm for inherited conditions causing hypokalemic alkalosis. *AME,* Apparent mineralocorticoid excess; *BP,* blood pressure; *COX,* cyclooxygenase; *GRA,* glucocorticoid-remediable aldosteronism; *FECl,* fractional excretion of chloride.

Treatment

Patients with neonatal Bartter syndrome have marked fluid and electrolyte disturbances that need to be corrected carefully. Saline infusion may be required in the neonatal period. Potassium chloride supplementation is commonly provided. Addition of spironolactone or amiloride improves hypokalemia and alkalosis but worsens salt wasting and thus increases the risk for hypovolemic shock. If used, sufficient salt supplementation is critical.[5]

A key problem in renal wasting disorders is that supplementation initially results in increased urinary losses. After supplementation, serum levels transiently rise, leading to an increased concentration in the glomerular filtrate with consequent loss in the urine and decreasing serum levels. Monitoring the efficacy of supplementation thus depends strongly on the timing of the blood sample. Although cardiac arrhythmias may occur with marked hypokalemia,[14] the dramatic swings in serum potassium associated with large doses of intermittent supplementation may be more harmful than consistent levels below the normal range. Moreover, large doses of supplementation may cause gastrointestinal disturbances, such as ulcers and diarrhea, that can worsen the electrolyte profile. Thus smaller but more frequent administration of electrolyte supplements may be better tolerated and safer.

A key component of treatment, especially for antenatal BS, is prostaglandin synthesis inhibition through cyclooxygenase (COX) inhibitors, such as indomethacin (1 to 3 mg/kg/24 h). Selective COX-2 inhibitors may provide similar efficacy but with less potential toxicity.[15] COX inhibitors act by interfering with the pathologic TGF in BS and by decreasing delivery of Na^+ and Cl^- to the distal nephron.[5] Treatment results in reduction of polyuria and polydipsia, improved growth and activity, and better control of plasma electrolytes. Serum levels of renin and aldosterone often decrease to the normal range.

Outcome

Dramatic complications, such as intracranial hemorrhage and bronchopulmonary dysplasia, are typically seen in patients with antenatal BS and are a consequence of extreme prematurity. There is a spectrum of severity; the electrolyte and acid-base imbalance itself can be severe, with complications such as arrhythmias, paralysis, rhabdomyolysis, and apnea, yet others may have few symptoms, and disease in some patients is diagnosed incidentally later in life when a blood test is obtained for an unrelated reason. Importantly, even patients with more severe electrolyte imbalance usually improve clinically with appropriate therapy. Progressive chronic kidney disease can be a complication of prematurity, but also can be seen in patients with BS3 born at term and is common in BS4. The reasons for this are unclear.

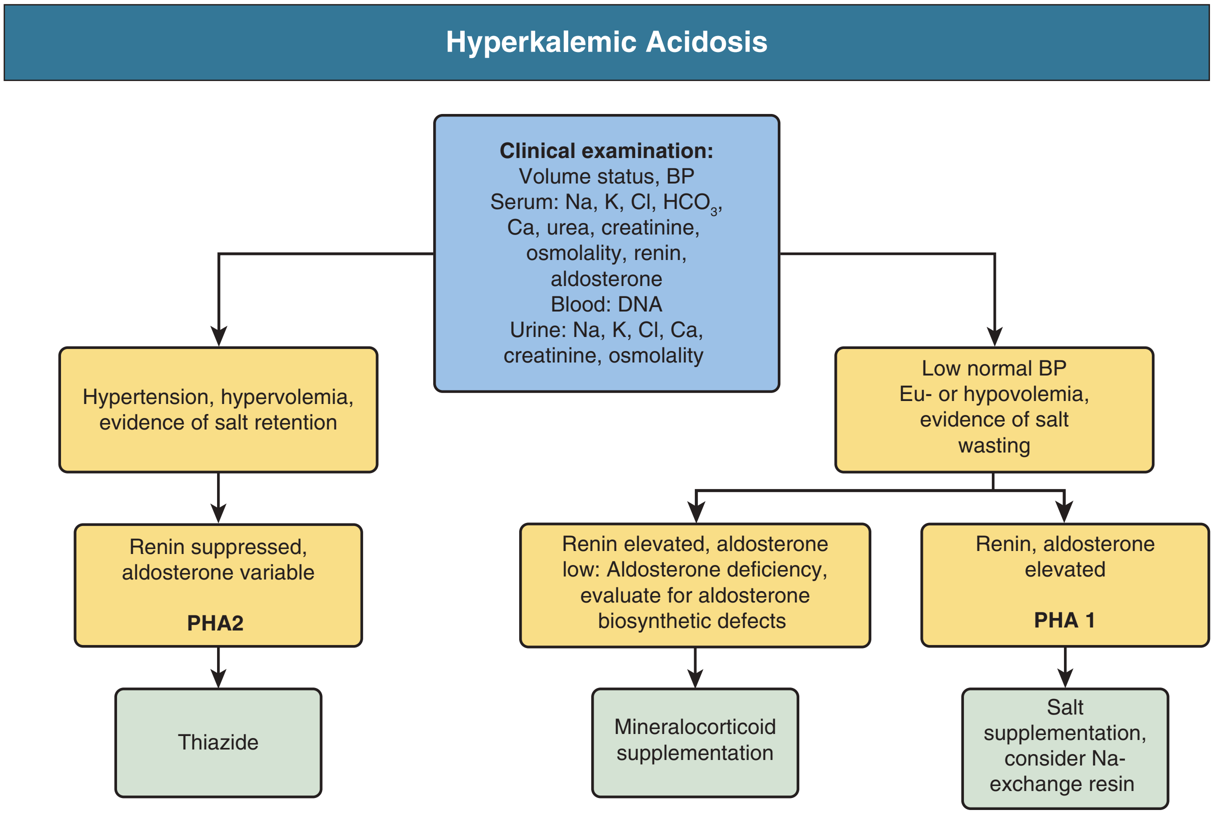
Hyperkalemic Acidosis
Clinical examination:
Volume status, BP
Serum: Na, K, Cl, HCO3, Ca, urea, creatinine, osmolality, renin, aldosterone
Blood: DNA
Urine: Na, K, Cl, Ca, creatinine, osmolality
Hypertension, hypervolemia, evidence of salt retention
Low normal BP
Eu- or hypovolemia, evidence of salt wasting
Renin suppressed, aldosterone variable
PHA2
Renin elevated, aldosterone low: Aldosterone deficiency, evaluate for aldosterone biosynthetic defects
Renin, aldosterone elevated
PHA 1
Thiazide
Mineralocorticoid supplementation
Salt supplementation, consider Na-exchange resin

Fig. 47.5 Diagnostic and management algorithm for inherited conditions causing hyperkalemic acidosis *BP,* Blood pressure; *PHA1,* pseudohypoaldosteronism type 1; *PHA2,* pseudohypoaldosteronism type 2.

TABLE 47.2 Features Differentiating Bartter and Gitelman Syndromes

	Bartter Syndrome		
Feature	**Neonatal**	**Classic**	**Gitelman Syndrome**
Age at onset	Neonatal period	Infancy/ childhood	Childhood/later
Maternal hydramnios	Common	Rare	Absent
Polyuria, polydipsia	Marked	Present	Rare
Dehydration	Present	Often present	Absent
Tetany	Absent	Rare	Present
Growth retardation	Present	Present	Absent
Urinary calcium	Very high	Normal or high	Low
Nephrocalcinosis	Present	Rare	Absent
Serum magnesium	Normal	Occasionally low	Low
Urine prostaglandins (PGE_2)	Very high	High or normal	Normal
Response to PG synthetase inhibitors* (e.g., indomethacin)	Good	Good	Rare

*Improvement of hypokalemia and renal salt wasting.
In addition to these clinical and laboratory features, molecular diagnosis is now possible.
PGE_2, Prostaglandin E2.

Gitelman Syndrome

Gitelman syndrome is an autosomal recessive condition with a prevalence of estimated at approximately 1 in 40,000 in White populations, making it arguably the most frequently inherited tubulopathy.[16]

Pathogenesis

The similarity between the features of Gitelman syndrome and those caused by thiazide administration originally suggested that the defect might be in the distal convoluted tubule, which was confirmed when the condition was shown to be due to inactivating mutations in *SLC12A3*, the gene encoding the thiazide-sensitive transporter NCCT (see Fig. 47.1).[17] Loss of NCCT function results in Na^+ and Cl^- wasting from this segment, leading to hypovolemia with secondary activation of the renin-aldosterone system. As in Bartter syndrome, the resulting increase in Na^+ reabsorption in the CD is counterbalanced by K^+ and H^+ excretion, causing hypokalemic alkalosis.

The hypocalciuria may be caused by enhanced proximal tubular calcium reabsorption, secondary to plasma volume contraction.[18] The renal magnesium wasting is caused by downregulation of the epithelial magnesium channel TRPM6 in the distal convoluted tubules.

Clinical Manifestations and Diagnosis

The severity of symptoms varies widely. More severely affected patients report a decreased quality of life with generalized muscle weakness, inability to work for extended periods, salt craving, and polyuria.[19] Cardiac disturbances, muscle cramps, and tetany are only exceptionally present. Chondrocalcinosis and sclerochoroidal calcifications can occur later in life.[16] Laboratory evaluation shows hypokalemic hypochloremic metabolic alkalosis with hypocalciuria and hypomagnesemia with elevated

TABLE 47.3 Features of Liddle Syndrome, Apparent Mineralocorticoid Excess, and Glucocorticoid-Remediable Aldosteronism

Feature	Liddle Syndrome	AME	GRA
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal dominant
Chief features	Significant hypertension, polyuria, growth retardation	Low birth weight, early-onset hypertension, polyuria, growth retardation	Significant hypertension, hemorrhagic stroke
Plasma aldosterone	Reduced	Reduced	Elevated
Plasma renin activity	Reduced	Reduced	Reduced
Urinary mineralocorticoid metabolites	Normal	Elevated ratios of THF + allo-THF to THE; free cortisol to cortisone	Elevated cortisol C-18 oxidation products
Response of the Hypertension to:			
Glucocorticoids	No	Satisfactory	Satisfactory
Triamterene	Satisfactory	Satisfactory	Satisfactory
Spironolactone	No	Satisfactory	Satisfactory

These syndromes are all characterized by hypokalemia, metabolic alkalosis, and hypertension.
AME, Apparent mineralocorticoid excess; *GRA,* glucocorticoid-remediable aldosteronism; *THE,* tetrahydrocortisone; *THF,* tetrahydrocortisol.

urinary Cl^-, K^+ and Mg^{2+} excretion. BP will usually be in the low-normal range. The differential diagnosis includes Bartter syndrome, especially BS3, HNF1B-related disease, and EAST syndrome, as well as acquired disorders, such as thiazide abuse and Sjögren syndrome.[16] Genotyping should be performed to confirm the diagnosis.

Treatment

Gitelman syndrome is primarily a salt-wasting disorder, and treatment consists of a liberal salt intake, if not pharmacologic supplementation. K^+ and Mg^{2+} supplements are usually given to improve muscle weakness or cramps. However, dosing may be limited by diarrhea and abdominal discomfort, and values in the normal range are typically not achieved. In exceptional cases of severe symptoms, parenteral Mg^{2+} has been infused. COX inhibitors are usually not helpful. K^+-sparing diuretics may improve the biochemistry but compound the salt wasting and should be used carefully.

The long-term prognosis for cardiac and renal function as well as for general health is good, although some patients do complain about markedly impaired quality of life. There is no clear association between severity of the electrolyte imbalance and symptoms, which complicates adjustment of treatment.

EAST Syndrome

EAST (also called SESAMe) syndrome is characterized by the cardinal manifestation of *e*pilepsy, *a*taxia, *s*ensorineural deafness and *t*ubulopathy.[20,21] It is due to mutations in the basolateral K-channel KCNJ10. The tubulopathy is identical to Gitelman syndrome. Treatment is symptomatic.

CONDITIONS WITH HYPOKALEMIA, METABOLIC ALKALOSIS, AND HYPERTENSION

Conditions with hypokalemia, metabolic alkalosis, and hypertension are caused by primary activation of the MR or its downstream effector, the epithelial Na^+ channel ENaC.

Liddle Syndrome

Liddle syndrome is an autosomal dominant disorder caused by gain-of-function mutations in ENaC.[22] Consequently, the enhanced Na^+ reabsorption through ENaC is independent of MR activation and renin and aldosterone levels are suppressed, and there is no response to MR blockers, such as spironolactone or eplerenone. However, triamterene and amiloride, which are blockers of ENaC, correct hypertension, renal K^+ loss, and hypokalemia.[23]

Pathogenesis

Liddle syndrome is caused by mutations of the β (SCNN1B) or γ (SCNN1G) subunit of ENaC. The majority of patients carry a mutation that impairs retrieval of the channel from the membrane, leading to enhanced ENaC activity.[24]

Clinical Manifestations and Diagnosis

Liddle syndrome is a rare disorder of hypertension that typically presents in teenage children with hypokalemic metabolic alkalosis and low blood levels of renin and aldosterone. However, onset as early as the newborn period has been described.

This condition is easily distinguished from primary hyperaldosteronism or renal artery stenosis by the finding of low renin and aldosterone levels. Other conditions with similar phenotype include apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism (Table 47.3), as well as 11β-hydroxylase (steroid 11β-monooxygenase) or 17α-hydroxylase (steroid 17α-monooxygenase) deficiency and can be separated by urinary steroid profiles and genetic testing. An activating mutation of the MR with exacerbation of hypertension in pregnancy has also been reported and should be differentiated.[25]

Treatment

Therapy consists of ENaC blockade with triamterene or amiloride, which usually normalizes the BP and K^+ levels. Because the pathogenetic disorder is not correctable with age, lifelong therapy is required. Some patients require additional antihypertensives, presumably because of fixed microvascular injury caused by the hypertension. Among those who develop end-stage renal disease from uncontrolled hypertension, there is no recurrence of the disease after transplantation because the graft does not contain the genetic alteration.

Apparent Mineralocorticoid Excess

Pathogenesis

Apparent mineralocorticoid excess (AME) is an autosomal recessive condition resulting from deficiency of the type II (renal and placental) isoform of the enzyme 11β-hydroxysteroid dehydrogenase. Clinical features of AME are similar to those of Liddle syndrome, but symptoms typically present earlier (in infancy) and more severely.

Normally, aldosterone is the principal ligand for the MR and in this way increases synthesis of various proteins, chiefly Na^+,K^+-ATPase on the basolateral surface and ENaC on the apical surface. These proteins facilitate the increased Na^+ reabsorption and K^+ secretion in the aldosterone-sensitive distal nephron (see Fig. 47.1). MR is not specific for aldosterone, but can also bind cortisol, which circulates in blood at roughly 1000-fold higher concentration than aldosterone. To provide specificity, the MR is protected by the activity of the 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2), which is highly expressed in the distal nephron and metabolizes cortisol to cortisone, which lacks MR binding ability.

Loss-of-function mutations in HSD11B2 thus cause AME by allowing nonspecific activation of MR by cortisol.[26] Carbenoxolone and glycyrrhizic acid (found in licorice compounds) are potent inhibitors of this enzyme, so licorice consumption can lead to an acquired form of AME. HSD11B2 is also expressed in the placenta, likely explaining the intrauterine growth restriction typically seen in patients with AME.

Clinical Manifestations and Diagnosis

Apparent mineralocorticoid excess is characterized by early onset of severe hypertension in childhood, hypokalemia, metabolic alkalosis, with suppressed plasma levels of renin and aldosterone, and increased metabolites of cortisol in the urine. A history of low birth weight and subsequent failure to thrive is typical.[27] Untreated, stroke and other complications of severe hypertension are seen even during childhood. Milder clinical manifestations can be seen with mutations that retain some functionality of the enzyme. Polyuria resulting from a urinary concentrating defect is another typical feature and likely linked to the electrolyte abnormalities in blood and urine because it improves after treatment of AME.[28]

The diagnosis of AME should be prompted by the electrolyte profile and early-onset hypertension with suppressed renin and aldosterone levels. A urinary steroid profile is diagnostic by showing elevated urinary levels of hydrogenated metabolites of cortisol (tetrahydrocortisol plus allotetrahydrocortisol) compared with cortisone (tetrahydrocortisone). The ratio of urinary free cortisol to cortisone is also increased. Genetic testing confirms the diagnosis.

Treatment

Blockers of MR (e.g., spironolactone or eplerenone) or its main effector ENaC (e.g., amiloride or triamterene) provide specific treatment. However, because MR blockers are competitive antagonists and in AME compete against the 1000-fold higher cortisol concentrations (compared with aldosterone), large doses are needed and ENaC blockers (or a combination of both) are usually more effective in clinical practice.

Glucocorticoid-Remediable Aldosteronism

Glucocorticoid-remediable aldosteronism (GRA) is an autosomal dominant condition. Patients present with features typical of primary hyperaldosteronism: hypertension, suppressed plasma renin activity, and hypokalemia. Unlike primary hyperaldosteronism (secondary to aldosterone-producing adrenal adenoma), hypersecretion of aldosterone in GRA can be reversed by the administration of corticosteroids. Affected individuals have early-onset hypertension. There is a high prevalence of hemorrhagic stroke, largely from ruptured intracranial aneurysms.

Pathogenesis

Patients with GRA have adrenocorticotropic hormone (ACTH)-sensitive aldosterone production occurring in the zona fasciculata of the adrenal gland, which is normally responsible only for cortisol synthesis. The two isoenzymes of 11β-hydroxylase involved in the biosynthesis of aldosterone and cortisol are steroid 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), respectively. The genes for these isoenzymes are located close to each other on the long arm of chromosome 8. Unequal meiotic crossovers may produce hybrid genes by fusion of the promoter end of *CYP11B1* with the coding sequence of *CYP11B2,* so that *CYP11B2* encoding aldosterone synthase is inappropriately regulated by ACTH.[29]

Diagnosis

Patients with GRA are often misdiagnosed as having primary hypertension. Hypertensive patients with early-onset hypertension, early cerebral hemorrhage (<40 years), hypokalemia before or after diuretic therapy, and refractoriness to standard antihypertensive medication are candidates for GRA testing, especially in the presence of a family history of hypertension or early death. Similar to other genetic forms of hypertension (Liddle syndrome, AME, Gordon syndrome), plasma renin activity is low. Aldosterone levels are normal to high and do not change with posture but are suppressed by dexamethasone.

A urinary steroid profile will show the biochemical hallmark of GRA increased levels of the so-called hybrid steroids (18-hydroxycortisol and 18-oxocortisol). Genetic testing confirms the diagnosis.

Treatment

Treatment with low-dose corticosteroid is effective in patients with GRA because it suppresses ACTH and thus the aberrant ACTH-mediated aldosterone production in the zona fasciculata. Typically, dexamethasone 0.125 to 0.25 mg or prednisolone 2.5 to 5 mg is administered at bedtime. Therapeutic goals are normotension and normalization of biochemical markers (urinary 18-oxosteroid, serum aldosterone). MR antagonists (spironolactone, eplerenone) and ENaC antagonists are also useful treatments.

The contrasting features of Liddle syndrome, AME, and GRA are summarized in Table 47.3.

Adrenal Enzymatic Disorders

Inherited deficiency of 11β- or 17α-hydroxylase also causes mineralocorticoid excess with hypertension and hypokalemic metabolic alkalosis. These disorders are not discussed here. Hypertension is caused by excessive mineralocorticoid production. Again, a urinary steroid profile helps establish the diagnosis, which can be confirmed by genetic testing.

CONDITIONS WITH HYPONATREMIA, HYPERKALEMIA, METABOLIC ACIDOSIS, AND NORMAL/LOW BLOOD PRESSURE

Conditions with hyponatremia, hyperkalemia, metabolic acidosis, and low-normal BP have features of mineralocorticoid deficiency either because of a synthetic defect or because of end-organ resistance.

Pseudohypoaldosteronism

Pseudohypoaldosteronism (PHA) is a state of renal tubular unresponsiveness to the action of aldosterone. Symptoms start in infancy with marked salt wasting and failure to thrive.

PHA1 exists in an autosomal dominant (adPHA1) and an autosomal recessive form (arPHA1). The adPHA1 is due to inactivating mutations in the MR *(NR3C2)*.[30] In contrast, arPHA1 is due to inactivating mutations of the α, β, or γ subunits of ENaC.[31]

Diagnosis

PHA1 presents typically in the first few days of life with weight loss, hypovolemia, and poor feeding. The typical electrolyte profile shows mild to moderate hyponatremia, often severe (arPHA1) hyperkalemia, and metabolic acidosis. Urinary Na^+ is high, with virtually absent K^+ excretion. Occasionally, patients with BS2 can present similarly (see "Bartter Syndrome"). PHA1 can be distinguished from aldosterone deficiency states, such as congenital adrenal hyperplasia, by the massively elevated aldosterone levels in blood. The diagnosis can be confirmed by genetic testing. An acquired form of PHA1 can be seen with urinary tract obstruction and/or pyelonephritis.

Clinical Features

The clinical manifestations are dominated by the electrolyte abnormalities and hypovolemia, which if untreated can lead to circulatory shock. ENaC is also expressed in the skin and lungs, where it mediates salt reabsorption. Consequently, patients with arPHA1 have increased sweat Na^+ concentration and can develop a miliary rash from blockage of the sweat glands. In addition, patients can have cystic fibrosis–like lung disease secondary to viscous high-salt containing bronchial secretions.

Treatment

Initial treatment consists of volume resuscitation with 0.9% saline. Without treatment, PHA1, especially arPHA1, can be lethal. Maintenance treatment consists of NaCl and $NaHCO_3$ supplementation adjusted to maintain euvolemia, normonatremia, and acid-base homoeostasis. In arPHA1, Na^+ exchange resins can help stabilize patients by providing a steady source of Na^+ and an alternative means for K^+ excretion. Patients with adPHA1 typically improve spontaneously over the first few months of life and maintain normal serum electrolytes without supplementation, although may have increased renin-aldosterone levels.[32]

Aldosterone Biosynthetic Defects

Patients with defects in aldosterone biosynthesis show salt wasting with hyponatremia, hyperkalemia, hypovolemia, and elevated plasma renin activity, yet obviously low or absent aldosterone levels. These conditions are not discussed here.

A CONDITION WITH HYPERKALEMIA, METABOLIC ACIDOSIS, AND HYPERTENSION

Pseudohypoaldosteronism Type 2 (Gordon Syndrome)

The clinical mirror image of Gitelman syndrome, Gordon syndrome is an autosomal dominant condition characterized by hypertension, hyperkalemia, and mild hyperchloremic metabolic acidosis.

Pathogenesis

Initially, two genes were identified as responsible for PHA2.[33] These genes encode two members of the with-no-lysine kinase family: WNK1 and WNK4, both expressed in the convoluted tubule and the CDs. WNK4 acts as a negative regulator of thiazide-sensitive NCCT function reducing cell surface expression of NCCT. WNK4 also downregulates ROMK and epithelial chloride flux. Mutations in *WNK4* are missense and cause loss of function, so that WNK4 loses its ability to suppress NCCT and ROMK, leading to Na^+ and K^+ retention. WNK1 prevents WNK4 from interacting with NCCT. Mutations in *WNK1* are intronic deletions that increase WNK1 expression. Subsequently, two further causative genes were identified: *CUL3 and KLHL3*.[34] Their encoded proteins form a ubiquitin-ligase complex that regulates WNK1 and 4 abundance. Mutations in KLHL3 also can be autosomal recessive. Moreover, mutations in CUL3 are frequently *de novo*, so the absence of a family history does not exclude the diagnosis. An acquired form of PHA2 may occur as a side effect of calcineurin inhibitors, especially tacrolimus, which affect WNK activity.[35]

Clinical Manifestations and Diagnosis

Hyperkalemia may be present from birth, but as in GRA, hypertension may not be manifested until later in life. Patients show hyperchloremic metabolic acidosis; plasma renin and aldosterone are reduced to variable degrees. Patients with CUL3 mutations appear to be phenotypically more seriously affected with higher serum K^+ levels, more pronounced acidosis and hypertension and consequently younger age at diagnosis.[34] In addition, most patients with CUL3 mutations have failure to thrive and growth impairment.

Treatment

Thiazides are able to completely correct the clinical and biochemical features of Gordon syndrome. Establishing the diagnosis is thus critical for targeted and effective treatment.

INHERITED DISORDERS OF WATER HANDLING

Congenital Nephrogenic Diabetes Insipidus

Congenital nephrogenic diabetes insipidus (NDI) is a rare polyuric disorder characterized by the failure to concentrate urine despite elevated levels of vasopressin. Congenital NDI is caused by mutations in key proteins controlling water reabsorption in the CD. Acquired DI is much more common, and its diagnosis and management are discussed in Chapter 8.

Pathogenesis

More than 90% of patients have X-linked recessive NDI with mutations in *AVPR2,* the gene for the arginine vasopressin type 2 receptor (AVPR2). Consequently, most patients are male, although female carriers can have a urinary concentrating defect of variable severity, presumably resulting from non-random X-inactivation.[36] AVPR2 is expressed predominantly in the kidney, where it mediates urinary concentration, but to some degree also in the vasculature, where it mediates vasodilatation and release of von Willebrand factor.[37] In less than 10% of the families, congenital NDI has an autosomal recessive inheritance with mutations in *AQP2,* the gene encoding the water channel AQP2, the final effector protein in the vasopressin-initiated signaling cascade. A rare autosomal dominant form of NDI, resulting from dominant negative mutation in *AQP2,* has also been reported. Some inherited diseases, such as Bartter syndrome and AME also can be associated with so-called secondary inherited NDI.[38] The cause of the AQP2 deficiency in these disorders is unclear, but likely related to blood and/or urinary electrolyte abnormalities.

Clinical Features

Manifestations of congenital NDI typically appear within the first weeks to months of life. NDI does not cause polyhydramnios because the osmotic load is cleared by the placenta. Clinical features at presentation are polyuria and failure to thrive, as well as a history of vigorous sucking followed by vomiting.[36] Unrecognized and untreated, the baby can experience repeated episodes of hypernatremic dehydration, with delayed development and cognitive impairment as possible consequences. Cranial computed tomography may occasionally show dystrophic calcification in the basal ganglia and the cerebral cortex in such untreated patients.

Behavioral abnormalities in the form of attention-deficit hyperactivity disorder and impaired school performance are commonly reported and may be secondary to preoccupation with drinking and voiding. An adult with congenital NDI usually drinks and voids about 10 to 12 l/day. Urinary tract dilatation can be seen, especially if there are voiding abnormalities.

Some mutations in either AVPR2 or AQP2 may retain partial functionality of the protein, leading to a phenotype of partial NDI, in which urinary concentration is possible but subnormal. Clinical symptoms are consequently milder, and the disease may remain undiagnosed throughout life.[39]

Diagnosis

The initial diagnosis of DI rests on the combination of an inappropriately dilute urine in the context of hypernatremic dehydration. Thus simple blood and urine chemistries easily establish the diagnosis, yet most parents of affected infants report repeated visits to hospital because of vomiting when they were sent home and reassured as the assessing medical personnel mistakenly considered the large urine output as inconsistent with severe dehydration, rather than as an important clue to DI. Once the diagnosis of DI has been established, the nephrogenic form can then be proven by the absence of a response in urinary concentration after administration of desamino-8-D-arginine vasopressin (DDAVP), a vasopressin analogue with high specificity for AVPR2. A complication of the DDAVP test is acute hyponatremia in those patients who respond to the drug, yet keep on drinking. The risk for this is low because most patients will simply stop drinking with normalization of serum osmolality, but patients with habitual polydipsia and infants hungry for milk are at risk. Limiting the volume of fluid intake equal to the volume of urine produced during the test is key to avoidance of this complication. Administering DDAVP 0.3 mcg/kg intravenously has the advantage of the shortest observation period (2 hours) combined with certainty of administration. It also allows the distinction between X-linked and autosomal NDI; as patients with autosomal NDI still express AVPR2, they will show the vascular effects in the form of a small drop in BP, an increase in heart rate and release of von Willebrand factor, whereas these changes are absent in patients with AVPR2 mutations. Serum levels of DDAVP with other modes of administration are not sufficient to appreciate these changes.[37] A normal renal response to DDAVP is an increase in urine osmolality to greater than 800 mOsm/kg, whereas patients with NDI show no response and urine osmolality remains below 200 mOsm/kg. An intermediate response may represent partial NDI or simply a washout of the medullary concentration gradient. The latter can be confirmed by achieving a urine osmolality of greater than 800 mOsm/kg after repeated administration of DDAVP. As normal urinary concentrating ability develops only during the first year of life, a response less than 800 (but >300) mOsm/kg may be normal in infants.

Differential Diagnosis

Patients with central DI or habitual polydipsia can be distinguished by a normal response to DDAVP. Patients with secondary inherited NDI typically have other electrolyte abnormalities, such as hypokalemia and hypercalciuria, in addition to other features typical for the primary diagnosis, such as polyhydramnios in Bartter syndrome and hypertension in AME. Onset of polyuria later in childhood or adulthood argues for acquired forms of NDI. Patients with partial NDI represent a diagnostic challenge. Further blood tests and a renal ultrasound can help exclude underlying structural or parenchymal renal disease, such as nephronophthisis or tubulointerstitial or cystic kidney disease. Genetic testing can help confirm the diagnosis.

Treatment

Management of NDI concentrates on reducing polyuria, avoiding episodes of dehydration, and providing sufficient calories to allow normal physical growth and development. A key determinant of overall urine output is the osmotic load, which mainly derives from protein and salt intake. The higher the osmotic load, the more water is required to excrete it. Involvement of a dietician is key (especially in infancy) to minimize osmotic load while ensuring that protein and caloric intake meets the recommended daily intake. A goal of 15 mOsm/kg is typically achievable; consequently, a patient with an average urine osmolality of 100 mOsm/kg would need 150 ml/kg/day to excrete this load.

Thiazide diuretics (e.g., hydrochlorothiazide 1 to 2 mg/kg every 12 hours) are effective in reducing urine output when combined with reduction of salt intake. Thiazides inhibit salt reabsorption in distal convoluted tubules, which leads to mild volume depletion. Hypovolemia stimulates fluid reabsorption in the PTs, thereby diminishing water delivery to the CDs. Combination therapy with amiloride 0.1 to 0.2 mg/kg every 8 to 12 hours, helps control the potential hypokalemia from thiazide treatment and may enhance the antipolyuric effect.

COX inhibitors are typically the most effective drugs in reducing urine volume, at least during infancy, probably by enhancing proximal sodium reabsorption. Indomethacin 1 to 2 mg/kg/day is used most often but may reduce GFR and cause gastrointestinal side effects. Selective COX2 inhibitors, such as celecoxib might be preferable, but their use in NDI has so far not been reported.

Nephrogenic Syndrome of Inappropriate Antidiuresis

NSIAD represents the mirror image to NDI and this clinically is the inherited equivalent to the syndrome of inappropriate antidiuresis (SIADH) (see Chapter 8).

Pathogenesis

NSIAD is due to gain-of-function mutations in AVPR2, leading to constitutive activation of the urinary concentrating mechanism in the CD, irrespective of serum osmolality.[40] The inheritance is X-linked dominant, although males are typically more severely affected.[41]

Clinical Features, Diagnosis, and Treatment

NSIAD is characterized by an inappropriately concentrated urine (>100 mOsm/kg) in the context of hyponatremia and hypoosmolality. In contrast to SIADH, vasopressin levels are suppressed. Genetic testing will confirm the diagnosis. Severely affected patients (typically males) may have recurrent episodes of severe symptomatic hyponatremia, whereas others may have no apparent symptoms. Avoidance of fluid intake, mediated by low serum osmolality, constitutes simple and intuitive treatment and may explain the absence of symptoms in some patients.[39] Fluid restriction is difficult in infancy as fluid and caloric intake is coupled. Increasing the osmotic load (e.g., by urea supplementation) may help symptomatic patients. AVPR2 antagonists (aquaretics) are typically not helpful because there is no vasopressin excess.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following conditions is characteristically associated with hypocalciuria?
   A. Bartter syndrome
   B. Liddle syndrome
   C. Gitelman syndrome
   D. Gordon syndrome
2. The treatment of Bartter syndrome may include which of the following? (More than one answer may be correct.)
   A. Amiloride
   B. Prostaglandin synthesis inhibitors
   C. KCl supplementation
   D. NaCl supplementation
   E. All are correct
3. Which of the following is a sign of hypokalemic, hypochloremic metabolic alkalosis?
   A. Aldosterone deficiency
   B. Enhanced Na^+ transport through the epithelial Na^+ channel ENaC in the collecting duct
   C. Pseudohypoaldosteronism type 1
   D. Pseudohypoaldosteronism type 2
4. Which of the following is the best suited maintenance fluid solution in patients with nephrogenic diabetes insipidus needing intravenous fluids?
   A. 0.9% saline
   B. Hartman solution
   C. 5% Dextrose in water
   D. 0.45% saline

48

Fanconi Syndrome and Other Proximal Tubule Disorders

John W. Foreman

The proximal tubule reabsorbs the majority of several key solutes, including glucose, amino acids, bicarbonate, and phosphate. This chapter describes a number of disorders, mainly heritable, that affect proximal tubule reabsorption. Chapters 10 and 12 discuss familial forms of hyperphosphaturia and renal tubular acidosis (RTA), respectively.

Most nonelectrolyte solutes are reabsorbed in the proximal tubule through specific transport proteins that cotransport them in conjunction with sodium (Fig. 48.1). The driving force for this solute transport is the electrochemical gradient for sodium entry maintained by the enzyme Na^+,K^+-ATPase. Most disorders of isolated solute reabsorption are related to defects in specific transport proteins, whereas disorders affecting multiple solutes, such as Fanconi syndrome, are probably secondary to defects in energy generation, Na^+,K^+-ATPase activity, or dysfunction of cellular organelles involved with membrane protein recycling.

FANCONI SYNDROME

Definition

In the 1930s de Toni, Debré, and coworkers and Fanconi independently described several children with the combination of renal rickets, glycosuria, and hypophosphatemia. Fanconi syndrome now refers to a global dysfunction of the proximal tubule leading to excessive urinary excretion of amino acids, glucose, phosphate, bicarbonate, uric acid, and other solutes handled by this nephron segment. These losses lead to the clinical problems of acidosis, dehydration, electrolyte imbalance, rickets, osteomalacia, and growth failure. Numerous inherited or acquired disorders are associated with Fanconi syndrome (Box 48.1).

Etiology and Pathogenesis

The sequence of events leading to Fanconi syndrome is incompletely defined and probably varies with each cause. Possible mechanisms include widespread abnormality of most or all of the proximal tubule carriers, such as a defect in sodium binding to the carrier or insertion of the carrier into the brush border membrane, "leaky" brush border membrane or tight junction, inhibited or abnormal Na^+,K^+-ATPase pump, or impaired mitochondrial energy generation (see Fig. 48.1). An abnormality in energy generation has been implicated in multiple disorders, including hereditary fructose intolerance, galactosemia, mitochondrial cytopathies, and heavy metal poisoning, as well as in several experimental models of Fanconi syndrome. Abnormal subcellular organelle function, such as the lysosome in cystinosis or the megalin-cubilin endocytic pathway in Dent disease, is also a cause of Fanconi syndrome (Fig. 48.2).

In adults, the most common causes of persistent Fanconi syndrome are an endogenous or exogenous toxin such as a heavy metal, a medication, or dysproteinemia. In children, the most common persistent cause is an inborn error of metabolism, such as cystinosis. Specific causes of Fanconi syndrome are discussed after a general description of the clinical manifestations and treatment of the syndrome.

Clinical Manifestations

Fanconi syndrome gives rise to a number of clinical abnormalities (Box 48.2).

Aminoaciduria

Aminoaciduria is a cardinal feature of Fanconi syndrome. Virtually every amino acid is found in excess in the urine, thus the term *generalized aminoaciduria.* However, there are no clinical consequences because the losses are trivial (0.5 to 1 g/day) in relation to dietary intake.

Glycosuria

Glycosuria in the absence of hyperglycemia secondary to proximal tubule dysfunction is another of the cardinal features of Fanconi syndrome and results from impaired tubular reabsorption of glucose. It is often one of the first diagnostic clues (Fig. 48.3). As with aminoaciduria, glycosuria rarely causes symptoms such as weight loss or hypoglycemia.

Hypophosphatemia

Hypophosphatemia from impaired phosphate reabsorption is common in Fanconi syndrome. Tubular phosphate handling can be assessed by measuring the tubular reabsorption of phosphate (TRP) which is normally greater than 80% by the following equation:

$$\text{TRP} = 1 - (U_p \times P_c / U_c \times P_p) \times 100\%$$

where U_p, P_p, U_c, and P_c are the urinary and serum phosphate and creatinine concentrations, respectively. Subtle changes in phosphate reabsorption can be assessed by measuring the maximum phosphate reabsorption in relation to the glomerular filtration rate (TmP/GFR) on fasting urine and blood samples, as shown in Fig. 10.15. Elevated parathyroid hormone (PTH) and low vitamin D levels also may play a role in the phosphaturia of Fanconi syndrome, although these hormonal abnormalities are not always present. A few patients have impaired conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D; metabolic acidosis, another feature of Fanconi syndrome, also may impair this conversion. Another mechanism for the hypophosphatemia is impairment of the megalin-dependent reabsorption and degradation of filtered PTH.[1] Unabsorbed PTH then binds to receptors in more distal portions of the proximal tubule, leading to increased endocytosis of apical phosphate transporters and increased phosphaturia. The hypophosphatemia, especially if accompanied by hyperparathyroidism and

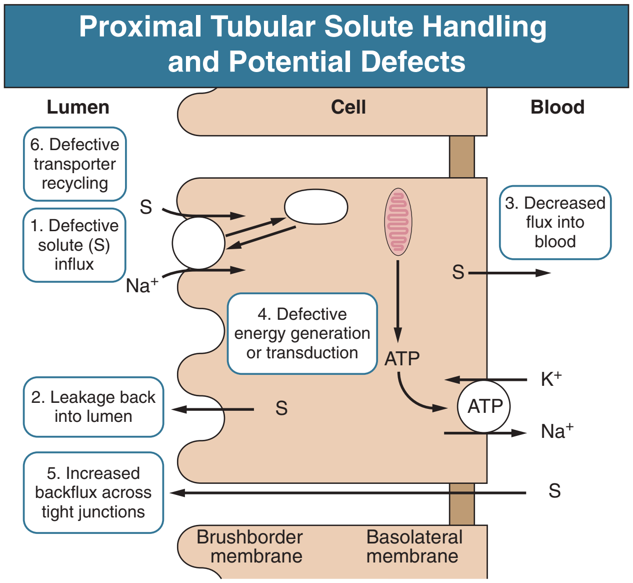
Proximal Tubular Solute Handling and Potential Defects
Lumen
Cell
Blood
6. Defective transporter recycling
1. Defective solute (S) influx
S
Na^+
3. Decreased flux into blood
S
4. Defective energy generation or transduction
ATP
K^+
ATP
Na^+
2. Leakage back into lumen
S
5. Increased backflux across tight junctions
S
Brushborder membrane
Basolateral membrane

Fig. 48.1 Defects and potential defects in proximal tubular solute handling. Solute uptake by the brush border membrane from the lumen is coupled to Na^+ influx. The favorable electrochemical driving force for luminal Na^+ is maintained by the Na^+,K^+-ATPase pump. Transported solute is then either used by the cell or returned to the blood across the basolateral membrane. Fanconi syndrome could arise because of a defect in one of six areas as shown. *ATP,* Adenosine triphosphate.

BOX 48.1 Causes of Fanconi Syndrome

Inherited Causes

- Cystinosis
- Galactosemia
- Hereditary fructose intolerance
- Tyrosinemia
- Wilson disease
- Lowe syndrome
- Dent disease
- Glycogenosis
- Mitochondrial cytopathies
- Idiopathic

Acquired Causes*

- Drugs: *Cisplatin, ifosfamide, tenofovir, cidofovir, adefovir,* didanosine, gentamicin, azathioprine, valproic acid (sodium valproate), suramin, streptozocin (streptozotocin), ranitidine
- Dysproteinemias: *Multiple myeloma, Sjögren syndrome, light-chain proteinuria, amyloidosis*
- Heavy metal poisoning: Lead, cadmium
- Other poisonings: Chinese herbal medicine, glue sniffing
- Other: Nephrotic syndrome, renal transplantation, acute tubular necrosis

*Italics indicates more common causes.

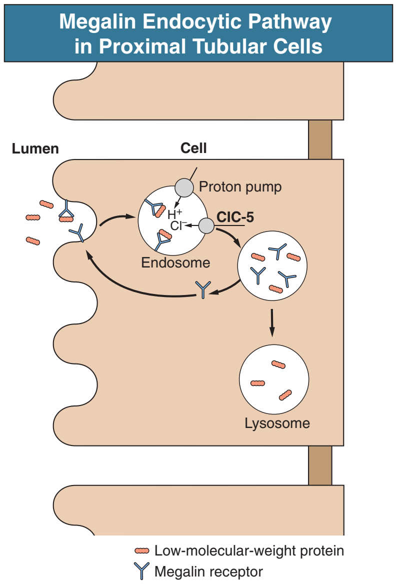
Megalin Endocytic Pathway in Proximal Tubular Cells
Lumen
Cell
Proton pump
H^+
Cl^-
ClC-5
Endosome
Lysosome
Low-molecular-weight protein
Megalin receptor

Fig. 48.2 Megalin -cubilin endocytic pathway in proximal tubular cells. Low-molecular-weight proteins in the luminal fluid bind to the megalin-cubilin complex and are endocytosed. The recycling of megalin and further catabolism of these proteins depend on acidification of the vesicle by a proton pump. The *ClC-5* chloride channel provides an electrical shunt for efficient functioning of the proton pump. This endocytosis pathway plays a role in membrane transporter recycling, and disruption of this pathway interferes with absorption of other luminal solutes.

BOX 48.2 Features of Fanconi Syndrome

Metabolic Abnormalities

- Glycosuria
- Hyperaminoaciduria
- Hypophosphatemia
- Acidosis
- Hypokalemia
- Hypouricemia
- Hypocarnitinemia

Clinical Features

- Rickets, osteomalacia
- Growth retardation
- Polyuria
- Dehydration
- Proteinuria

low 1,25-hydroxyvitamin D levels, often leads to significant bone disease, manifesting with pain, fractures, rickets, or growth failure.

Natriuresis and Kaliuresis

Natriuresis and kaliuresis are common in Fanconi syndrome and can give rise to significant and even life-threatening problems. The decreased proximal reabsorption of sodium leads to increased potassium excretion secondary to increased distal delivery of sodium and activation of the renin-aldosterone system from hypovolemia. In some cases, sodium and potassium losses are so great that metabolic alkalosis results, simulating Bartter syndrome despite the lowered bicarbonate threshold.

Hyperchloremic Metabolic Acidosis

Hyperchloremic metabolic acidosis, another feature of Fanconi syndrome, is a result of impaired bicarbonate reabsorption by the proximal tubule (proximal or type 2 RTA; see Chapter 12). This impaired reabsorption can lead to the loss of more than 30% of the normal filtered load of bicarbonate. As the serum bicarbonate concentration ($[HCO_3^-]$) falls, the filtered load falls, and excretion drops such that the serum $[HCO_3^-]$ usually remains between 12 and 18 mmol/l. On occasion, there is an associated defect in distal acidification, usually in association with long-standing hypokalemia or nephrocalcinosis. Ammoniagenesis is usually normal or increased because of the hypokalemia and acidosis, unless there is an associated impairment in GFR.

Polyuria and Polydipsia

Polyuria, polydipsia, and frequent bouts of severe dehydration are common symptoms in young patients with Fanconi syndrome. The polyuria is mainly related to the osmotic diuresis from the excessive

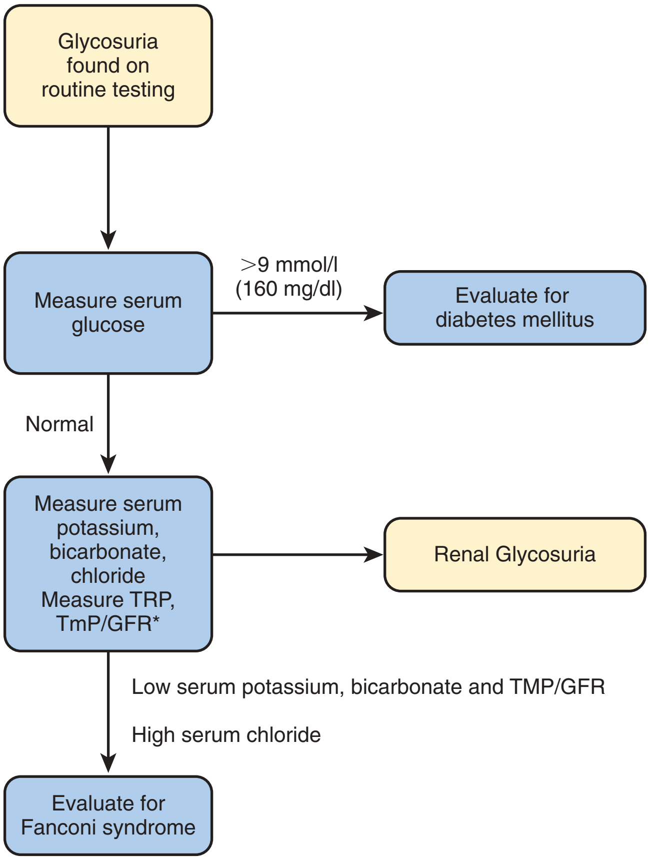
Glycosuria found on routine testing
Measure serum glucose
>9 mmol/l (160 mg/dl)
Evaluate for diabetes mellitus
Normal
Measure serum potassium, bicarbonate, chloride Measure TRP, TmP/GFR*
Renal Glycosuria
Low serum potassium, bicarbonate and TMP/GFR
High serum chloride
Evaluate for Fanconi syndrome

Fig. 48.3 Evaluation of glycosuria. *GFR,* Glomerular filtration rate; *TmP,* tubular maximum reabsorptive capacity; *TRP,* tubular reabsorption of phosphate.

urinary solute losses; but some patients have an associated concentrating defect, especially those with prolonged hypokalemia.

Growth Retardation

Growth retardation in children with Fanconi syndrome is multifactorial. Hypophosphatemia, disordered vitamin D metabolism, and acidosis contribute to growth failure, as do chronic hypokalemia and extracellular volume contraction. Glycosuria and aminoaciduria probably do not play a role. However, even with correction of all these metabolic abnormalities, most patients fail to grow, especially those with cystinosis.

Hypouricemia

Hypouricemia, caused by impairment in renal handling of uric acid, is often present in Fanconi syndrome, especially in adults. Urolithiasis from the uricosuria only rarely has been reported, probably because the urine flow and pH are increased, inhibiting uric acid crystallization.

Proteinuria

Proteinuria is usually minimal, except when Fanconi syndrome develops in association with the nephrotic syndrome. Typically, only low-molecular-weight proteins (<30,000 d) are excreted, such as vitamin D and A binding proteins, enzymes, immunoglobulin light chains, and hormones.

Treatment of Fanconi Syndrome

Therapy should be directed at the underlying causes of Fanconi syndrome when possible (see later discussion). This includes avoidance of the offending nutrient in galactosemia, hereditary fructose intolerance, or tyrosinemia; penicillamine or other copper chelators for treatment of Wilson disease; or chelation therapy for treatment of heavy metal intoxication. In these patients, resolution of Fanconi syndrome usually is complete.

In all patients with Fanconi syndrome, therapy is also directed at the biochemical abnormalities secondary to the renal solute losses and the bone disease often present in these patients. The proximal RTA (type 2 RTA) usually requires large doses of alkali for correction. Some patients benefit from hydrochlorothiazide to minimize the volume expansion associated with these large doses of alkali. Potassium supplementation usually is also needed, especially if there is significant RTA. If given in combination with a metabolizable anion, such as potassium citrate, lactate, or acetate, these supplements will correct not only the hypokalemia but also the acidosis. A few patients will require sodium supplementation along with potassium, and even fewer will require sodium chloride supplementation (especially those who have alkalosis as a result of volume contraction from large urinary NaCl losses). Magnesium supplementation may be required. Adequate fluid intake is essential. Correction of hypokalemia and its effect on the concentrating ability of the distal tubule may lessen the polyuria.

Bone disease is multifactorial, including urinary loss of vitamin D binding protein and vitamin D, decreased synthesis of calcitriol in some patients, hypercalciuria, chronic acidosis, and hypophosphatemia, which is the major factor. Hypophosphatemia should be treated with 1 to 3 g/day of oral phosphate with the goal of normalizing serum phosphate levels. Many patients with Fanconi syndrome will require supplemental vitamin D for adequate treatment of the rickets and osteomalacia. It is unclear whether standard vitamin D (calciferol [ergocalciferol]) or a vitamin D metabolite is better for supplementation, but most clinicians use a vitamin D metabolite, such as 1,25-dihydroxycholecalciferol (calcitriol). These metabolites obviate the concern of inadequate vitamin D hydroxylation by the proximal tubule mitochondria and reduce the risk for prolonged hypercalcemia because of their shorter half-life. Vitamin D therapy will also improve the hypophosphatemia and lessen the risk for hyperparathyroidism. Supplemental calcium is indicated in those with hypocalcemia after supplemental vitamin D is started. Hyperaminoaciduria, glycosuria, proteinuria, and hyperuricosuria usually do not lead to clinical difficulties and do not require specific treatment. Carnitine supplementation, to compensate for the urinary losses, may improve muscle function and lipid profiles, but the evidence is inconsistent.

INHERITED CAUSES OF FANCONI SYNDROME

Cystinosis

Definition

Cystinosis, or cystine storage disease, is characterized biochemically by excessive intracellular storage, particularly in lysosomes, of the amino acid cystine.[2] Three different types of cystinosis can be distinguished based on clinical course, age at onset, and intracellular cystine content. Benign or adult cystinosis is associated with cystine crystals in the cornea and bone marrow only, as well as the mildest elevation in intracellular cystine levels; no renal disease occurs. Infantile or nephropathic cystinosis is the most common form of cystinosis and is associated with the highest intracellular levels of cystine and the earliest onset of renal disease. In the intermediate or adolescent form, intracellular cystine levels are between those of the infantile and adult forms, with later onset of renal disease.

Etiology and Pathogenesis

Nephropathic cystinosis is transmitted as an autosomal recessive trait localized to the short arm of chromosome 17, with an estimated incidence of 1 in 200,000 live births. The *CTNS* gene codes for a lysosomal membrane protein, cystinosin, that mediates the transport of cystine from the lysosome.[3] The benign and intermediate forms of cystinosis are also associated with *CTNS* mutations but still have some functional transport protein, leading to lower intracellular cystine levels and slower onset of renal disease in the intermediate form and no renal disease in the benign form. Recently, cystinosin has been shown to play a role in other cellular processes besides lysosomal cystine transport, which may explain the persistence of the Fanconi syndrome in spite of cystine depletion.[4]

Clinical Manifestations

The first clinical symptoms and signs in nephropathic cystinosis are those of Fanconi syndrome and usually appear in the second half of the first year of life. Subtle abnormalities of tubular function can be demonstrated earlier in families with index cases, but there always is a delay between birth and the first symptoms. Rickets is common after the first year of life, along with growth failure. The growth failure occurs before the GFR declines and despite correction of electrolyte and mineral deficiencies. The GFR invariably declines and end-stage renal disease (ESRD) occurs by late childhood.

Nephrocalcinosis is relatively common, and a few patients have renal calculi. Photophobia is another common symptom that occurs by 3 years of age and is progressive. Older patients with cystinosis may develop visual impairment and blindness. Children with cystinosis usually have a fair complexion and blond hair, but dark hair has been observed in some. Cystinosis has been observed in other ethnic groups but is less common than in Whites.

The diagnosis is based on the demonstration of elevated intracellular levels of cystine, usually in white blood cells or skin fibroblasts. Patients with nephropathic and intermediate cystinosis have intracellular cystine levels that exceed 2 nmol half-cystine per mg protein (normal <0.2 nmol half-cystine per mg protein). Heterozygotes for cystinosis have levels that range from 0.2 to 1 nmol half-cystine/mg protein. A slit-lamp demonstration of corneal crystals strongly suggests the diagnosis[2] (Fig. 48.4). A prenatal diagnosis can be made with amniocytes or chorionic villi.

Common late complications of cystinosis include hypothyroidism, splenomegaly and hepatomegaly, decreased visual acuity, swallowing difficulties, pulmonary insufficiency, and corneal ulcerations.[5] Less frequently, older patients have developed insulin-dependent diabetes mellitus, myopathy, and progressive neurologic disorders. Decreased brain cortex also has been noted on imaging in some patients. Older patients may develop vascular calcification, especially of the coronary arteries, which can lead to myocardial ischemia.

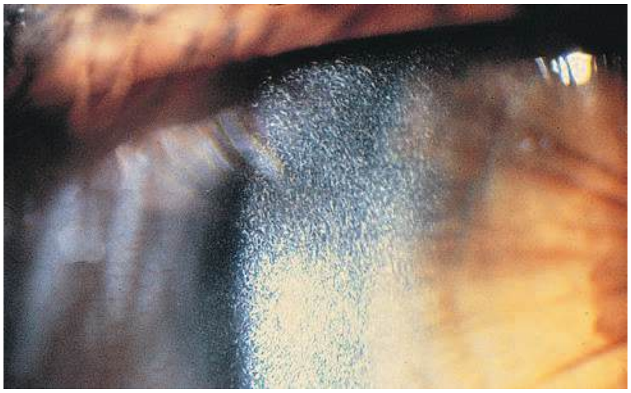

Fig. 48.4 Corneal opacities in cystinosis. Tinsel-like refractile opacities in the cornea of a patient with cystinosis under slit-lamp examination. (From reference 39.)

Renal Pathology

The morphologic features of the kidney in cystinosis vary with the stage. Early in the disease, cystine crystals are present in tubular epithelial cells, interstitial cells, and rarely glomerular epithelial cells[6,7] (Fig. 48.5A). A swan-neck deformity or thinning of the first part of the proximal tubule is an early finding but is not unique to cystinosis. Later, there is pronounced tubular atrophy, interstitial fibrosis, and abundant crystal deposition with giant cell formation of the glomerular visceral epithelium, segmental sclerosis, and eventual glomerular obsolescence. Electron microscopy (EM) demonstrates intracellular crystalline inclusions consistent with cystine (see Fig. 48.5B). Peculiar "dark cells," unique to the cystinotic kidney, also have been observed. These are mostly macrophages and some podocytes and are probably dark because of a reaction of cystine with osmium tetroxide.

Treatment

Nonspecific therapy for infantile cystinosis consists of vitamin D therapy and replacement of the urinary electrolyte losses, followed, in due course, by the management of the progressive renal failure (Table 48.1). Cysteamine therapy can lower tissue cystine levels and slow the decline in GFR, especially in children with a normal serum creatinine

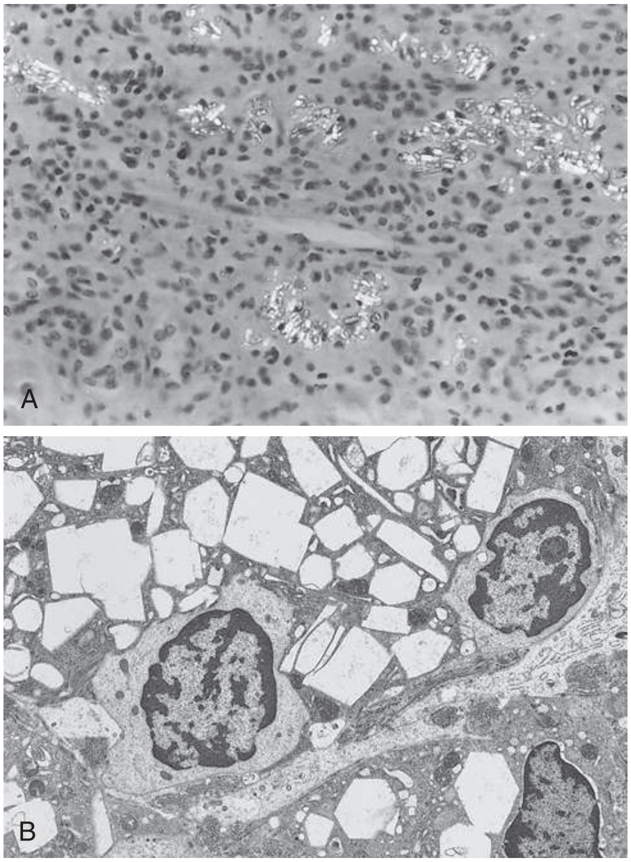

Fig. 48.5 Cystine crystals in the kidney in cystinosis. (A) Crystals are seen in photomicrograph of alcohol-fixed nephrectomy specimen, taken through incompletely crossed polarizing filters. Birefringent crystals are evident in tubular epithelial cells and free in the interstitium. (B) Electron micrograph of a renal biopsy specimen shows hexagonal, rectangular, and needle-shaped crystals in macrophages within the interstitium. (Original magnification ×3000.) (*A* from reference 6; *B* from reference 7.)

concentration treated before 2 years of age[8] (Fig. 48.6). Cysteamine therapy also improves linear growth but not Fanconi syndrome. The most common problems associated with cysteamine therapy are nausea, vomiting, and a foul odor and taste. Treatment should begin with a low dose of cysteamine soon after the diagnosis is made, increased during 4 to 6 weeks to 60 to 90 mg/kg/day in four divided doses as close to every 6 hours as possible. Slowly increasing the dose minimizes the risk for neutropenia, rash, and arthritis. Leukocyte cystine levels should be checked every 3 to 4 months to monitor effectiveness and compliance, with the goal of achieving and maintaining a cystine level below 2.0 and preferably below 1.0 nmol half-cystine/mg protein. A long-acting formulation of cysteamine is available that allows twice-daily dosing. This formulation is equally effective and may aid compliance, but is significantly more expensive than the standard formulation of cysteamine. A 50-mM solution of cysteamine applied topically onto the eye has proved useful in depleting the cornea of cystine crystals, but it requires administration 6 to 12 times a day to be effective.

Treatment of ESRD in these children poses no greater problems than in other children. Successful renal transplantation reverses the renal failure and Fanconi syndrome but does not appear to improve the extrarenal manifestations of cystinosis. Cysteamine therapy should be continued after transplantation. Cystine does not accumulate in the transplanted kidney, except in infiltrating immunocytes.

TABLE 48.1 Treatment of Cystinosis

Problem	Therapy
Removal of lysosomal cystine	Cysteamine, 0.325 g/m^2 q6h Delayed-release cysteamine, 0.65 g/m^2 q12h Goal: Maintain leukocyte cystine level <1 nmol half-cystine*/mg protein
Correction of Tubulopathy	
Dehydration	2-6 l/day fluid
Acidosis	2-15 mmol/kg/day K^+ citrate
Hypophosphatemia	1-4 g/day K^+ phosphate
Rickets	0.25-1 mcg/day calcitriol
Adjunct therapies	NaCl, carnitine, indomethacin, hydrochlorothiazide
Later Therapies	
Growth failure	Growth hormone
Hypothyroidism	Thyroxine
Renal failure	Renal replacement therapy, ideally renal transplantation

*By convention, units are half-cystine because the cystine originally was converted to two cysteine molecules, or "broken in half," before measurement.

Galactosemia

Etiology and Pathogenesis

Galactosemia is an autosomal recessive disorder of galactose metabolism. It is most often the result of deficient activity of the enzyme galactose-1-phosphate uridyltransferase, the incidence of which is 1 in 62,000 live births.[9] Deficiency of this enzyme leads to the intracellular accumulation of galactose-1-phosphate, with damage to the liver, proximal renal tubule, ovary, brain, and lens. A less frequent cause of galactosemia is a deficiency of galactose kinase, which forms galactose-1-phosphate from galactose. Cataracts are the only manifestation of this form of galactosemia.

The pathogenesis of the symptoms of galactosemia is not clear. Accumulation of galactose-1-phosphate subsequent to the ingestion of galactose can inhibit pathways for carbohydrate metabolism, and its level correlates somewhat with clinical symptoms. Defective galactosylation of proteins also has been postulated. Proposed as a pathogenetic mechanism, formation of galactitol from galactose by aldose reductase is probably responsible for the cataract formation.

Clinical Manifestations

Affected infants ingesting milk containing lactose (the most common source of galactose in the diet) rapidly develop vomiting, diarrhea, and failure to thrive. Jaundice from unconjugated hyperbilirubinemia is common, along with severe hemolysis. Continued intake of galactose leads to hepatomegaly and cirrhosis. Cataracts appear within days after birth, although at first they often are detectable only with a slit lamp. Cognitive dysfunction or developmental delay may develop within a few months. Fulminant *Escherichia coli* sepsis has been described, possibly a consequence of inhibited leukocyte bactericidal activity.

In addition to these clinical findings, galactose intake leads within days to hyperaminoaciduria and albuminuria. Increased urine sugar excretion is principally a result of galactosuria and not glycosuria. There seems to be little or no impairment in glucose handling by the proximal tubule. Galactosemia should be suspected whenever there is a urinary reducing substance that does not react in a glucose oxidase test. The diagnosis can be confirmed by demonstration of deficient transferase activity in red blood cells, fibroblasts, leukocytes, or hepatocytes. Most infants with galactosemia are found through newborn metabolic screening.

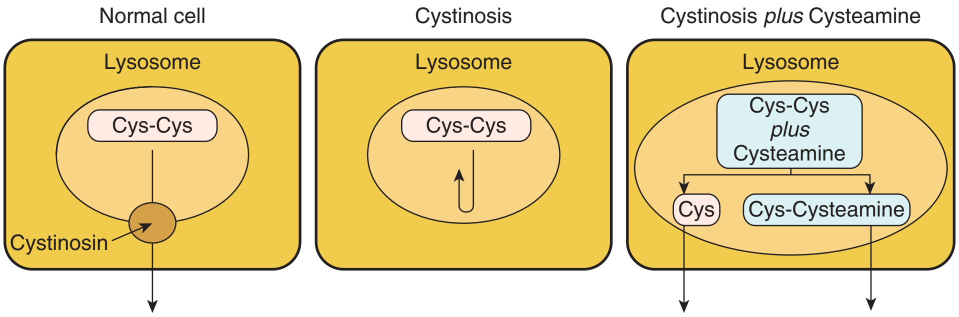

Fig. 48.6 Effect of cysteamine on lysosomal cystine. In cystinosis, the transporter (cystinosin) for cystine *(Cys-Cys)* egress from the lysosome is defective and cysteine accumulates. Cysteamine can easily enter the lysosome and combine with cystine, forming cysteine *(Cys)* and the mixed disulfide cysteamine-cysteine. Both these compounds can exit the lysosome through a transporter other than the cystine carrier.

Treatment

Galactosemia is treated by elimination of galactose from the diet. Acute symptoms and signs resolve in a few days. Cataracts will also regress to some extent. Even with early elimination of galactose, developmental delay, speech impairment, ovarian dysfunction, and growth retardation are common. Profound intellectual deficits are rare even in infants treated late.

Hereditary Fructose Intolerance

Etiology and Pathogenesis

Hereditary fructose intolerance is another disorder of carbohydrate metabolism associated with Fanconi syndrome.[10] Fructose intolerance is inherited as an autosomal recessive trait, with an estimated incidence of 1 in 20,000 live births. It is caused by a deficiency of the B isoform of the enzyme fructose-1-phosphate aldolase, which cleaves fructose-1-phosphate into D-glyceraldehyde and dihydroxyacetone phosphate. Deficient activity of aldolase B leads to tissue accumulation of fructose-1-phosphate and reduced levels of adenosine triphosphate (ATP). Experimentally, mice with aldolase B deficiency can be rescued by blocking fructokinase, which prevents the accumulation of fructose-1-phosphate and maintains ATP.

Clinical Manifestations

Symptoms of hereditary fructose intolerance appear at weaning when fruit, vegetables, and sweetened cereals that contain fructose, sucrose, or sorbitol (the latter is converted to fructose in the body) are introduced. Affected children experience nausea, vomiting, and symptoms of hypoglycemia shortly after ingestion of fructose, sucrose, or sorbitol. These symptoms may progress to seizures, coma, and even death, depending on the amount consumed. When they are exposed to fructose, infants may have a catastrophic illness, with severe dehydration, shock, acute liver impairment, bleeding, and acute kidney injury (AKI). Concomitant serum biochemical findings after fructose ingestion are decreased glucose, phosphate, and bicarbonate and increased uric acid and lactic acid. Chronic exposure to fructose leads to failure to thrive, hepatomegaly and fatty liver, jaundice, hepatic cirrhosis, Fanconi syndrome, and nephrocalcinosis. Children with hereditary fructose intolerance quickly develop an aversion to sweets.

Diagnosis

The diagnosis should be suspected when symptoms develop after the ingestion of fructose. This can be confirmed by assaying the activity of fructose-1-phosphate aldolase in a liver biopsy specimen and increasingly by genetic testing using leukocytes.

Treatment

Treatment of hereditary fructose intolerance involves strict avoidance of foods containing fructose and sucrose, but because most patients develop a strong aversion to such foods, this is usually easy. The greatest risk occurs during infancy, before those affected learn to avoid fructose.

Glycogenosis

Most patients with glycogen storage disease and Fanconi syndrome have an autosomal recessive disorder characterized by heavy glycosuria and increased glycogen storage in the liver and kidney, known as the *Fanconi-Bickel syndrome*, or *glucose-losing syndrome*, because the glucose losses can be massive.[11] The defect is deficient activity of the sugar transporter GLUT2 (Fig. 48.7). GLUT2 facilitates sugar exit from the basolateral side of the proximal tubule and intestinal cell and sugar entry and exit from the hepatocyte and pancreatic β cell. A few patients with type I glycogen storage disease have mild Fanconi syndrome but not Fanconi-Bickel syndrome. The therapy for this disorder is directed at the renal solute losses, treatment of rickets (which can be severe), and frequent feeding to prevent ketosis. Uncooked cornstarch has been shown to lessen the hypoglycemia and to improve growth.

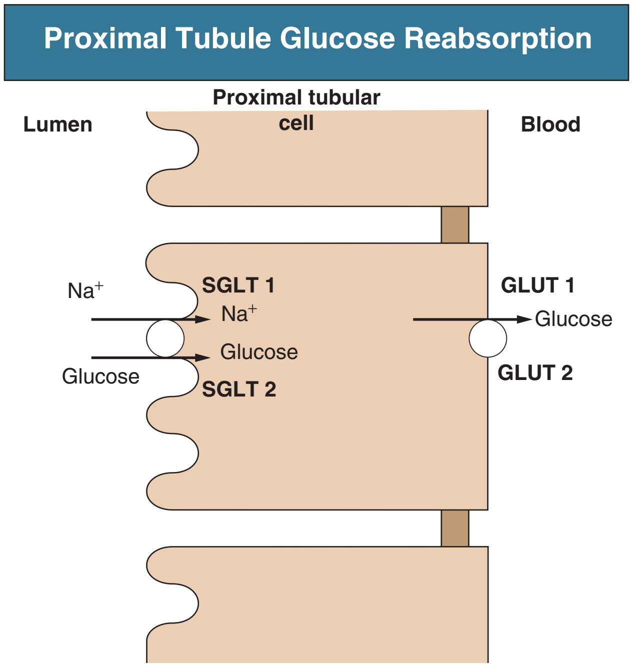

Fig. 48.7 Proximal tubule glucose reabsorption. Glucose enters the proximal tubule cell coupled to Na^+ reabsorption from the lumen through a high-capacity, low-affinity transporter *(SGLT2)* in the early proximal tubule and a low-capacity, high-affinity transporter *(SGLT1)* in the late proximal tubule. Glucose exits the cell through the transporters *GLUT1* and *GLUT2* located in the late and early proximal tubule, respectively.

Tyrosinemia

Definition

Hereditary tyrosinemia type I, also known as *hepatorenal tyrosinemia*, is a defect of tyrosine metabolism affecting the liver, kidneys, and peripheral nerves.[12]

Etiology and Pathogenesis

The cause of hereditary tyrosinemia type I is a deficiency of fumarylacetoacetate hydrolase (FAH) activity; it is an autosomal recessive disorder. Decreased or absent FAH activity leads to accumulation of maleylacetoacetate (MAA) and fumarylacetoacetate (FAA) in affected tissues. These compounds can react with free sulfydryl groups, reduce intracellular levels of glutathione, and act as alkylating agents. MAA and FAA are not detectable in plasma or urine but are converted to succinylacetoacetate and succinylacetone. Succinylacetone is structurally similar to maleic acid, a compound that causes Fanconi syndrome experimentally in rats and may be the cause of Fanconi syndrome in humans affected with tyrosinemia.

Clinical Manifestations

The liver is the major organ affected, evident as early as the first month of life. Such infants usually have severe disease and die in the first year. All children with tyrosinemia will eventually develop macronodular cirrhosis, and many develop hepatocellular carcinoma. Acute, painful peripheral neuropathy and autonomic dysfunction also can occur. Proximal renal tubular dysfunction is evident in all patients with tyrosinemia, especially those presenting after infancy. Nephromegaly is very common, and nephrocalcinosis may be seen. Glomerulosclerosis and impaired GFR may be seen with time.

Diagnosis

The diagnosis should be suspected with elevated plasma tyrosine and methionine levels together with their *p*-hydroxy metabolites. The presence of succinylacetone in blood or urine is diagnostic of hereditary tyrosinemia type I.

Treatment

The institution of a diet low in phenylalanine and tyrosine dramatically improves the renal tubular dysfunction. Nitisinone, which inhibits the formation of MAA and FAA, dramatically improves the renal and hepatic dysfunction.[12] Liver transplantation has been successfully used to treat patients with severe liver failure and prevent the development of hepatocellular carcinoma. Liver transplantation leads to rapid correction of Fanconi syndrome.

Wilson Disease

Definition

Wilson disease is an inherited disorder of copper metabolism that affects numerous organ systems.[13,14] It has an overall incidence of 1 in 30,000 live births. About 40% of patients present with liver disease, 40% with extrapyramidal symptoms, and 20% with psychiatric or behavioral abnormalities.

Etiology and Pathogenesis

Wilson disease is caused by a defect in the P-type copper–transporting adenosine triphosphatase ATP7B, which is highly expressed in the liver, kidney, and placenta. It impairs biliary copper excretion and the incorporation of copper into ceruloplasmin. These abnormalities cause excessive intracellular accumulation of copper in the liver, with subsequent overflow into other tissues, such as brain, cornea, and renal proximal tubule.

Clinical Manifestations

Patients typically present with chronic liver disease, often with relatively high serum bilirubin relative to alkaline phosphatase (bilirubin [mg/dl]/alkaline phosphatase >4). Excessive storage of copper in the kidney leads to renal tubular dysfunction in most patients and full-blown Fanconi syndrome in some. Hematuria also has been noted. Renal plasma flow and GFR decrease as the disease progresses, but death from extrarenal causes occurs before the onset of renal failure. Fanconi syndrome usually appears before the onset of hepatic failure. Hypercalciuria with development of renal stones and nephrocalcinosis also have been reported. Besides proximal tubular dysfunction, abnormalities in distal tubular function, decreased concentrating ability, and distal RTA (type 1 RTA) also have been observed. Neurologic abnormalities, such as dysarthria and gait disturbances, may be the presenting symptom in young adults with Wilson disease. Kayser-Fleischer rings, dense brown copper deposits around the iris, may be visible but typically can be seen only with a slit lamp.

Renal Pathology

Histologic examination of the kidney in untreated Wilson disease shows either no alteration on light microscopy or only some flattened proximal tubular cells without recognizable brush borders. EM shows loss of the brush border, disruption of the apical tubular network, electron-dense bodies probably representing metalloproteins in the subapical region of tubule cell cytoplasm, and cavitation of the mitochondria with disruption of the normal cristae pattern. Rubeanic acid staining shows intracytoplasmic copper granules. The copper content of kidney tissue is greatly elevated.

Diagnosis

The diagnosis of Wilson disease should be suspected in children and young adults with unexplained neurologic disease, chronic active hepatitis, acute hemolytic crisis, behavioral or psychiatric disturbances, or the appearance of Fanconi syndrome. In such patients, the presence of Kayser-Fleischer rings is an important clue in making the diagnosis. Serum ceruloplasmin levels are decreased in 96% of patients with Wilson disease. A greatly increased urinary copper level is also useful in making the diagnosis, especially if it increases significantly with D-penicillamine. Liver copper levels are increased in untreated patients. Mutational analysis is also available.

Treatment

Treatment with penicillamine 1 to 1.5 g/day reverses the renal dysfunction and potentially the hepatic and neurologic disease, depending on the degree of damage before the onset of therapy. Recovery, however, is quite slow. Trientine also can chelate copper and is indicated in patients who cannot tolerate penicillamine. Tetrathiomolybdate is a potent agent in removing copper from the body and has been used in some patients with neurologic disease to prevent the immediate worsening of symptoms that can occur with penicillamine. Zinc salts, which induce intestinal metallothionein and blockade of intestinal absorption of copper, are useful in maintenance therapy. Liver transplantation has been successful in some patients but should be reserved for those with liver failure.

Lowe Syndrome

Lowe syndrome (oculocerebrorenal syndrome) is characterized by congenital cataracts and glaucoma, severe developmental delay, hypotonia with diminished to absent reflexes, and renal abnormalities.[15,16] Fanconi syndrome is followed by progressive renal impairment. ESRD usually does not occur until the third to fourth decade of life.

Lowe syndrome is transmitted as an X-linked recessive trait. Despite this inheritance pattern, Lowe syndrome has occurred in a few females. The defective gene codes for phosphatidyl inositol 4,5-bisphosphate 5-phosphatase, *OCRL1*, involved with cell trafficking and signaling.

Light microscopy of the kidney is normal early in the disorder, with endothelial cell swelling and thickening and splitting of the glomerular basement membrane seen by EM. In the proximal tubule cells, there is shortening of the brush border and enlargement of the mitochondria, with distortion and loss of the cristae. Only symptomatic treatment is available.

Dent Disease

Definition

Dent disease is an X-linked recessive disorder characterized by low-molecular-weight proteinuria, hypercalciuria, nephrolithiasis, nephrocalcinosis, and rickets.[17,18] Affected males often have aminoaciduria, phosphaturia, and glycosuria. Renal failure is common and may occur by late childhood. Hemizygous females usually have only proteinuria and mild hypercalciuria. X-linked recessive nephrolithiasis and X-linked recessive hypophosphatemic rickets have similar features, and most have a defect in the renal ClC-5 chloride channel. Dent disease type 2 is a clinically similar disease affecting males, but there is a mutation in the same gene that causes Lowe syndrome, although patients with Dent type 2 do not have the brain or eye involvement seen in Lowe syndrome.[17]

Etiology and Pathogenesis

Most of these disorders are caused by a mutation in the *CLCN5* gene leading to inactive ClC-5 chloride channel function (see Fig. 48.2). The ClC-5 chloride channel spans the membrane of preendocytic vesicles just below the brush border of the proximal tubule. This channel plays a role in the acidification of these vesicles by a proton pump. Lack of this Cl^- channel interferes with protein reabsorption from the tubule through the megalin-cubilin receptor system and cell surface receptor recycling, which may explain the phosphaturia, glycosuria, and aminoaciduria.

The defective *OCRL1* in patients with Dent disease type 2 interferes with normal cell protein trafficking. The renal disease is similar to that seen in type 1 Dent disease. Although patients do not have the eye and brain disease seen in patients with Lowe, a few patients with Dent type 2 have a mild intellectual deficit, hypotonia, and subclinical cataracts.

Filtered PTH is also reabsorbed by the megalin-cubilin system for degradation in the lysosome. Decreased PTH reabsorption allows increased binding to luminal PTH receptors and increased endocytosis of luminal phosphate transporters, leading to increased phosphaturia.[1]

Mitochondrial Cytopathies

Definition

Mitochondrial cytopathies are a diverse group of diseases with abnormalities in mitochondrial DNA that lead to mitochondrial dysfunction in various tissues.[19]

Clinical Manifestations

Most of the mitochondrial cytopathies manifest with neurologic disorders such as myopathy, myoclonus, ataxia, seizures, external ophthalmoplegia, stroke-like episodes, and optic neuropathy. Other manifestations include retinitis pigmentosa, diabetes mellitus, exocrine pancreatic insufficiency, sideroblastic anemia, sensorineural hearing loss, pseudo-obstruction of the colon, hepatic disease, cardiac conduction disorders, and cardiomyopathy.

The most common renal manifestation associated with mitochondrial cytopathies is Fanconi syndrome, although a number of patients have been described with focal segmental glomerulosclerosis (FSGS) and corticosteroid-resistant nephrotic syndrome. All the patients with renal abnormalities have had extrarenal disorders, mainly neurologic disease. Most patients present in the first months of life and die soon afterward.

Diagnosis

A clue to mitochondrial cytopathies is elevated serum or cerebrospinal fluid lactate levels, especially in association with an altered lactate-to-pyruvate ratio, suggesting a defect in mitochondrial respiration. The presence of "ragged red fibers," a manifestation of abnormal mitochondria, in a muscle biopsy specimen is another clue, especially with large abnormal mitochondria on EM of muscle tissue.

Treatment

There is little to offer these patients in terms of definitive therapy. Low mitochondrial enzyme complex III activity can be treated with menadione or ubidecarenone. Deficient mitochondrial enzyme complex I activity may be treated with riboflavin and ubidecarenone. Ascorbic acid has been used to minimize oxygen free radical injury. High-lipid, low-carbohydrate diet has been tried in cytochrome c oxidase deficiency.

Idiopathic Fanconi Syndrome

A number of patients develop the complete Fanconi syndrome in the absence of any known cause. Traditionally called *adult* Fanconi syndrome because it was thought that only adults were affected, it is now clear that children may be affected, and a more proper designation is *idiopathic* Fanconi syndrome. Not all the features of Fanconi syndrome may be present when the patient is first seen, but do appear with time. Idiopathic Fanconi syndrome can be inherited in an autosomal dominant, autosomal recessive, or even X-linked pattern. However, most cases occur sporadically, with no evidence of genetic transmission. The prognosis is variable, and some patients develop ESRD 10 to 30 years after onset of symptoms. A few patients have undergone renal transplantation; in some, Fanconi syndrome has recurred in the allograft without evidence of rejection, suggesting an extrarenal cause of the idiopathic form.

Renal morphologic descriptions of such cases are scanty. In some reports, no abnormalities were found, and, in others, tubular atrophy with interstitial fibrosis was interspersed with areas of tubular dilation. Greatly dilated proximal tubules with swollen epithelium and grossly enlarged mitochondria with displaced cristae also have been noted.

ACQUIRED CAUSES OF FANCONI SYNDROME

Numerous substances can injure the proximal renal tubule. Injury can range from an incomplete Fanconi syndrome to acute tubular necrosis (ATN) or ESRD. The extent of the tubular damage varies depending on the type of toxin, amount ingested, and host. A careful history of possible toxin exposure and recent medications is important in patients with tubular dysfunction. Box 48.1 lists the more common causes of acquired Fanconi syndrome.

Heavy Metal Intoxication

A major cause of proximal tubular dysfunction is acute heavy metal intoxication, principally lead and cadmium. In lead poisoning, the renal tubular dysfunction, mainly aminoaciduria and mild glycosuria and phosphaturia, is usually overshadowed by the development of chronic kidney disease and involvement of other organs, especially the central nervous system.[20] Fanconi syndrome associated with cadmium poisoning is associated with severe bone pain, giving rise to the name itai-itai ("ouch-ouch") disease for its occurrence in Japanese patients affected by industrial contamination of the soil.[21]

Tetracycline

Outdated tetracycline causes reversible Fanconi syndrome even in therapeutic doses. Recovery is rapid when the degraded drug is stopped. The compound responsible for the tubule dysfunction is anhydro-4-tetracycline, formed from tetracycline by heat, moisture, and low pH.

Cancer Chemotherapy Agents

A number of cancer chemotherapy agents have been associated with Fanconi syndrome and renal tubular dysfunction, especially cisplatin and ifosfamide. Carboplatin has been associated with reduced GFR and magnesium wasting but not Fanconi syndrome. The nephrotoxicity of both cisplatin and ifosfamide is dose dependent and often irreversible. Besides the usual manifestations of Fanconi syndrome, cisplatin toxicity is characterized by hypomagnesemia, caused by hypermagnesuria, which can be extremely severe, persistent, and difficult to treat.[22,23] Ifosfamide is more often associated with hypophosphatemic rickets.[22] Chloroacetaldehyde, a metabolite of ifosfamide, appears experimentally to cause Fanconi syndrome. Both ifosfamide and cisplatin can cause an irreversible reduction in GFR.

Other Drugs and Toxins

Exposure to a wide range of toxins may give rise to Fanconi syndrome, often in association with a reduced GFR, including 6-mercaptopurine, toluene (glue sniffing), and Chinese herbal medicines containing *Aristolochia* spp.[24] In addition, anecdotal reports have associated Fanconi syndrome with valproic acid (valproate), suramin, gentamicin, and ranitidine. Antiviral medications, especially antiretroviral agents such as tenofovir, are an increasingly common cause of Fanconi syndrome.[25]

Dysproteinemias

Dysproteinemia[26] from multiple myeloma, light-chain proteinuria,[27] Sjögren syndrome, and amyloidosis is sometimes associated with Fanconi syndrome, which appears to be correlated with urinary free light chains that can cause proximal tubule dysfunction through intracellular crystallization or lysosomal dysfunction.[28]

Glomerular Disease

Nephrotic syndrome has been rarely associated with Fanconi syndrome. Most of these patients have FSGS, and the occurrence of Fanconi syndrome heralds a poor prognosis.

After Acute Kidney Injury

Tubular dysfunction can occur transiently during recovery from AKI from any cause, regardless of whether a known tubular toxin was originally implicated.

After Renal Transplantation

Fanconi syndrome has appeared rarely after renal transplantation. The pathogenesis probably is multifactorial, including sequelae of ATN, rejection, nephrotoxic drugs, ischemia from renal artery stenosis, and residual hyperparathyroidism.

FAMILIAL GLUCOSE-GALACTOSE MALABSORPTION AND HEREDITARY RENAL GLYCOSURIA

Definition

Renal glycosuria refers to the appearance of readily detectable glucose in the urine when the serum glucose concentration is in a normal range (see Fig. 48.3). When the serum glucose concentration is in a physiologic range, virtually all the filtered glucose is reabsorbed in the proximal tubule.[29] Filtered glucose enters the proximal tubule through two specific carriers (SGLT1 and SGLT2) coupled to sodium and exits the cell through the sugar transporters GLUT1 and GLUT2 (see Fig. 48.7). However, when the serum level exceeds the physiologic range, the filtered load exceeds the capacity of these carriers, and glucose begins to appear in the urine; this is termed the *renal threshold.*

Etiology and Pathogenesis

Familial glucose-galactose malabsorption is a rare autosomal disorder caused by mutations in the gene coding for the brush border sodium-glucose cotransporter SGLT1, which is found in the intestinal cell and the S_3 segment of the proximal renal tubule cell. The disorder is characterized by the neonatal onset of life-threatening diarrhea from the intestinal malabsorption of glucose and galactose, which resolves rapidly with the removal of glucose and galactose and its dipeptide, lactose, from the diet. These patients frequently also have mild renal glycosuria.

Familial renal glycosuria occurs with an incidence of 1 in 20,000 live births and can be inherited as a heterozygous, homozygous, or mixed heterozygous trait.[29] This disorder is caused by mutations in the *SLC5A2* gene that codes for the SGLT2 glucose transporter found in the early portion of the proximal tubule. Inhibitors of SGLT2, which mimic this genetic defect, have been used recently in type 2 diabetes to lower hyperglycemia without causing weight gain or aggravating hyperinsulinism.

In the past, renal glycosuria was divided into three types based on the reabsorption patterns observed during glucose infusion studies, but this typing system has been questioned because clearance data suggest patients with renal glycosuria have rates of glucose reabsorption that vary from virtually no reabsorption to near-normal rates, rather than three distinct types, reflecting different mutations in the *SLC5A2* gene and differing amounts of functional protein.

Natural History

Patients with familial glucose-galactose malabsorption appear to grow and develop normally with removal of the offending sugars from the diet. The clinical course of hereditary renal glycosuria is benign, except for a few patients with polyuria and salt wasting, and it is not a precursor to diabetes mellitus. Patients need to be aware of the condition in order not to receive unnecessary diagnostic investigations or even treatment for presumed diabetes mellitus.

AMINOACIDURIAS

As with glucose, amino acids are almost completely reabsorbed in the proximal tubule by a series of specific carriers. Studies have described a number of inherited disorders resulting in the incomplete reabsorption of a specific amino acid or a group of amino acids[30,31] (Table 48.2). Most do not result in kidney disease.

Cystinuria

Definition

Cystinuria is characterized by the excessive urinary excretion of cystine and the dibasic amino acids ornithine, lysine, and arginine and accounts for about 1% to 2% of all kidney stones and 6% to 8% of pediatric kidney stones.[32]

Etiology and Pathogenesis

These four amino acids share a transport system on the brush border membrane of the proximal tubule. Because of the relative insolubility of cystine when its urine concentration exceeds 250 mg/l (1 mmol/l), patients with cystinuria have recurrent renal calculi.

Cystinuria is an autosomal recessive trait with a disease incidence of 1 in 15,000 births.[33] Early studies suggested there were three genetic types on the basis of in vitro studies of intestinal transport and amino acid excretion in heterozygotes. More recently, two genes (*SLC3A1* coding for the protein rBAT and *SLC7A9* for the protein $b^{0,+}$AT) have been identified that are defective in cystinuria. *SLC3A1* heterozygotes have normal excretion rates for cystine. *SLC7A9* heterozygotes have cystine excretion rates that range from normal to almost that of homozygous patients. Based on these data, a newer classification proposed type A for mutations in both *SLC3A1* genes and type B for mutations in *SLC7A9*.[33] Type AB is compound heterozygote. Type A accounts for 38% of cystinuria patients, type B for 47%, and type AB for 14%.

TABLE 48.2 **Inherited Aminoacidurias**

Disease	Clinical Findings	Urine Amino Acids
Cystinuria	Urolithiasis	Cystine, lysine, ornithine, arginine
Hartnup disease	Rash, neurologic disease	Neutral amino acids
Iminoglycinuria	None	Proline, hydroxyproline glycine
Lysinuric protein intolerance	Hyperammonemia, vomiting, diarrhea	Dibasic amino acids

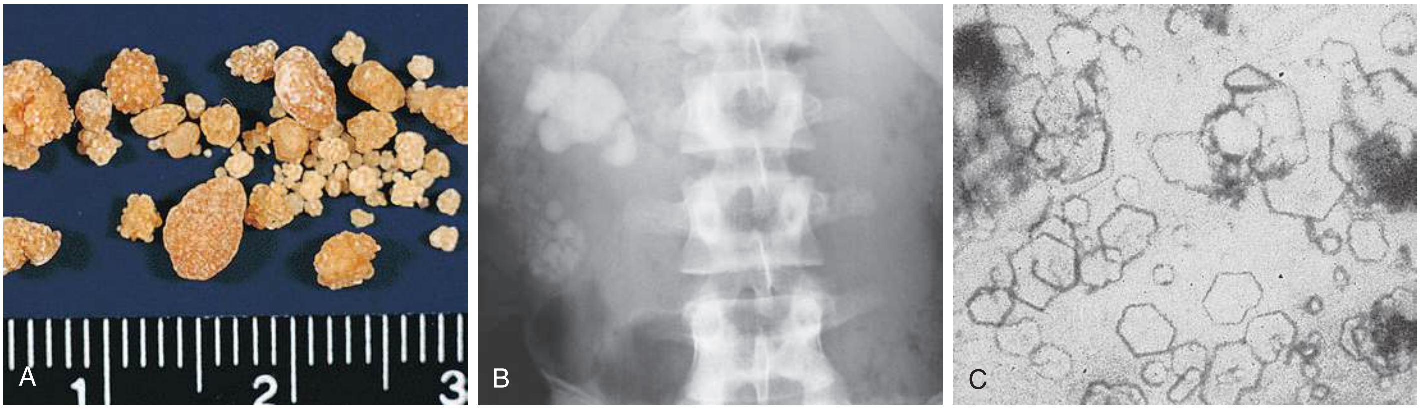

Fig. 48.8 **Cystinuria.** (A) Rough and smooth cystine calculi. (B) Plain radiograph of a cystine calculus in the right renal pelvis and further multiple parenchymal calculi. (C) Urine microscopy showing characteristic flat hexagonal crystals (see also Fig. 4.4G).

Clinical Manifestations

Cystine stones (calculi) are typically yellow-brown (Fig. 48.8A) and radiopaque (see Fig. 48.8B). Cystine crystals appear as microscopic, flat hexagons in the urine (see Fig. 48.8C), and this is a clue to the diagnosis.

Diagnosis

Patients can be screened for cystinuria with the cyanide-nitroprusside test, but type B heterozygotes also may give a positive result. The definitive test is to quantify cystine and dibasic amino acid excretion in a 24-hour urine specimen. Homozygotes excrete more than 118 mmol cystine per mmol creatinine (250 mg/g creatinine).

Treatment

The aim of therapy in cystinuria is to lower the urine cystine concentration to below 300 mg/l (1.25 mmol/l). The first step is to increase fluid intake. However, because most patients with cystinuria excrete 0.5 to 1 g/day of cystine, a urine output of 2 to 4 l/day is needed to achieve this goal. Cystine solubility increases in alkaline urine, but the urine pH must be above 7 to 7.5 to be effective. In patients with recurrent stone disease, thiols such as penicillamine and tiopronin, are extremely useful through the formation of a more soluble, mixed disulfide of the thiol and cysteine from cystine. Tiopronin is the most commonly prescribed thiol because it has fewer side effects than penicillamine and is started at a low dose (100 mg bid) and slowly increased (maximum 1200 mg/day) to a to achieve a urine cystine concentration below 300 mg/l in conjunction with a high fluid intake. Penicillamine is also effective and the dose should be slowly increased to minimize side effects. Captopril can be useful (an effect resulting from its thiol structure, not its angiotensin-converting enzyme inhibitor effect), but the dose range (75 to 150 mg/day) may be limited by its hypotensive effects.

HEREDITARY DEFECTS IN URIC ACID HANDLING

Hereditary Renal Hypouricemia

Hereditary renal hypouricemia is a rare autosomal recessive disorder characterized by very low serum uric acid levels (<2.5 mg/dl; [<150 μmol/l] in adult men and <2.1 mg/dl [<124 μmol/l] in adult women) and increased uric acid clearance, ranging from 30% to 150% of the filtered load.[34] In the normal kidney, uric acid is both reabsorbed and secreted in the proximal tubule by two different uric acid–anion exchange transporters and a voltage-sensitive pathway. In some patients, the defect is in the gene *SLC22A12* that codes for the protein URAT1; other patients have been found to have mutations in *SLC2A9 (GLUT9)*. Most patients do not have symptoms, and hypouricemia is found incidentally when a low serum uric acid concentration is noted during routine serum chemistry evaluation. About one fourth of patients with renal hypouricemia have had renal stones, but only one third of these were uric acid stones. There also may be hypercalciuria, and a few patients have had exercise-induced AKI, thought to be caused by acute tubular injury by passage of uric acid "gravel" in association with volume depletion and reduced urine pH. Most patients require no treatment, but if forming uric acid stones, they should maintain a high fluid intake. Urine alkalinization and allopurinol can be used for patients with persistent uric acid stones.

Familial Juvenile Hyperuricemic Nephropathy, Medullary Cystic Kidney Disease Type 2, and Uromodulin Mutations

Familial juvenile hyperuricemic nephropathy (FJHN) and medullary cystic kidney disease type 2 (MCKD2) are rare autosomal dominant conditions characterized by hyperuricemia, early-onset gout, and tubulointerstitial nephropathy.[35] Most patients with either FJHN or MCKD2 have a defect in the gene *UMOD,* on chromosome 16p12, coding for the Tamm-Horsfall/uromodulin protein, which is synthesized in the epithelial cells of the thick ascending limb (TAL) of the loop of Henle. The defective protein is retained in the endoplasmic reticulum and probably leads to inflammation, interstitial fibrosis, and functional abnormalities of the TAL. The defective protein also causes decreased salt and water reabsorption because *UMOD* plays a role in regulating the sodium-potassium-chloride transporter[36] and the rat outer medullary potassium channel.[37] The decreased salt and water reabsorption leads to increased proximal salt reabsorption and secondarily of uric acid, leading to hyperuricemia.

Diagnosis is suggested by a fractional excretion of uric acid of less than 5% (normal, 10% to 15%). Definitive diagnosis can be made by genetic testing of the *UMOD* gene. Controversy exists as to whether lowering of serum uric acid slows the progression of CKD; the studies reporting benefit have usually involved starting a xanthine oxidase inhibitor early in the disease.

More recently from genome-wide association studies, variants in the *UMOD* gene have been identified as risk factors for chronic kidney disease and hypertension.[38] The variants are common and are in the noncoding regions of the *UMOD* gene and lead to an increase in functional UMOD protein in contrast to FJHN/MCKD2.

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SELF-ASSESSMENT QUESTIONS

A 3-year-old boy presents with failure to thrive and photophobia. His urine contains glucose and +1 protein with a pH of 5.5. Serum chemistries are:

Na^+ 135 mmol/l
K^+ 2.5 mmol/l
Cl^- 111 mmol/l
HCO_3^- 15 mmol/l
Glucose 91 mg/dl (5 mmol/l)
Phosphorus 2.5 mg/dl (0.8 mmol/l) (normal for age 4.5-5.5 mg/dl)
Creatinine 0.4 mg/dl (35 μmol/l)

1. Slit-lamp examination of his eyes shows tinsel-like refractile opacities in his cornea. What is the most likely diagnosis?
   - **A.** Lowe syndrome
   - **B.** Cystinosis
   - **C.** Tyrosinemia
   - **D.** Hereditary fructose intolerance
   - **E.** Galactosemia
2. Cystinuria is associated with which amino acids in the urine besides cystine?
   - **A.** Arginine, lysine, ornithine
   - **B.** Arginine, lysine, histidine
   - **C.** Lysine, ornithine, histidine
   - **D.** Ornithine, glycine, alanine
   - **E.** Ornithine, glycine, serine
3. What is the most common cause of Fanconi syndrome in adults?
   - **A.** Multiple myeloma
   - **B.** Medications
   - **C.** Nephrotic syndrome
   - **D.** Cystinosis
   - **E.** Cadmium
4. The defect in familial glycosuria is an abnormality in which transporter?
   - **A.** GLUT1
   - **B.** ClC-5
   - **C.** Na^+-K^+-$2Cl^-$
   - **D.** Na^+/H^+
   - **E.** SLGT2
5. Most patients with Dent disease have a mutation in which transporter?
   - **A.** Na^+-K^+-$2Cl^-$
   - **B.** GLUT2
   - **C.** Na^+/H^+
   - **D.** ClC-5
   - **E.** Na^+-Cl^-

49

Sickle Cell Diseases and the Kidney

Claire C. Sharpe, Fatiu A. Arogundade

SICKLE CELL DISEASE

Epidemiology

Sickle cell disease (SCD) is an autosomal recessive inherited disorder that predominantly affects persons of African, Mediterranean, Indian, and Middle Eastern descent but was first recognized in West Africa. The high prevalence of SCD in this region probably represents a survival benefit because the presence of the sickle cell gene protects against malaria. SCD is now a worldwide health problem because the carrier state has spread throughout Africa, around the Mediterranean, and to the Middle East and India, as well as to the Caribbean, North America, and Northern Europe. The prevalence of the sickle cell gene is about 8% in African Americans and about 25% in adult Nigerians. Of babies born with SCD, 25% worldwide are born outside of sub-Saharan Africa.[1-3]

Genetics

The sickle hemoglobin (Hb) mutation (hemoglobin S, or HbS) results in the replacement of the normal glutamine by valine in the sixth position of the β-globin subunit, thereby changing the configuration of the Hb tetramer molecule in the homozygous person from $\alpha 2\beta 2$ to $\alpha 2\beta^S 2$. SCD occurs in those homozygous for HbS (commonly referred to as *sickle cell anemia*,) or in heterozygotes when HbS coexists with another abnormal or missing β-chain (e.g., HbC ($\alpha 2\beta^S\beta^C$) or HbSβ thalassemia ($\alpha 2\beta S$). Sickle cell trait occurs in those heterozygous for HbS when the other Hb molecule is normal (HbAS ($\alpha 2\beta^A\beta^S$).

Restriction enzyme techniques have identified several HbS haplotypes—mutations of the HbS molecule that have probably arisen independently of each other. There are four major types in Africa—the Benin, Senegal, Cameroon, and Bantu (or Central African Republic)—and one Asian haplotype. Variations in these haplotypes determine disease severity; for example, the Senegalese haplotype is associated with a higher fetal Hb (HbF) concentration (a key driver of disease severity) and has a better prognosis than others. In a sample population of Nigerians, Benin haplotype was detected in 92%. Gender also influences disease severity; female HbSS patients with Benin haplotype have a higher HbF level than male patients.[4,5]

Pathophysiology

The driving pathophysiologic factor is HbS polymerization. During cellular or tissue hypoxia, dehydration, or oxidative stress, the mutated β-globin chains of the HbS molecule tend to crystallize to a polymer nucleus. Polymerization disrupts the architecture and changes the shape of the red blood cell (RBC) to a characteristic crescent or sickle, which increases its rigidity (Fig. 49.1). Polymerization is dynamic and depends on local oxygen tension. It is also promoted by acidosis (which decreases the affinity of HbS for oxygen) and hyperosmolarity (which increases RBC Hb concentration). As a consequence of repeated polymerization cycles, sickle RBCs exhibit abnormally high adhesion to activated endothelium, owing to acquired membrane changes and retained adhesion receptors on reticulocytes, especially the stress reticulocytes. This increases microvascular transit time, thereby stimulating further sickling. This results in premature destruction (hemolysis) of the RBCs and frequent, widespread vaso-occlusive episodes with subsequent acute and chronic organ damage.

The tendency of HbS to polymerize is influenced by the presence or absence of HbF, which contains γ-Hb chains in place of β-Hb ($\alpha 2\gamma 2$). In RBCs that contain HbF (known as F cells) the presence of HbF dilutes the concentration of HbS, thus increasing the threshold at which polymerization occurs. In addition, both HbF and its mixed hybrid tetramer ($\alpha 2\beta^S\gamma$) cannot enter the deoxy sickle Hb polymer phase, further limiting the degree of polymerization that can occur within a cell.[6] The main determinant of disease severity, therefore, is the rate and extent of HbS polymerization, which drives the two major pathophysiologic processes: vaso-occlusion with ischemia-reperfusion injury and hemolytic anemia (Fig. 49.2).[7]

Vaso-occlusion occurs in all patients, often triggered by inflammation, and is typically found in clinical states of infection, hypoxia, hypovolemia, hypothermia, acidosis, and hyperosmolality. Vaso-occlusion is probably caused by dynamic endothelial-leukocyte-RBC adhesive interactions in the postcapillary venules and precapillary obstruction by rigid, deformed RBCs. Episodic microvascular occlusion and ischemia can be interrupted by restoration of blood flow and reperfusion, which further promote inflammatory stress and tissue injury. In addition, hemolysis contributes to the development of progressive vasculopathy, characterized by endothelial dysfunction and proliferative changes in the intima and smooth muscle of blood vessels. An important role is ascribed to free Hb, which inactivates nitric oxide and generates reactive oxygen species. These separate pathologic processes have been used to explain the distinct subphenotypes of clinical complications of SCD whereby some patients present with frequent vaso-occlusive crises, acute chest syndrome (ACS), and osteonecrosis, and others have more severe anemia, recurrent leg ulceration, pulmonary hypertension, priapism, and chronic kidney disease (CKD).[8,9]

Natural History and Clinical Manifestations

SCD is a highly variable condition, though life expectancy is reduced in all subjects, especially in those with symptomatic disease. Although few data are available, median survival in some parts of sub-Saharan Africa may be as low as 5 years whereas it is 45 to 55 years in the United States and Jamaica.[5,10] The clinical manifestations of SCD are individualized and age dependent (Fig. 49.3).[11] Newborn babies are

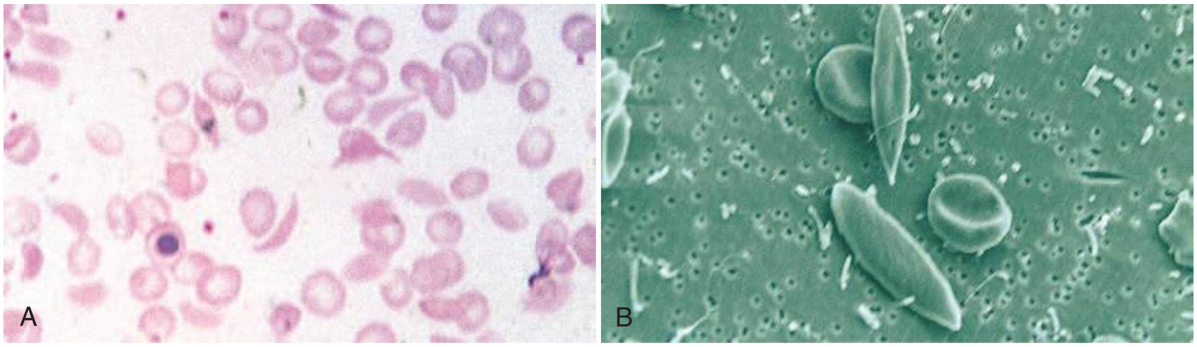


Fig. 49.1 Sickle cells. (A) Characteristic sickle cell erythrocytes in peripheral blood film of a patient with homozygous sickle cell anemia. (B) Electron micrograph showing two normal and two sickle-shaped erythrocytes. (Courtesy Professor Sally C. Davies.)

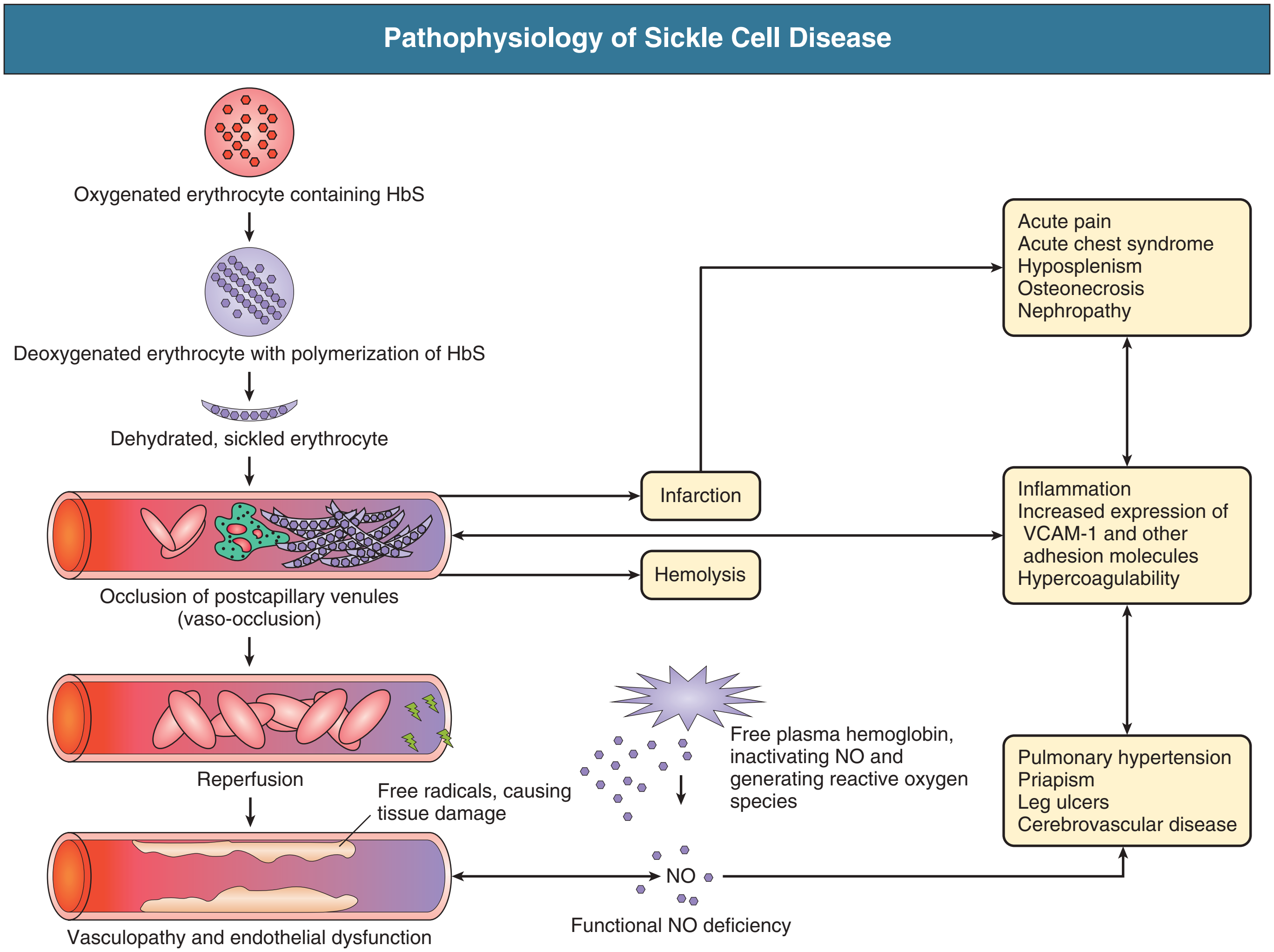

Pathophysiology of Sickle Cell Disease
Oxygenated erythrocyte containing HbS
Deoxygenated erythrocyte with polymerization of HbS
Dehydrated, sickled erythrocyte
Occlusion of postcapillary venules (vaso-occlusion)
Reperfusion
Free radicals, causing tissue damage
Vasculopathy and endothelial dysfunction
Infarction
Hemolysis
Free plasma hemoglobin, inactivating NO and generating reactive oxygen species
NO
Functional NO deficiency
Acute pain
Acute chest syndrome
Hyposplenism
Osteonecrosis
Nephropathy
Inflammation
Increased expression of VCAM-1 and other adhesion molecules
Hypercoagulability
Pulmonary hypertension
Priapism
Leg ulcers
Cerebrovascular disease

Fig. 49.2 Pathophysiology of sickle cell disease. *HbS,* Hemoglobin S (sickle Hb); *NO,* nitric oxide; *VCAM-1,* vascular cell adhesion molecule 1. (Modified from reference 7.)

asymptomatic for the first couple of months of life because fetal Hb predominates at this age. However, as γ-chains are rapidly replaced through β-chain synthesis, symptoms, often potentially life-threatening, begin to occur, including dactylitis, ACS, overwhelming sepsis, and acute splenic sequestration. Stroke is also a feature of early childhood, with the median age of onset of 6 years and an incidence of 8% by aged 14, rising to 11% by the age of 20. However, this has been largely mitigated in developed countries by screening at-risk children with transcranial Doppler (looking for increased blood flow velocity, which is suggestive of arterial stenosis) and the use of chronic transfusion for both primary and secondary prevention.[12] Human parvovirus B19 infection can lead to a severe and sudden fall in Hb in children and adolescents with SCD because the virus destroys red cell precursors for 8 to 10 days, which results in severe anemia. After the age of 5 years, when

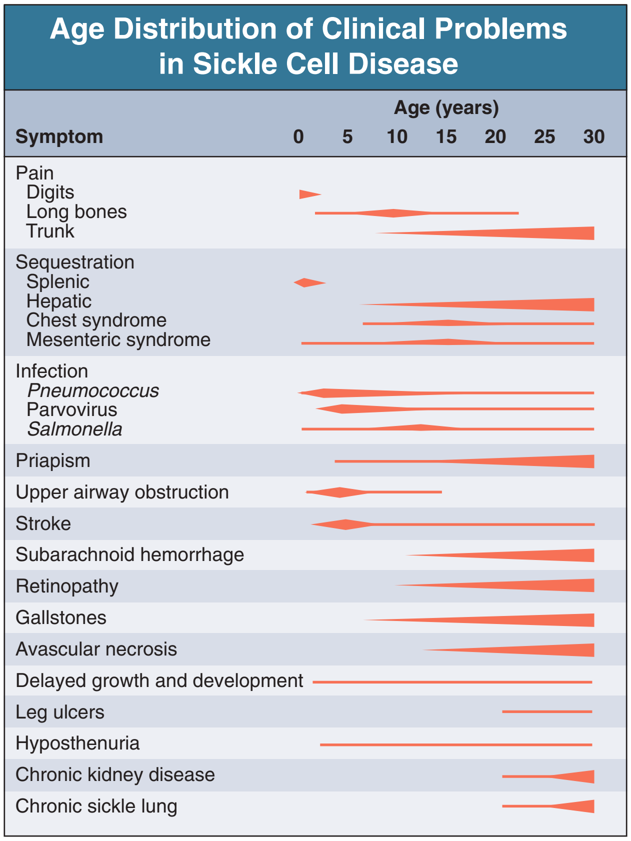


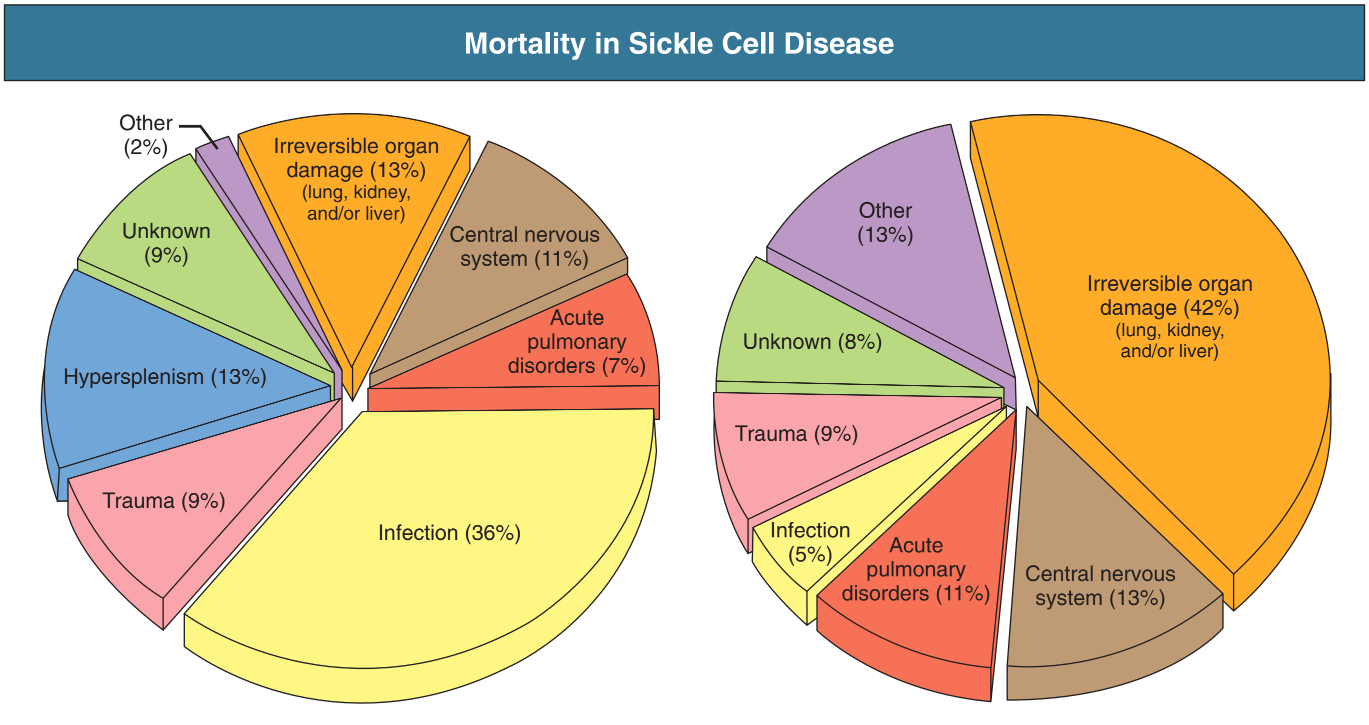
Fig. 49.3 Age distribution of clinical problems in sickle cell disease. (Modified from reference 11.)

active bone marrow is withdrawn from the small bones, dactylitis is replaced by the classic painful vaso-occlusive crisis (VOC), which increases in frequency with increasing age. In addition, adolescence is associated with nocturnal enuresis, avascular necrosis of the hip, leg ulcerations, delayed puberty, and priapism. Over the age of 25 to 30 years, the frequency of VOC tends to reduce and is replaced with signs and symptoms of chronic organ damage, including heart failure, pulmonary hypertension, sickle hepatopathy, and sickle cell nephropathy.[5] In younger patients, the primary cause of death is usually infection, whereas in older patients, the primary cause of death is commonly irreversible organ damage (Fig. 49.4).[13]

SICKLE CELL NEPHROPATHY

Sickle cell nephropathy (SCN) develops slowly, starting in the very young with glomerular hyperfiltration, leading to microalbuminuria in late childhood or early adulthood. Although many patients do not progress further, a number develop proteinuria and progressive CKD. These patients are at increased risk for acute kidney injury (AKI) complicating VOC or other interim illnesses; events that often precipitate a further decline in their baseline renal function. The prevalence of microalbuminuria is approximately 60% in those over 45 years, but only 4% to 12% of patients with SCD develop end-stage renal disease (ESRD), though this figure may increase as the patient cohort ages.[13,14] In keeping with this, in 2008, advanced CKD was reported in 24% of patients with SCD who had survived to 60 years of age or more and was the cause of death in 45%.[15]

In general, SCN is more prevalent and more severe in those with HbSS- and HbSβ^0-thalassemia than in those with milder forms of SCD such as HbSC.[10,16]



<20 years of age, n = 46 **>20 years of age, n = 186**

Fig. 49.4 **Mortality in sickle cell disease.** Causes of death among 232 HbSS patients, comparing patients younger than 20 years (46 died) with patients older than 20 years (186 died). The infection category includes both bacterial and viral diseases. (Modified from reference 13.)

Genetic Modifiers of Risk for Developing Sickle Cell Nephropathy

Other genetic modifiers are also associated with disease severity and risk for developing SCN, often through their influence on HbF levels. A polymorphism in the *BCL11A* gene (a fetal Hb silencing factor) leads to higher HbF levels, reduced hemolysis, and amelioration of SCD-related complications. Co-inheritance of α-thalassemia and SCD is found in approximately one third of patients and is associated with reduced hemolysis and protection from albuminuria. Over the past decade, genetic risk factors for CKD have been identified in the African American population, the most important of which are haplotypes of the *APOL1* gene. These are associated with increased risk for hemolysis and, when combined with genotypes for α-thalassemia and BCL11A, can be used to stratify risk for progressive CKD in SCD patients.[17] Using estimated glomerular filtration rate (eGFR) as a marker of renal function, the transforming growth factor-β/bone morphogenic protein (TGF-β/BMP) pathway[18] has been implicated as a cause of progressive kidney function loss in SCN.

Pathophysiology of Sickle Cell Nephropathy

The pathogenesis of SCN is directly related to the blood supply of the kidney and its circulation. In health the kidneys receive approximately 25% of the cardiac output to achieve effective filtration of the plasma at a rate of approximately 100 ml/min/1.73 m^2, despite representing less than 1% of total body weight. As a consequence, the cortex of the kidney is at risk for receiving excess oxygen, which is mitigated by shunting of oxygen from the afferent arteriole to the efferent arteriole. The vessels (vasa recta) that supply the medulla of the kidney branch off early from the efferent arteriole taking only a fraction of the total renal blood flow (RBF) with them. Much of the blood that enters the renal cortex is therefore delivered back to the venous circulation without entering the medulla at all. The maintenance of the relatively sluggish but intricate medullary blood flow is critical to maintaining the corticomedullary interstitial solute gradient generated by the countercurrent multiplier system of the loop of Henle, which drives water and solute reabsorption and allows for effective urinary concentration.[19] The resulting hypoxia (partial pressure of oxygen 10 to 35 mm Hg), acidosis, and hyperosmolarity of the inner medulla make it an ideal environment for the polymerization of deoxygenated HbS and subsequent sickling of erythrocytes. Over time, repeated cycles of sickling and sludging cause microinfarcts and ischemic injury leading to the chronic microvascular disease that is apparent in established SCN (Fig. 49.5).[20] Local activation of hypoxia inducible factor 1α (HIF1α) upregulates the expression of endothelin-1 which, in the presence of reduced nitric oxide, leads to an increase in reactive oxygen species and vasoconstriction, thus feeding into a cycle of chronic medullary hypoxia (Fig. 49.6).[21]

Despite reduced circulation in the renal medulla, total RBF and GFR are paradoxically increased. The subsequent hyperfiltration eventually results in proteinuria and glomerulosclerosis, which together with tubulointerstitial fibrosis marks the onset of progressive CKD.[22] Although in part the result of the increased cardiac output seen in patients with SCD, this increase in RBF cannot be completely explained by anemia or increased plasma volume, as it is not reversed by correction of the anemia with transfusion. One explanation involves the hemoxygenase-carbon monoxide system. Heme oxygenase-1 (HO-1) is upregulated in injured kidneys (and other tissues) in response to ongoing hemolysis in SCD. HO-1 is responsible for the conversion of heme to biliverdin with the subsequent release of carbon monoxide. Both biliverdin and carbon monoxide at these levels are potent antioxidants, and the carbon monoxide acts locally as a vasorelaxant, thus increasing both RBF and GFR.[23] This provides a possible link between the degree of hemolysis experienced by a patient and the likelihood of developing proteinuria.

The endothelial dysfunction and vasculopathic state of SCD described earlier is also pivotal to the development of SCN. Cross-talk between glomerular endothelial cells and podocytes is important to maintain healthy glomerular function; when the endothelium is dysfunctional this could lead to podocyte injury and the development of glomerular lesions and proteinuria. FMS-like tyrosine kinase 1 is a receptor for

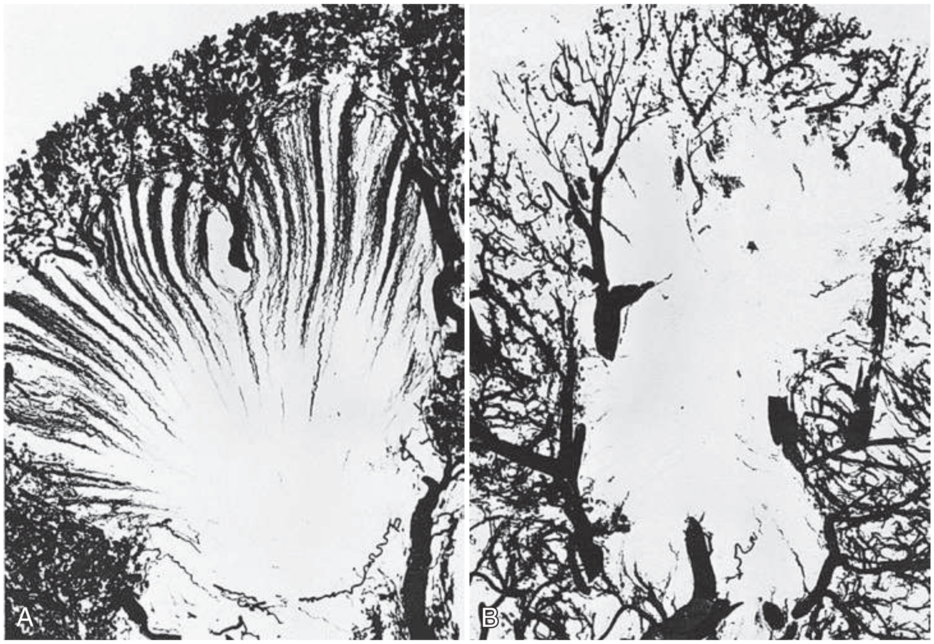


Fig. 49.5 **Microradioangiography showing loss of vasa recta in sickle cell nephropathy.** (A) Kidney from control, with normal vasa recta. (B) Patient with sickle cell anemia, with the absence of the vasa recta. (From reference 20.)

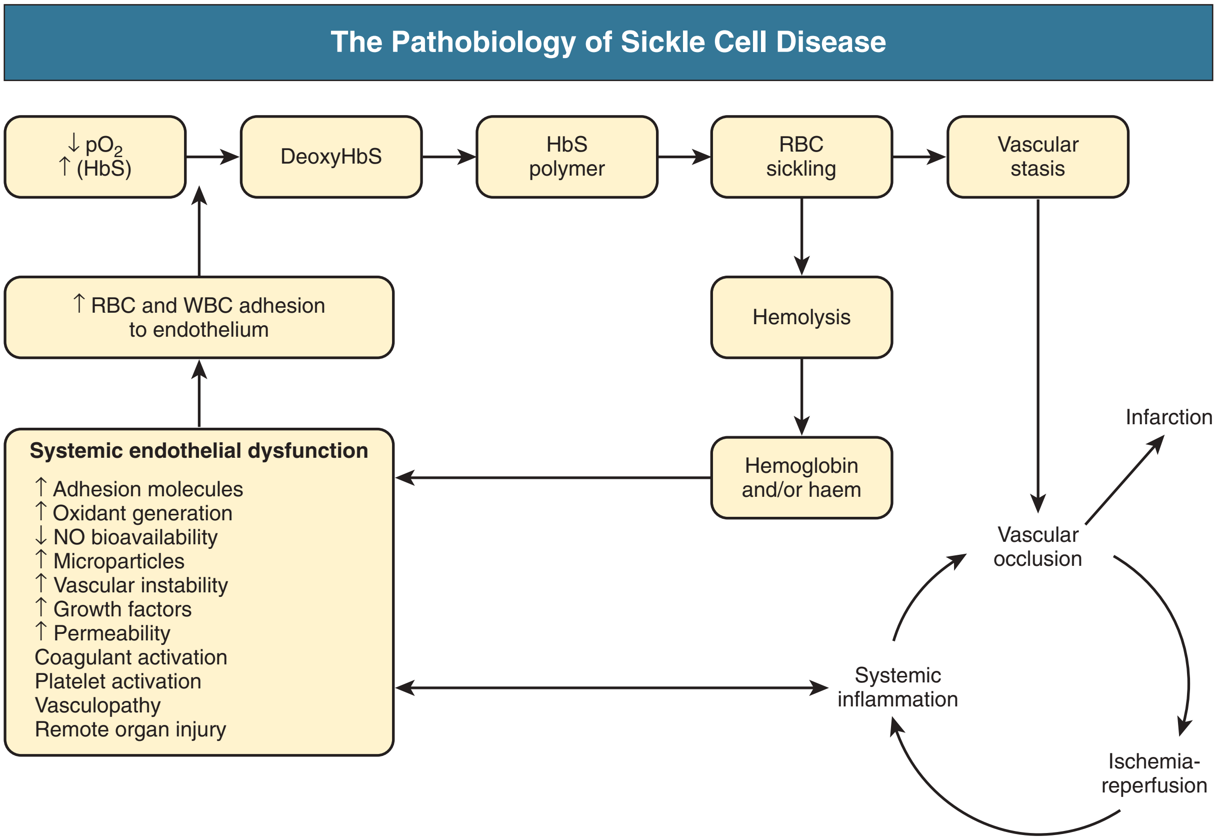

The Pathobiology of Sickle Cell Disease
↓ pO2
↑ (HbS)
DeoxyHbS
HbS polymer
RBC sickling
Vascular stasis
↑ RBC and WBC adhesion to endothelium
Hemolysis
Systemic endothelial dysfunction
↑ Adhesion molecules
↑ Oxidant generation
↓ NO bioavailability
↑ Microparticles
↑ Vascular instability
↑ Growth factors
↑ Permeability
Coagulant activation
Platelet activation
Vasculopathy
Remote organ injury
Hemoglobin and/or haem
Infarction
Vascular occlusion
Systemic inflammation
Ischemia-reperfusion

Fig. 49.6 The pathobiology of sickle cell disease. (From Nath 2015 (Modified from reference 23 with permission). *deoxyHbS,* Deoxygenated HbS; *HbS,* sickle hemoglobin; *NO,* nitric oxide; *p*O_2, partial pressure of oxygen; *RBC,* red blood cell; *WBC,* white blood cell.)

vascular endothelial growth factor (VEGF), and increased levels of the soluble form (sFlt-1) have been associated with endothelial dysfunction in pre-eclampsia. Serum levels of sFLT-1 are raised in SCD and so may play a role in the development of proteinuria.[23]

CLINICAL MANIFESTATIONS OF SICKLE CELL NEPHROPATHY

Glomerular Abnormalities

Hyperfiltration

Glomerular hypertrophy is ubiquitous in SCD and has been reported in children as young as 1 to 3 years of age (Fig. 49.7).[24] Increased renal growth is observed from infancy in children with SCD and accompanies the early rise in GFR.[25,26] GFR continues to rise throughout childhood and early adulthood, often exceeding 200 ml/min/1.73 m^2. However, in contrast to diabetic nephropathy, this hyperfiltration is not associated with an increase in systemic blood pressure (BP), because patients with SCD tend to have reduced systemic vascular resistance and hence lower mean arterial pressure when compared with age and ethnicity-matched controls.[23,27]

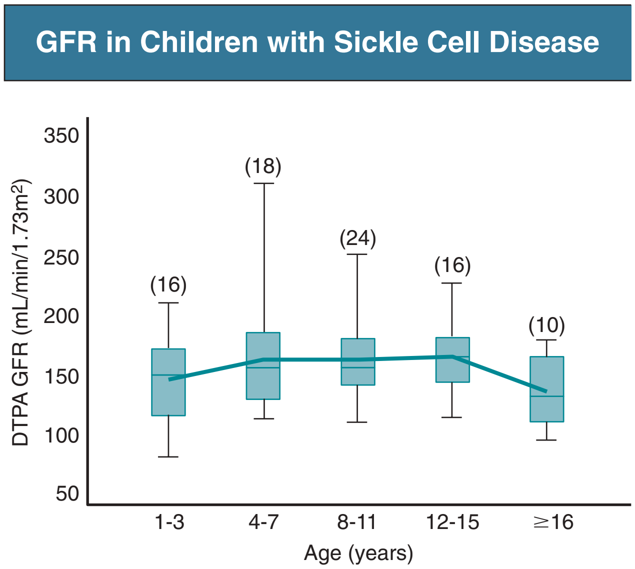


Fig. 49.7 Diethylenetriaminepentaacetic acid (DTPA) glomerular filtration rates in children with sickle cell disease. (From reference 24.)

Microalbuminuria and Proteinuria

The appearance of albumin in the urine at levels above those detected in normal individuals occurs after a period of prolonged hyperfiltration and is apparent in some patients from late childhood. Unlike hyperfiltration, the prevalence of microalbuminuria continues to increase with age, reaching more than 60% of all patients with HbSS SCD over the age of 45 years.[14,28] In some patients, microalbuminuria can develop into frank proteinuria (ratio of urine protein to creatinine ratio [uPCR] >50 mg/mmol), occasionally reaching the nephrotic range (>3.5 g/24 h), which is associated with increased mortality.[16] Nephrotic syndrome, although uncommon (~4% of all those with proteinuria) is associated with a very poor renal prognosis. One rare recognized cause of sudden onset of nephrotic syndrome in patients with SCD is recent infection with human parvovirus B19 (HPV B19). Although widespread in the community, this usually benign infection becomes significant in patients with SCD because it causes acute but self-limiting red cell aplasia. In combination with severe hemolysis, this leads to life-threatening anemia requiring supportive transfusion. Several reports have described patients in whom infection was followed by acute nephrotic syndrome within 2 to 3 months. In cases in which biopsy has been performed early, the collapsing variant of focal segmental glomerulosclerosis (FSGS) has been found (with or without evidence of direct HPV B19 infection). Although the acute features of the nephrotic syndrome are self-limiting, the sequelae of the condition are worsening glomerulosclerosis, tubulointerstitial fibrosis, and progressive renal dysfunction.[29]

Tubular Abnormalities

Hyposthenuria

Hyposthenuria (the excretion of urine of low specific gravity secondary to inability of the kidney to concentrate the urine) is almost universal in people with SCD, who can rarely achieve a urine osmolality above 450 mOsm/kg, even under water-deprived conditions, and also occurs in older people with sickle cell trait. It often leads to enuresis in children and can cause marked dehydration. It is primarily caused by sickling in the vasa recta, leading to microthrombi, infarction, and collateral formation of blood vessels. As a consequence there is a defect in the countercurrent exchange mechanism resulting in insufficient trapping of solute in the inner medulla leading to abnormalities in renal water conservation.[20] In addition, the increased delivery of salt and water in the tubular filtrate secondary to the high GFR and the intermittent hypoxia caused by sickling in the microvasculature, lead to local endothelin-1 (ET-1) release. ET-1 is not only a potent vasoconstrictor but also has marked natriuretic and diuretic properties through stimulation of ET type b receptors in the renal collecting ducts, leading to increased salt and water loss.[30] Although hyposthenuria is reversible by blood transfusion until the age of 10 years, after this age it becomes irreversible and is associated with a permanently damaged microvasculature and increased urine output, leading to a tendency to dehydration.[20,31]

Increased Proximal Tubular Function

The increase in sodium and water loss from the nephron leads to a reactive increase in sodium and water reabsorption by the proximal tubule secondary to tubuloglomerular feedback. This reabsorption of sodium is the driving force for the reabsorption of other solutes such as phosphate and β2-microglobulin, and hence many patients have hyperphosphatemia. There is also an increase in proximal tubular secretion of other solutes, such as creatinine and uric acid. Despite this, serum levels of uric acid are often raised as a result of severe hemolysis and may result in episodes of acute gout. In contrast, up to 30% of the total creatinine excretion can arise from tubular secretion resulting in low serum creatinine levels and over-estimation of renal function when creatinine-based formulas for GFR are used.[32] Increased sodium reabsorption requires increased oxygen consumption and hypermetabolism of the renal tubules; a phenomenon that may exacerbate renal hypoxia in SCD.[23]

Acidification Defect

A retrospective study in 2014 of 411 homozygous SCD patients with eGFR greater than 60 ml/min/1.73 m^2 revealed that 42% had partial metabolic acidosis as assessed by serum levels of carbon dioxide (52% of women, 27% of men), apparently because of a lack of ammonia buffering capacity rather than a defect in the distal tubule. Although serum potassium levels were not linked to acidosis in this study, hyperkalemia is a common phenomenon in patients with SCD and has been attributed by others to hyperchloremic metabolic acidosis linked to type IV renal tubular acidosis or resistance of the distal tubule to aldosterone.[23]

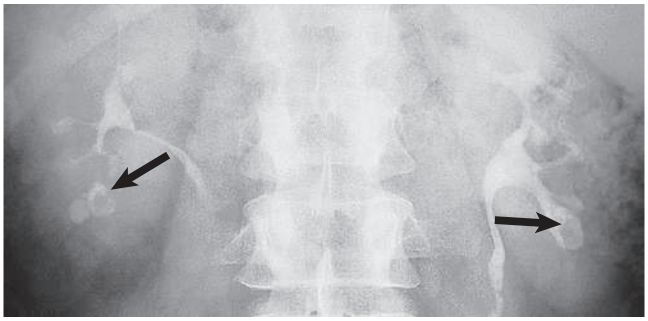


Fig. 49.8 Papillary necrosis in sickle cell disease. Intravenous urography shows abnormal calyces with filling defects *(arrows)*.

Hematuria, Papillary Necrosis, and Renal Medullary Carcinoma

Hematuria is common in patients with SCD and sickle cell trait. It can range from painless microhematuria, through visible and painless, to visible and painful. It is usually self-limiting but occasionally can be severe enough to require transfusion. Microinfarcts, capillary congestion, and rupture are often the cause, but occasionally, complete occlusion of the vasa recta can lead to renal papillary necrosis with sloughing of the ischemic papilla, severe hemorrhage, and obstruction, which may be complicated by superimposed infection and painful clot colic (Fig. 49.8).[18] The left-sided predominance of hematuria has been attributed to the so-called nutcracker phenomenon, with compression of the left renal vein between the aorta and the superior mesenteric artery, increasing the pressure in the renal vein. This may contribute to the development of hematuria in in patients with SCD, because the increased renal vein pressure could worsen anoxia in the renal medulla, increasing the likelihood of sickling in the left kidney.

Renal medullary carcinoma is an aggressive form of renal cell carcinoma that uniquely affects patients with sickle cell hemoglobinopathies, particularly sickle cell trait or HbSC, especially in teenagers and young adults. Chronic medullary hypoxia is thought to contribute to its pathogenesis. The tumors are resistant to chemotherapy and tend to be metastatic at diagnosis, with a reported postsurgical mean survival of only 15 weeks. It is not yet clear whether regular evaluation for renal medullary carcinoma in young patients with SCD or trait could result in an early diagnosis and a better survival. Gross hematuria, flank pain, and weight loss are ominous signs of malignancy, particularly in young patients with sickle cell trait. The tumor is typically located deep in the parenchyma, unlike Wilms tumor or renal cell carcinoma. Immunohistochemical analysis for epithelial cell markers (e.g., CAM 5.5), epithelial membrane antigen, and cytokeratin may assist in diagnosis.[22,33]

URINARY TRACT INFECTIONS

Patients with SCD have an increased susceptibility to bacterial infections; even low-grade bacteremia with a common organism may be fatal. In addition to the impaired immunity resulting from autosplenectomy, there is opsonic antibody deficiency, which predisposes to bacterial infections. Bacteriuria was found to be present in 26% of children with SCD presenting with fever in Nigeria, and urinary tract infection complicated pregnancy in 12% of mothers with SCD in a large UK cohort.[34,35]

Pyelonephritis and urosepsis, as with any infection, may precipitate a sickle cell crisis. The most common organisms isolated include *Escherichia coli, Klebsiella* spp., and other gram-negative Enterobacteriaceae.

CLINICAL SYNDROMES OF RENAL IMPAIRMENT

Acute Kidney Injury

Although much is known about CKD, there is little in the literature about AKI in patients with SCD. It is reported as a complicating factor in 2% to 8% of hospital admissions with painful VOC or ACS. The severity of the AKI appears to be directly related to the severity of the acute sickling crisis.[36,37] Other causes of AKI are rhabdomyolysis, sepsis, and drug nephrotoxicity. Less common causes of acute renal dysfunction are renal vein thrombosis and hepatorenal syndrome (caused by SCD related hepatic failure). Volume depletion due to inability to concentrate urine makes patients more susceptible to AKI. Although most patients recover, repeated episodes of AKI increase the risk for CKD. After severe episodes, renal function on recovery is often lower than before the acute event.[3,38] In addition, patients with underlying CKD are more prone to AKI, making this a vicious cycle in patients with frequent hospital admissions.

Progressive Chronic Kidney Disease

Progressive loss of renal function in SCN is an increasingly large problem as life expectancy increases. Similarly to diabetic nephropathy, patients with SCN progress through stages of tubular dysfunction and hyperfiltration, through microalbuminuria to heavy proteinuria, and eventually loss of GFR. Over time, single-nephron GFR increases as other nephrons are lost, resulting in worsening damage to the glomeruli (manifest by FSGS), increasing proteinuria, and subsequent interstitial fibrosis and tubular atrophy. Although hypertension is less common in patients with SCD than in an age- and ethnicity-matched cohort, when it is present it has a marked impact on the rate of progression of CKD.[39] Predictors of CKD are hypertension, proteinuria, nephrotic syndrome, hematuria, increasingly severe anemia, and inheritance of the Bantu, or Central African Republic, β-globin gene cluster haplotype. In our series, younger age at diagnosis and higher duration of SCD were found to strongly predict the development of nephropathy.[40,41]

As renal function declines, the ability of the kidney to synthesize erythropoietin (EPO) also declines. Chronic anemia and tissue hypoxia are strong drivers for EPO synthesis, and patients with SCD with normal kidney function often have EPO levels well above the normal range. However, when the GFR falls below approximately 60 ml/min, their ability to produce sufficient endogenous EPO also begins to decline, resulting in worsening anemia. In patients who develop progressive renal dysfunction secondary to SCN, the rate of decline can be quite rapid once the GFR falls below 40 ml/min/1.73 m^2, and so timely preparation for renal replacement therapy (RRT) is very important. Many patients who have suffered frequent vaso-occlusive crises and admissions to hospital often have very poor peripheral veins and so need expert surgical input when planning for dialysis access.

INVESTIGATION AND MANAGEMENT OF SICKLE CELL NEPHROPATHY

Serum cystatin C is promising as a more accurate marker of renal function than creatinine in adults and children with SCD and may detect decline in GFR earlier.[18] However, it has yet to be fully validated against gold standard measures that calculate true GFR, so at present creatinine and creatinine-based equations, which estimate GFR, should continue to be used in patients with SCD. It is therefore the pattern and rate of change of either serum creatinine or eGFR that should be considered rather than the absolute value, bearing in mind that relatively modest changes in creatinine at higher levels of GFR can represent significant decline in renal function. Renal function should be monitored at least annually. Creatinine levels are often low in people with SCD secondary to reduced muscle bulk, hyperfiltration, and increased proximal tubular secretion, resulting in a high eGFR. Increased rate of change of creatinine may therefore indicate declining renal function before the value moves out of the normal range. Anyone with an eGFR that is declining at more than 5 ml/min/year or an absolute value less than 60 ml/min should be identified and referred to a nephrologist (Fig. 49.9). Rigorous BP control is recommended, as for other causes of CKD.[39] A BP of 140/90 is permissible for patients with a negative dipstick result or those with an ACR less than 3.5 mg/mmol, but a target of 130/80 should be used for those with an ACR greater than 3.5 mg/mmol.[42] Urinary tract infections should be promptly treated with appropriate antibiotics. Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency), which may precipitate intravascular hemolysis, should be excluded because some antibiotics, including sulfonamides and nitrofurantoin, precipitate hemolysis by antagonizing folate synthesis. Long-term use of nonsteroidal antiinflammatory drugs should be avoided in patients with an eGFR less than 60 ml/min; if unavoidable, regular monitoring of renal function is recommended.[43]

The population at risk for developing SCN is also at risk for other diseases that affect the kidneys, including lupus nephritis, various forms of glomerulonephritis, blood-borne viruses, renal carcinoma, myeloma, and renal stones. This differential should be considered when investigating a patient with SCD and new-onset proteinuria or hematuria. Although it is common practice not to investigate patients with microalbuminuria (ACR >3.5 mg/mmol), patients with urinary protein to creatinine ratio (uPCR) greater than 50 mg/mmol should be evaluated for other causes of CKD (Fig. 49.9); if any of these investigations are abnormal, or the patient's signs and symptoms do not conform to those expected within the natural history of SCN as described previously, they should be referred for further renal or urologic evaluation. In particular, patients with sudden onset of heavy proteinuria, with or without nephrotic syndrome, warrant renal biopsy to look for causes other than SCN. There is no pathognomonic lesion that defines SCN. Glomerular hypertrophy with distended capillaries is universally found but is not confined to those who have developed microalbuminuria or proteinuria. FSGS is the most common lesion associated with proteinuria, but is not specific to SCN (Fig. 49.10). Other lesions that have been reported on renal biopsy in SCD include thrombotic microangiopathy and membranoproliferative glomerulonephritis, neither exclusive to SCN. The only characteristic interstitial lesion is abundant hemosiderin granules in proximal tubular epithelial cells.[44] Renal iron deposition also has been noted on magnetic resonance scans in patients with SCD but appears not to be related to liver iron concentration, a marker of total body iron load. Renal iron does appear to be correlated with markers of hemolysis but has not been shown to be associated with renal dysfunction or degree of albuminuria.[45]

Inhibition of the Renin-Angiotensin System

Only one small randomized, controlled trial evaluated angiotensin-converting enzyme (ACE) inhibition in patients with SCD and proteinuria; a more recent systematic review concluded that available evidence was insufficient to offer recommendations on treatment.[46] However, based on the evidence available for other causes of proteinuric renal disease, it is recognized practice to use ACE inhibitors or angiotensin receptor blockers (ARBs) in the treatment of SCN when the uPCR is greater than 50 to 100 mg/mmol. These drugs must be introduced cautiously because many patients have a low or normal BP, and so moderate doses can cause postural hypotension, which can be

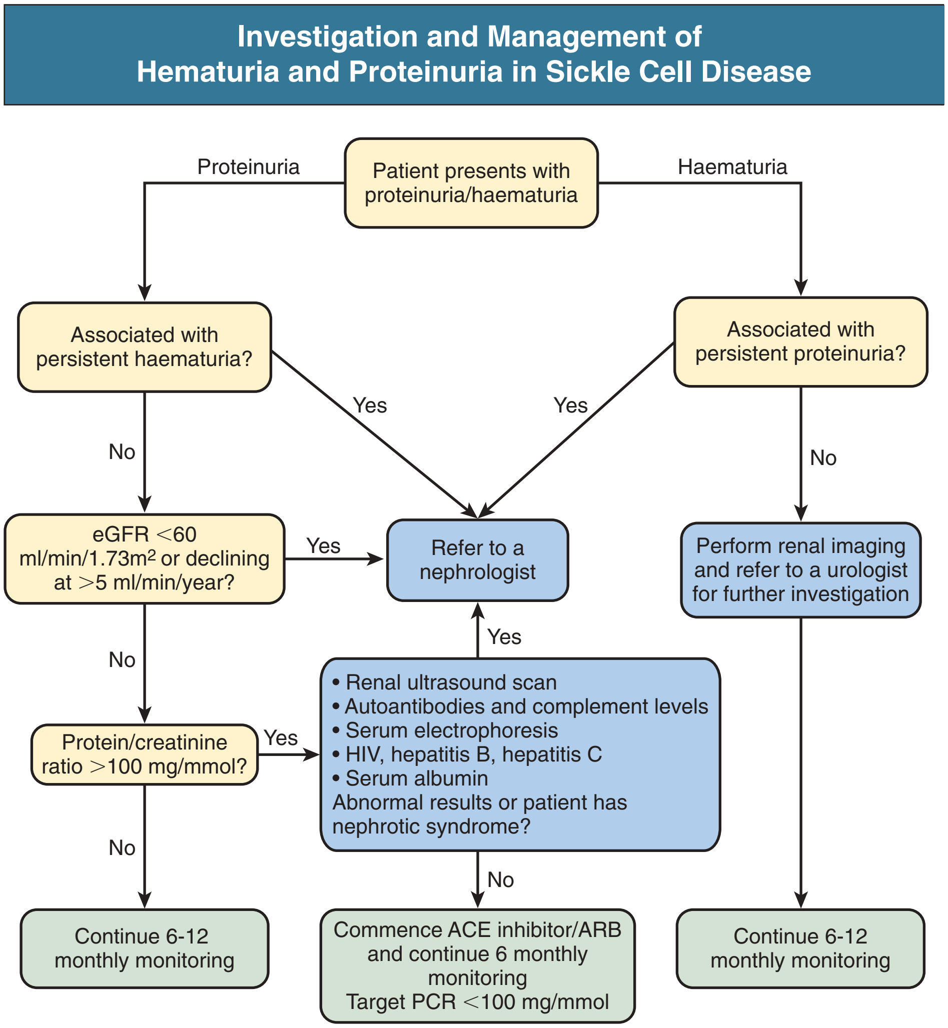

Investigation and Management of
Hematuria and Proteinuria in Sickle Cell Disease
Patient presents with proteinuria/haematuria
Proteinuria
Haematuria
Associated with persistent haematuria?
Associated with persistent proteinuria?
Yes
Yes
No
No
eGFR <60 ml/min/1.73m2 or declining at >5 ml/min/year?
Yes
Refer to a nephrologist
Perform renal imaging and refer to a urologist for further investigation
Yes
No
• Renal ultrasound scan
• Autoantibodies and complement levels
• Serum electrophoresis
• HIV, hepatitis B, hepatitis C
• Serum albumin
Abnormal results or patient has nephrotic syndrome?
Protein/creatinine ratio >100 mg/mmol?
Yes
No
No
Continue 6-12 monthly monitoring
Commence ACE inhibitor/ARB and continue 6 monthly monitoring
Target PCR <100 mg/mmol
Continue 6-12 monthly monitoring

Fig. 49.9 Investigation and management of hematuria/proteinuria in patients with sickle cell disease.

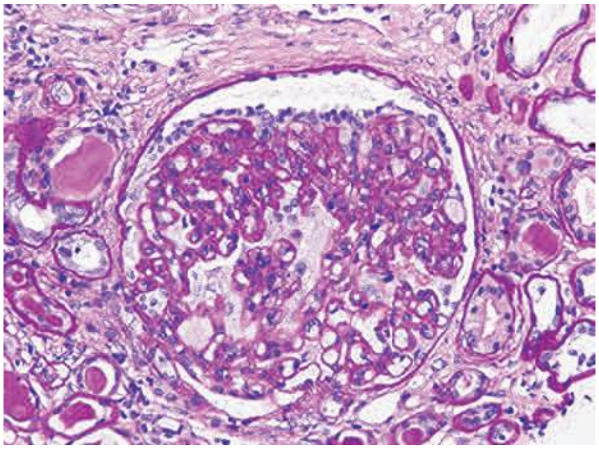


Fig. 49.10 Focal segmental glomerulosclerosis in sickle cell nephropathy. There is segmental sclerosis in the upper half of the glomerulus. (Courtesy Professor J. Weening.)

partially circumvented by taking the medication at bedtime. Patients have reported that this has the benefit of reducing nocturnal urinary frequency, presumably as a direct result of a functional drop in GFR. Patients with SCN are prone to hyperkalemia, which can be exacerbated by ACE inhibitor and ARB treatment and is often the dose-limiting factor. It is also particularly important to inform patients and other caregivers that ACE inhibitors and ARB should be temporarily stopped during acute illnesses associated with dehydration to mitigate the risk for AKI.[3]

Hydroxycarbamide and Blood Transfusion

Oral hydroxycarbamide (HC; also known as hydroxyurea) is the only licensed drug for the management of SCD. Although it has pleotropic effects, it primarily acts to increase levels of fetal Hb that serve to dilute the levels of HbS and reduce risk for polymerization. There are, however, no RCTs of HC in the management or progression of SCN in adults and only one in infants, which showed no impact on hyperfiltration, though urinary concentrating ability was improved.[47] A number of observational trials of HC in older children and adults have shown both a reduction in hyperfiltration and albuminuria.[3] Hydroxycarbamide therefore should be considered for patients with microalbuminuria/proteinuria or abnormal renal function alongside treatment with an ACE inhibitor or ARB (or in those intolerant of this treatment).

There is little evidence for the benefits of long-term RBC transfusions on prevention of renal complications of SCD. A retrospective analysis of 120 children with sickle hemoglobinopathies concluded that chronic transfusion protected against the onset of microalbuminuria when commenced before the age of 9 years. Two studies, however, found that chronic transfusion made no difference to onset of proteinuria and prolonged courses of transfusion therapy can lead to iron overload, which is particularly difficult to treat in patients with CKD.[3]

Erythropoiesis-Stimulating Agents

ESAs can be useful, particularly in combination with HC in patients who are intolerant of HC alone because of reticulocytopenia. They should be commenced when the Hb has fallen by approximately 10% to 15% from the normal baseline at steady state, though patients with CKD stages 3 to 4 often require very high doses of ESAs to have an impact on Hb levels. Although Hb targets should be lower than in the general population with CKD (80 to 100 g/dl) because of the increased risk for triggering vaso-occlusive crises, they are rarely achieved and most patients become transfusion dependent by the time they reach ESRD. However, it is often still beneficial to continue ESA therapy after the commencement of RRT because this can prolong the interval between RBC transfusion and minimize the risks for iron overload.[3] It is important to ensure that adequate iron stores are maintained to achieve maximum erythropoiesis. Intestinal losses of iron resulting from subclinical bleeding are significant in advanced CKD and absorption of oral iron is reduced. Intravenous iron supplementation may be necessary therefore in patients deficient in iron, on ESAs, and not receiving iron through regular transfusions.

Hemopoietic Stem Cell Transplantation

Hemopoietic stem cell transplantation (HSCT) is potentially curative but has largely been limited to children with severe cerebrovascular complications, ACS, or frequent VOC not responding to HC therapy. The few reports of HSCT in adults with SCN have mixed renal outcomes.[3]

RENAL REPLACEMENT THERAPY

Dialysis

Outcome data for patients with SCD on dialysis are few, but one report from the United States showed that the average age of those reaching ESRD was very young (23.1 years in patients with HbSS) and the mean time to death after was only 4 years despite regular hemodialysis.[41] Similar findings were reported in patients in Saudi Arabia; those with SCD suffered more infectious complications, lived on average for only 27 months after commencing RRT, and were significantly younger when they died (31 vs. 47.8 years) compared with patients with ESRD of other causes.[48] An examination of the U.S. Renal Data System of all patients who commenced RRT between 1992 and 1997 revealed that, not only was SCN an independent risk factor for death, but patients with SCD were much less likely to receive a kidney transplant.[49] More recently, a 5-year study of patients with SCD receiving hemodialysis in France reported that patients with SCD were much more likely to die over a 5-year period compared with a hemodialysis population with ESRD from other causes (46.3% vs. 6.4%) and were much less likely to receive a kidney transplant (26% vs. 53.5%).[50] Infectious complications and thrombosis of dialysis access was a common complication in the group with SCD.

Transplantation

Although there may be many obstacles in the path to kidney transplantation, it is probably the modality that offers the best outcome for patients with SCD requiring RRT.[51] SCN ceases to be an independent risk factor for death after transplantation. A study of the U.S. Renal Data System identified 82 patients who had received a renal transplant for SCN. The 1-year acute rejection rate and graft survival were not significantly different in these patients compared with ethnically matched controls who received grafts for other causes of renal failure, though the 3-year graft survival was lower (48% vs. 60%).[52] Although long-term graft and patient survival are not quite as good as for patients with other causes of ESRD, the prognosis for individuals with SCN is far better after transplantation with a projected 7-year survival of 67% (vs. 83% for other African Americans) when compared with a 10-year survival of only 14% for those who remain on dialysis.[22] Although outcomes after transplantation in SCD have improved over the last 20 years and the results are comparable to those in patient groups without SCD, it is not without complications. Delayed graft function and graft loss are more common than in other patient groups, and the recurrence of frequent VOC after transplantation as the Hb rises is problematic. Treatment with regular exchange transfusion aimed at keeping the HbS level below 30% may help reduce the risk for these complications.[3]

SICKLE CELL TRAIT AND CHRONIC KIDNEY DISEASE

In patients with heterozygous sickle cell trait, approximately 40% of their RBC Hb is HbS and the rest is normal HbA. In general these patients have normal Hb levels and do not have symptoms of hemolysis or vaso-occlusion. However, there have been reports of catastrophic vaso-occlusive crises and sudden death in young people with sickle cell trait under extreme adverse conditions such as excessive exercise or exposure to severe hypoxia. In addition, renal medullary carcinoma is more common in patients with SCT than SCD, though the reasons for this are unclear. Non-malignant microhematuria and macrohematuria are reported more frequently in patients with sickle cell trait than in the general population, and older patients exhibit a loss of urinary concentrating ability. Patients who co-inherit sickle cell trait and adult polycystic kidney disease (APKD) have a more rapid decline to ESRD than family members with APKD who do not carry an HbS gene. Whether having sickle cell trait alone is a risk factor for progressive CKD has been debated, but a recent study in the United States using data from five large prospective studies of African Americans concluded that patients with SCT had an odds ratio (OR) of developing incident CKD of 1.76, an OR of experiencing a decline in renal function of 1.32, and an OR of having albuminuria of 1.86 compared with noncarriers.[23,53,54]

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SELF-ASSESSMENT QUESTIONS

1. Hyperfiltration is an early sign of sickle cell nephropathy and can be detected from:
   - **A.** Infancy
   - **B.** Teenage years
   - **C.** Early adulthood
   - **D.** After the fourth decade of life
2. Albuminuria is more common in patients with:
   - **A.** HbSS disease than HbSbeta thalassemia
   - **B.** Sickle cell disease (SCD) and α-thalassemia than SCD alone
   - **C.** HbSS disease than HbSC disease
   - **D.** SCD but low levels of hemolysis
3. Inhibitors of the renin-angiotensin system:
   - **A.** Always should be avoided in patients with SCD because of the risk for hyperkalemia
   - **B.** Have been demonstrated to be effective in SCN in a large randomized, controlled trial
   - **C.** Should be stopped during acute sickle crisis
   - **D.** Always should be taken in the morning

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Congenital Anomalies of the Kidney and Urinary Tract

John O. Connolly, Melanie M. Y. Chan, Guy H. Neild

Congenital anomalies of the kidney and urinary tract (CAKUT) are a group of phenotypically diverse structural malformations characterized by defects in renal and urinary tract development. Nearly half of children who develop end-stage renal disease (ESRD) have asymmetric, irregularly shaped kidneys,[1,2] often referred to as *bilateral renal scarring* and frequently associated with lower urinary tract anomalies, including vesicoureteral reflux (VUR). These cases were previously described as reflux nephropathy or chronic pyelonephritis; but with advances in genetics and developmental biology, it is becoming clear that many are the result of primary renal malformations (renal dysplasia) often associated with congenital malformations of the ureter, bladder, and urethra. This is a change from the view that renal scarring and damage are secondary to the outflow problem and ureteral reflux. Although it is still a matter of some debate, the concept of acquired renal scarring is often wrong, and the British Association for Pediatric Nephrology now suggests that clinical distinction between reflux nephropathy and renal dysplasia is unnecessary.[1]

CLINICAL PRINCIPLES

Congenital renal tract abnormalities may present in one of the following five settings:

1. Antenatal diagnosis by fetal ultrasound screening
2. Failure to thrive in an infant or young child
3. Investigation of urinary tract infection (UTI)
4. An incidental finding in a child or adult
5. An adult with abnormal urinalysis, stones, hypertension, or renal impairment

The identification of these problems always poses the following questions:

- What is the cause?
- What is the natural history?
- Is surgical intervention required?

Such patients fall into two broad groups. First, there is a group of patients who appear to have normal bladders without outflow obstruction and normal caliber ureters when not micturating, described as having either primary VUR or primary renal dysplasia. Second, there is a group with some form of bladder outflow dysfunction that causes secondary VUR and dilated upper urinary tracts, the most common cause of which is posterior urethral valves in males.

As predicted by the Brenner hypothesis,[3] small asymmetric kidneys with reduced glomerular filtration rate (GFR) develop all the features of glomerular hyperfiltration, with the onset of progressive renal failure signaled by increasing proteinuria. This now can be significantly modified by treatment with renin-angiotensin system (RAS) blockade.[4] The details of antenatal and pediatric management of these patients are beyond the scope of this chapter, which focuses on management in adolescence and adult life.

DEVELOPMENT OF THE KIDNEY AND URINARY TRACT

The kidneys and urinary tract develop simultaneously from the cloaca and intermediate mesoderm (Fig. 50.1).[5-7] Kidney development can be divided into three phases; the pronephros, mesonephros, and metanephros. The pronephros develops 22 days after conception and forms a transient, rudimentary, and nonfunctioning system that degrades by day 28. It elongates caudally to meet the cloaca by day 26, becoming the mesonephric (Wolffian) duct, which ultimately contributes to the formation of the urinary bladder and male genital system (epididymis and caudal vas deferens). Functioning mesonephric tubules develop from the intermediate mesoderm and start to excrete urine, although most of these subsequently degenerate. By the 5th week of fetal life the ureteral bud branches from the caudal part of the mesonephric duct into the metanephric mesenchyme to become the metanephros, the precursor to the adult kidney (see Fig. 50.1A). This process is mediated by the GDNF/c-RET/Wnt-11 signaling pathway, disruptions of which can result in varying phenotypes, including renal agenesis. Reciprocal induction between the ureteral bud and the metanephric mesenchyme results in branching morphogenesis and elongation of the ureteral bud to form the collecting system and mesenchymal epithelial transformation of the metanephric mesenchyme to generate primitive nephrons (see Fig. 50.1B to D). The metanephros starts to function 6 to 10 weeks after fertilization, with nephrogenesis complete by 36 weeks. Sixty percent of nephrons are formed in the last trimester, which has important clinical implications for preterm and low-birth-weight infants, who have increased long-term risk for chronic kidney disease (CKD).[8] The extent to which reduced nephron number contributes to this increased risk relative to exposure to nephrotoxic insults and acute kidney injury as a neonate is not yet understood.

The lower urinary tract is formed from the endodermal cloaca, which is divided by the urorectal septum into ventral and dorsal parts that develop into the urogenital sinus and rectum, respectively (see Fig. 50.1E). The urogenital sinus gives rise to the early bladder, the urethra and vestibule of the vagina in females, and the posterior urethra in males. Growth of the anterior abdominal wall between the allantois and the urogenital membrane is accompanied by an increase in size and capacity of this bladder precursor. The allantois remains attached to the apex of the fetal bladder and extends into the umbilical root, although it loses its patency and persists as the urachal remnant, the

Development of the Urinary Tract

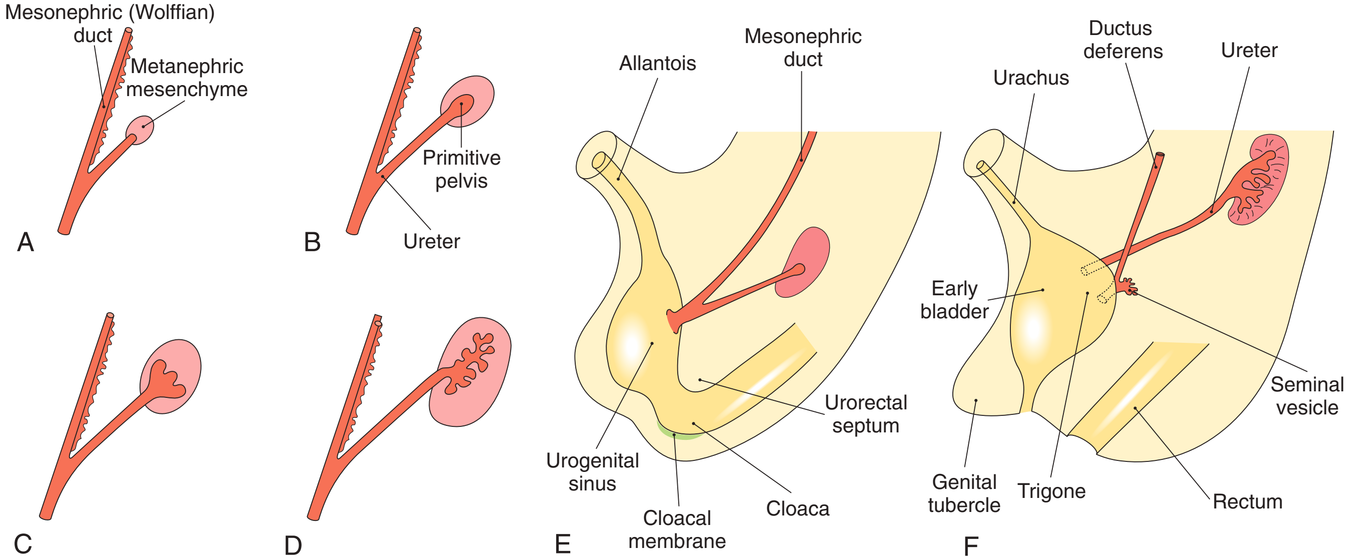


Fig. 50.1 Development of the urinary tract. Growth and development of the ureter, pelvis, and calyces are shown in parts (A) to (D). (A) The metanephric kidneys first become detectable as small areas in the mesoderm close to the aorta. The primitive epithelial ureter buds off from the mesonephric duct and makes contact with the metanephric mesenchyme. (B) Under the influence of signals from the ureter, the mesenchyme condenses and proliferates around the ureteral tip, with simultaneous elongation and branching of the ureteral tip. (C and D) A primitive pelvis appears, then branches to form the divisions of the calyces. The branching process continues, with the epithelial system eventually differentiating into the nephrons of the renal parenchyma. As the fetus grows, the kidney ascends because of the continuous rostral growth. (E) Growth and development of the cloaca during weeks 5 to 6 of gestation. (F) Growth and development of the urogenital sinus into bladder and outflow tract during weeks 8 to 9.

median umbilical ligament, which connects the bladder to the umbilicus (see Fig. 50.1F). By the seventh week, there is a separate opening of the distal mesonephric duct into the bladder at what will become the vesicoureteral opening and the area known as the *trigone*. At the same time the paramesonephric (müllerian) ducts start to regress in males and fuse in females to become the uterovaginal cord, which opens into the urogenital sinus and will go on to develop into the vagina.

PATHOGENESIS

Familial clustering, monogenic syndromes associated with urinary tract malformations, and animal models suggest a strong genetic basis for CAKUT. Ultrasound screening of asymptomatic first-degree relatives of patients with CAKUT reveals structural urinary tract malformations in up to 23%.[9] Developmental mouse models, candidate gene studies, genome-wide linkage analyses, targeted next-generation sequencing, and copy number variation analyses have all contributed to our current understanding of the genetic causes of CAKUT, with over 40 monogenic CAKUT-causing genes identified. However, the genotype-phenotype heterogeneity and incomplete penetrance seen in this disorder means that a genetic cause has been identified in less than 20% of patients.[10] Environmental and epigenetic factors are also thought to contribute to the pathogenesis of CAKUT. Pregestational maternal diabetes mellitus has been associated with an increased risk for kidney and urinary tract anomalies, with hyperglycemia shown to adversely affect nephron number in animal models.[10]

Renal development is tightly regulated by the expression of transcription factors, growth factors, and adhesion molecules.[6] Pathogenic variants of in genes encoding all classes of these molecules, affecting different stages of nephrogenesis, have been identified in patients with CAKUT (Table 50.1). Variants in the transcription factors *HNF1B* (hepatocyte nuclear factor 1B) and *PAX2* (paired box gene 2) are estimated to explain approximately 15% of CAKUT (both syndromic and isolated) and are associated with cystic kidneys and renal hypodysplasia, respectively.

- HNF1B mediates the development of the kidneys, liver, pancreas, and urinary tract. Heterozygous variants can result in renal cysts and diabetes syndrome[11] but have also been identified in a wide range of isolated CAKUT phenotypes, including renal hypodysplasia, cystic kidneys, single and horseshoe kidneys, and malformations of the collecting system.[12] *HNF1B* mutations are also associated with extrarenal phenotypes (mature-onset diabetes of the young [MODY] type 5, pancreatic hypoplasia, genital malformations, hyperuricemia, and hypomagnesemia), highlighting the utility of a molecular diagnosis in guiding screening for possible nonrenal associations.
- *PAX2* is expressed in the metanephros, in cell lineages forming nephrons, and in those destined to differentiate into the ureter, renal pelvis, and branching collecting duct system. *PAX2* homozygous mutant mice are born without kidneys, ureters, or genital tracts, suggesting its role in multiple steps of urogenital development.[13] Heterozygous variants in *PAX2* were first discovered in patients with renal-coloboma syndrome presenting with renal hypodysplasia, optic nerve abnormalities, and hearing loss, but variants have now been

TABLE 50.1 Monogenic Causes of CAKUT

Stage of Nephrogenesis	Gene	Associated Phenotype
Ureteric bud induction	*EYA1*	Branchio-oto-renal syndrome
	GATA3	HDR syndrome
	PAX2	Renal coloboma syndrome, FSGS
	RET	Renal agenesis and Hirschsprung disease
	ROBO2	VUR
	SALL1	Townes-brocks syndrome
	SIX1, SIX5	Branchio-oto-renal syndrome
Mesenchymal to epithelial transition	*WNT4*	Renal hypodysplasia, müllerian aplasia, hyperandrogenism
	SIX2	Renal hypodysplasia
Branching morphogenesis	*ACE*	All associated with renal tubular dysgenesis
	AGT	
	AGTR1	
	REN	
As yet unknown	*HNF1B*	Renal cysts and diabetes syndrome, genital malformations, hypomagnesaemia, abnormal LFTs, gout, autism
	DSTYK	CAKUT
	TNXB	VUR, joint hypermobility
	SOX17	VUR
	KAL1	Kallman syndrome
	FRAS1	Fraser syndrome
	FREM2	Fraser syndrome
	GRIP1	Fraser syndrome

FSGS, Focal segmental glomerulosclerosis; *HDR,* hypoparathyroidism, sensorineural deafness, and renal disease; *LFTs,* liver function tests; *VUR,* vesicoureteral reflux.

identified in a wide range of phenotypes, including VUR and multicystic dysplastic kidney (MCDK).[14]

- Normal development of the lower urinary tract requires urinary tract epithelial differentiation, formation of smooth muscle and neuromuscular differentiation to initiate peristalsis of urine from the fetal kidney to the bladder.[15] *UPK3A* is expressed in embryonic urothelial cells and believed to be important for urinary tract epithelial differentiation. Although *Upk3a*-null mice develop VUR,[16] variants in *UPK3A* have yet to be confirmed as pathogenic in CAKUT. Similarly, mice lacking the transcription factor Teashirt 3 *(Tshz3)* fail to develop normal smooth muscle in the ureter and have congenital hydronephrosis without anatomic obstruction[17]; however, no pathogenic variants have yet been identified in humans. Autosomal recessive mutations in heparanase 2 *(HPSE2)* have been detected in patients with urofacial syndrome, a congenital disease characterized by grimacing and incomplete bladder emptying, but have yet to be otherwise implicated in congenital bladder obstruction.[18]

Administration of angiotensin-converting enzyme (ACE) inhibitors during pregnancy in humans can cause hypotension and anuria in the baby with histologic features of renal tubular dysplasia. This phenotype is also seen in patients with recessive mutations in the genes renin *(REN)*, angiotensinogen *(AGT)*, *ACE* and angiotensin II receptor type 1 *(AGTR1)*,[19] emphasizing the importance of the RAS in maintaining an adequate systemic blood pressure (BP) and renal blood flow for normal fetal kidney development.

EPIDEMIOLOGY

CAKUT accounts for 20% to 30% of all developmental anomalies identified in the antenatal period and has a prevalence of 3 to 6 per 1000 births.[10] It usually occurs in isolation; however, 30% are associated with nonrenal abnormalities and have been described in over 200 different syndromes, including Fraser syndrome, Kallman syndrome, and branchio-oto-renal syndrome. CAKUT accounts for 40% to 50% of children with CKD and is the leading cause of ESRD in children, accounting for 42% of those requiring renal replacement therapy (RRT).[10] CAKUT also contributes significantly to the burden of renal disease in adults accounting for 4.3% of patients with ESRD, with an estimated median age for initiation of RRT of 31 years.[10] Individuals with reduced nephron mass secondary to a solitary functioning kidney appear to have a worse renal prognosis; evidence of renal injury (defined as hypertension, albuminuria, or use of renoprotective medications) is seen in up to a third of children at a mean age of 10 years, and observational data suggest that 20% to 50% of patients with a congenital solitary kidney require RRT by the age of 30.[20]

RENAL MALFORMATIONS

Congenitally abnormal kidneys may be large or small, cystic or irregular in outline, and absent or misplaced. These conditions were traditionally discussed based on findings on intravenous urography (IVU), but are now primarily investigated with computed tomography (CT), magnetic resonance imaging, and nuclear medicine imaging.

Large Kidneys

Enlarged kidneys resulting from congenital problems are usually hydronephrotic or cystic. Wilms tumor also must be considered. The differential diagnosis in adults of enlarged kidneys, both congenital and acquired, is shown in Chapter 5 (see Fig. 5.1), and the differential diagnosis of cystic kidney disease is discussed further in Chapters 44 and 45.

Irregular Kidneys

Irregularity of the renal outline may result from fetal lobulation or a "dromedary hump," neither of which has any functional implications. Much more important is the diagnosis of renal dysplasia.

Renal Dysplasia

Table 50.2 presents the range of dysplastic and other malformations of the kidney. Abnormalities of the ureter, bladder, and urethra are often associated with renal dysplasia. All types of renal dysplasia can also occur as isolated developmental anomalies. Renal dysplasia, although typically producing small, irregular kidneys, may be cystic or multicystic renal dysplasia.

Renal Hypoplasia (Oligomeganephronia)

Renal hypoplasia is defined as a congenitally small kidney (two standard deviations below the expected mean) that lacks evidence of either parenchymal maldifferentiation (renal dysplasia) or acquired disease sufficient to explain the reduced size. The term is often used loosely, and includes small kidneys with a normal number of nephrons as well as oligomeganephronia. This is a type of renal hypoplasia resulting from a congenital reduction in the number of nephrons. It results from arrested development of the metanephric blastema at 14 to 20 weeks of gestation with subsequent hypertrophy of glomeruli and tubules in the kidney. The hypertrophy and hyperfiltration result in progressive nephron injury and sclerosis later in life. Oligomeganephronia is recognized on renal biopsy by the large size of the glomeruli and tubules and the small number of glomeruli seen despite a good core of renal cortex.

TABLE 50.2 Definitions of Renal Dysplasia and Malformations

Term	Characteristics
Renal agenesis	Absence of the kidney or an identifiable metanephric structure.
Renal aplasia	Severe dysplasia with extremely small kidney, sometimes identifiable only by histologic examination.
Renal dysplasia	Abnormal differentiation of renal parenchyma with development of abnormal structures, including primitive ducts surrounded by collars of connective tissue, metaplastic cartilage, variety of nonspecific malformations such as preglomeruli of fetal type, and reduced branching of collecting ducts with cystic dilations and primitive tubules. Dysplastic kidneys often contain cysts.
Renal hypoplasia	Significantly reduced renal mass with either normal or reduced (oligomeganephronia) nephron number without evidence of maldevelopment of parenchyma.
Renal hypodysplasia	Reduced renal mass and nephron number with dysplastic features. Previously thought to be secondary to scarring from reflux or reflux nephropathy, but now increasingly considered to be primary dysplasia with associated reflux.
Renal multicystic dysplasia	Severe cystic dysplasia with extremely enlarged kidney full of cystic structures; occurs as an isolated renal lesion in response to ureteral atresia and urethral obstruction; 10% of patients have a family history.

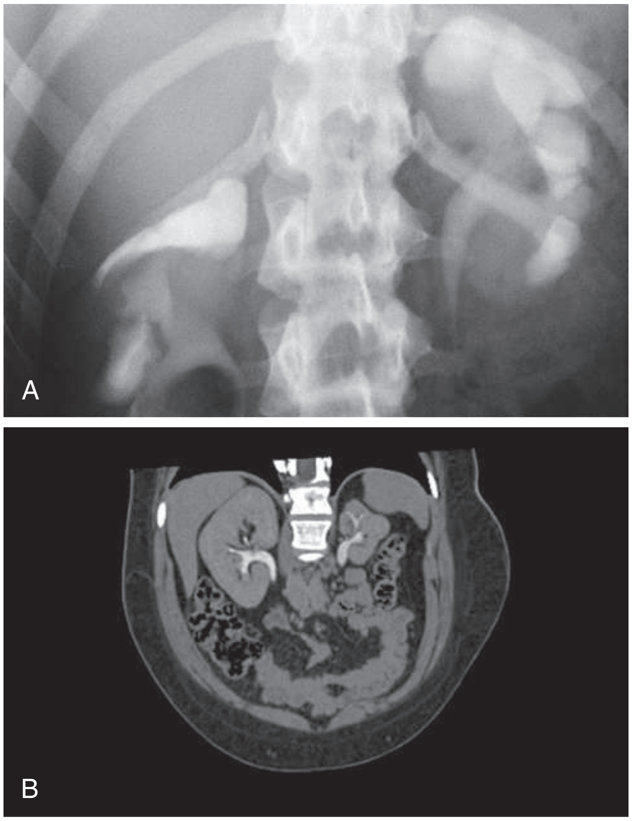


Fig. 50.2 Renal dysplasia. (A) Intravenous urogram (IVU) shows gross bilateral scarring in a 20-year-old woman who has been assessed since the age of 2 years. Progressive scarring has been observed in the absence of urinary tract infections and obstruction. This probably represents primary renal dysplasia. (B) Computed tomography IVU shows gross scarring of right kidney. (Courtesy Dr. A. Kirkham, University College Hospitals, London.)

Differential Diagnosis of Scarred Kidneys

Renal hypodysplasia versus reflux. Progressive scarring and renal failure were once considered to be caused by chronic parenchymal infection (so-called chronic pyelonephritis) and were regarded as a consequence of VUR. The 1980s, however, saw a retreat from the paradigm of the primary role of infection, and emphasis was placed on scarring as a result of reflux and the progressive nature of the glomerular lesion associated with glomerular hypertension (or hyperfiltration), so-called reflux nephropathy (see Chapter 61).[3] Current thinking is that scarring often follows from renal dysplasia, and that the reflux is a secondary or incidental feature (Fig. 50.2). Thus irregular kidneys with normal-caliber ureters are more likely to be caused by primary dysplasia, and no evidence of VUR may be seen.

Renal scarring in adults. A practical clinical problem is the differential diagnosis of scarred, asymmetric kidneys. With older patients, the differential diagnosis of scarred or "lumpy, bumpy" kidneys widens. Sometimes attributed to other diagnoses, including analgesic nephropathy, this appearance is now often designated reflux nephropathy. In older patients, multiple scarring from atheromatous arterial disease and embolization of the kidney is an increasingly important cause of renal failure. The diagnosis has historically been made by the radiologic features on IVU, but CT and magnetic resonance (MR) urography are now the gold standard, with scarring best demonstrated by technetium 99m–labeled dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy.

Absent Kidneys

Unilateral Renal Agenesis

Complete absence of one kidney occurs in 1 in 500 to 1000 births. It can be familial and is referred to as *hereditary renal aplasia* by pediatricians. It is an autosomal dominant trait with incomplete penetrance and variable expression and can be associated with bilateral renal agenesis or severe dysplasia. Pathogenic variants in the genes *RET, BMP4, ITGA8, FRAS1,* and *FREM2* have been identified.[10]

Typically, there is no ureter, and the ipsilateral half of the bladder trigone is missing. The remaining kidney is usually hypertrophic, but it may be ectopic, malrotated, or hydronephrotic with a megaureter. The more severe the dysplasia of the remaining kidney, the earlier is the presentation. The ipsilateral testis and seminal tract are usually absent, and in 10% of cases, the adrenal gland is also missing. Girls can have an absent fallopian tube or ovary or malformation of the vagina or uterus. Other associations include imperforate anus and malformations of the vertebrae and cardiovascular system. Agenesis could result from failure in formation of the metanephros or the ureteral bud; however, in association with cloacal abnormalities, the ureteral bud is more likely.

Normality of the single kidney should be confirmed by ^{99m}Tc-DMSA scintigraphy, normal isotopic GFR, and absence of proteinuria. If the remaining kidney is abnormal or GFR is less than 30 ml/min, lifelong follow-up is necessary. Ultrasound of the kidneys is recommended in all first-degree relatives of individuals with unilateral or bilateral renal agenesis.

Bilateral Renal Agenesis

Bilateral renal agenesis is lethal. It is associated with pulmonary hypoplasia and a characteristic facial appearance (Potter facies) caused by

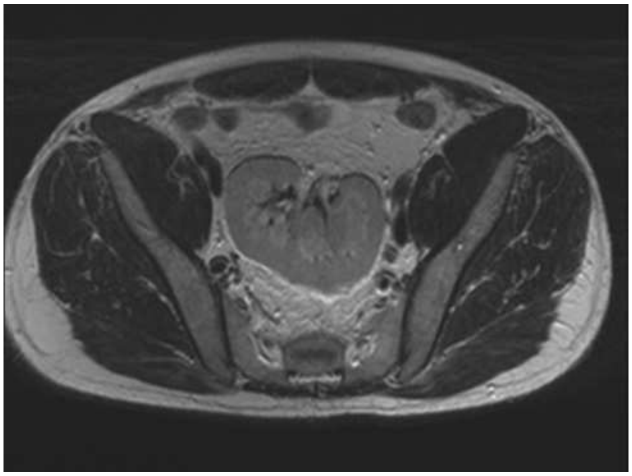


Fig. 50.3 **Single pelvic kidney.** MR scan, transverse section, shows single midline pelvic kidney. (Courtesy Dr. A. Kirkham, University College Hospitals, London.)

intrauterine compression, which is a consequence of oligohydramnios. The prevalence is about 1 in 10,000 births, with risk for occurrence in siblings of about 3%, unless there is a family history of agenesis, in which risk rises to 15% to 20%.

Misplaced Kidneys

Renal Ectopia, Malrotation, and Crossed Fused Kidneys

The starting position of the fetal kidney is deep in the pelvis. Kidneys that fail to ascend properly and therefore remain lower than usual occur in 1 in 800 births (Fig. 50.3). During development and ascent of the kidney, the renal pelvis comes to face more medially. The most common anomaly is for the pelvis to face forward. The more ectopic the kidney, the more severe is the rotation and more abnormal the appearance. In more than 90% of ectopia, there is fusion of both kidneys. This is best visualized on CT or MR urography (Fig. 50.4). Symptoms and complications, if any, are caused by associated reflux or pelviureteral junction (PUJ) obstruction.

Horseshoe Kidney

If both kidneys are low, they may join at the lower pole and are usually drained by two ureters (Fig. 50.5). The kidneys lie lower than normal, and further ascent is prevented by the root of the inferior mesenteric artery. Horseshoe kidney occurs in 1 in 400 to 1800 births and is more common in males (2:1). Patients present, if at all, with complications of reflux, obstruction, or stone formation.

Calyceal Abnormalities

Hydrocalyx and Hydrocalycosis

Dilated calyces are usually caused by obstruction. Focal dilation also can be caused by congenital infundibular stenosis, extrinsic compression from vessel or tumor, stones, or tuberculosis. If obstruction is excluded, the appearance is likely to be a congenital abnormality and can be an incidental finding. Moreover, if the GFR is normal and the divided function of the kidneys is 50:50, surgery to improve the anatomy should not be attempted.

Megacalycosis

In megacalycosis, there is bizarre dysplasia of the calyceal system with an increase in the number of calyces. There is no obstruction, and the cause is malformation of renal papillae. Megacalycosis is congenital, usually unilateral, and an incidental finding. It is much more common in males (6:1) and has been described only in Caucasians. Bilateral disease is confined to males, and segmental, unilateral disease to females, which suggests an X-linked partially recessive gene with reduced penetrance in females. There may be an associated ipsilateral segmental megaureter, usually affecting the distal third.

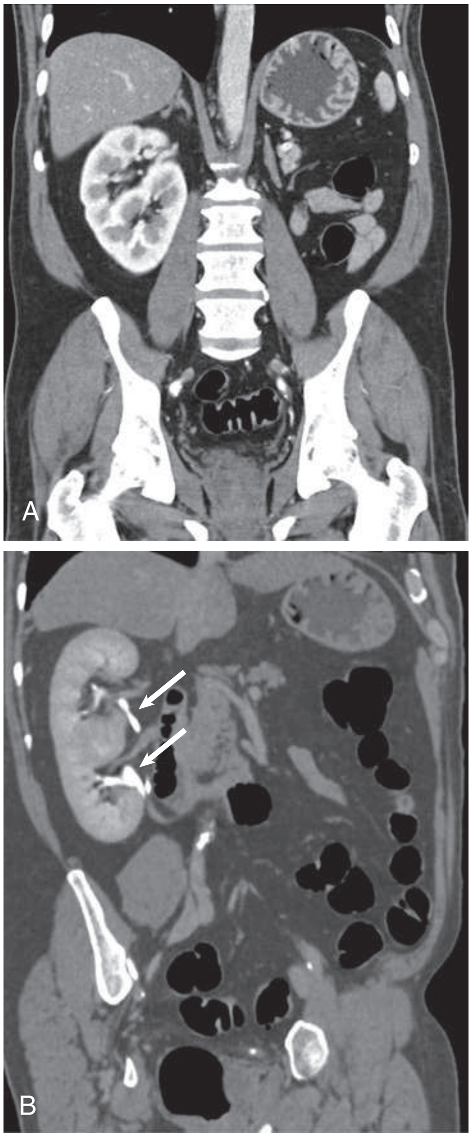


Fig. 50.4 **Crossed fused ectopia.** (A) MR scan shows fused kidneys on right. (B) There are two ureters *(arrows)*. (Courtesy Dr. A. Kirkham, University College Hospitals, London.)

Calyceal Diverticulum (Calyceal Cyst)

A calyceal diverticulum is a cavity peripheral to a minor calyx that is not a closed cyst but rather is connected to the calyx by a narrow channel (Fig. 50.6). It is usually an incidental finding and may manifest with symptoms relating to stones or infection within the cavity.

Bardet-Biedl Syndrome

Multiple calyceal clubbing and calyceal diverticula are the characteristic features of the renal dysplasia seen in Bardet-Biedl syndrome (formerly known as *Laurence-Moon-Biedl syndrome*). This autosomal recessive condition is characterized by retinitis pigmentosa, dysmorphic extremities (sometimes with polydactyly), obesity, and hypogonadism. Calyceal

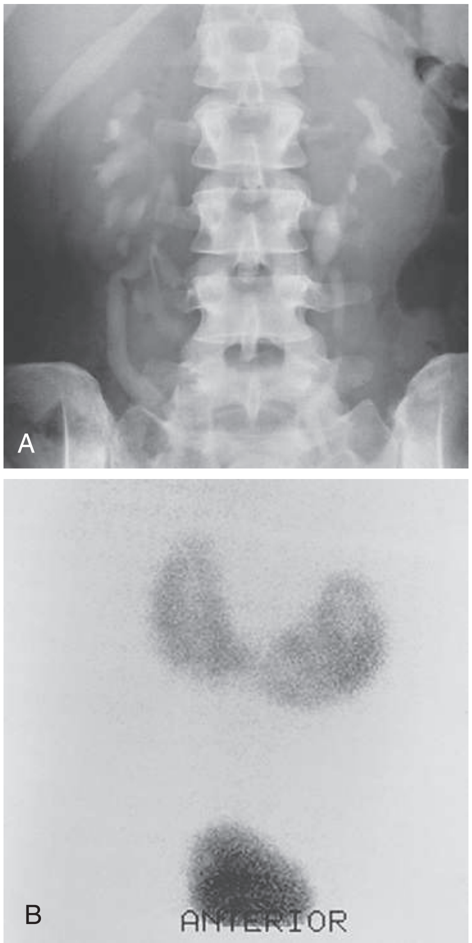

A
B
ANTERIOR

Fig. 50.5 Horseshoe kidney. (A) IVU soon after pregnancy in a 25-year-old woman shows not only the horseshoe kidney joining in the midline but also dilated ureters as a transient effect of pregnancy. (B) Dimercaptosuccinate scan shows a horseshoe kidney.

malformation is associated with parenchymal dysplasia; renal failure in early adult life is common. It has now been shown that Bardet-Biedl syndrome is caused by a defect of the basal body of ciliated cells,[21] and mutations in 20 genes coding for different proteins located in the basal body and cilia of the cell have been reported, making the syndrome an archetypal ciliopathy.

Pelviureteral Junction Obstruction

In children, PUJ obstruction is one of the most frequent causes of obstructive uropathy. The condition is usually congenital but can have an acquired mechanical basis caused by stenosis or external compression from adhesions, aberrant lower pole vessels, or kinking of the most proximal ureter. Associated abnormalities are common, and up to 50% of infants have another urologic abnormality, such as contralateral PUJ obstruction, contralateral renal dysplastic and multicystic kidney, minor degrees of VUR, and contralateral renal agenesis.

Older children can present with an abdominal mass or with flank pain, hematuria secondary to mild trauma, or UTI. Hypertension is unusual but can occur temporarily after surgical correction.

Diagnostic procedures need to differentiate between significant obstruction that requires surgical correction and congenital ectasia of the renal pelvis, in which case surgery is not indicated (Fig. 50.7). Indications for surgical intervention include impairment of renal function, pyelonephritis, renal stones, and pain. Kidneys with good function can

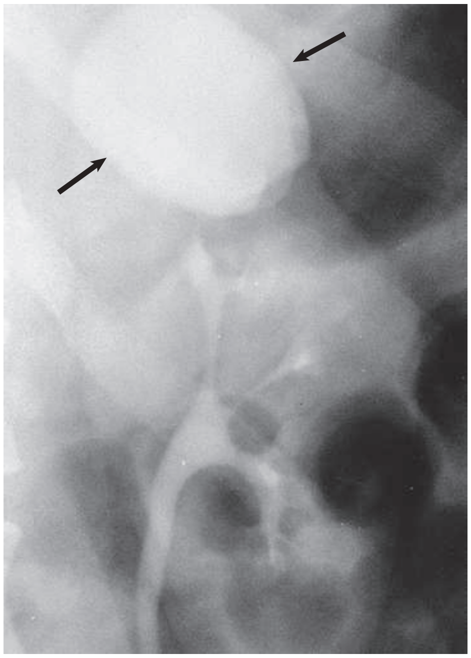


Fig. 50.6 Calyceal cyst. IVU shows an upper pole calyceal cyst filled with contrast *(arrows)*. Plain abdominal radiograph showed a group of stones in the floor of the cyst.

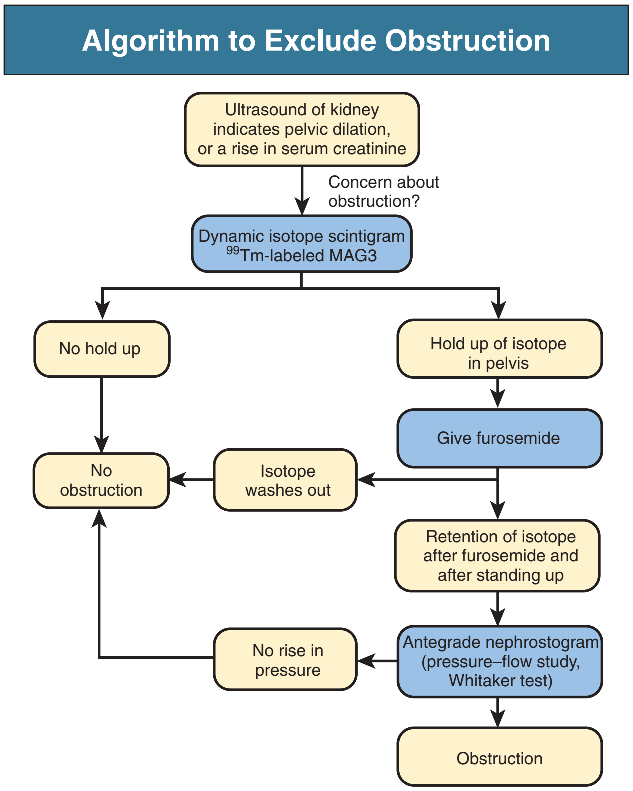

Algorithm to Exclude Obstruction
Ultrasound of kidney indicates pelvic dilation, or a rise in serum creatinine
Concern about obstruction?
Dynamic isotope scintigram ^{99}Tm-labeled MAG3
No hold up
Hold up of isotope in pelvis
Give furosemide
No obstruction
Isotope washes out
Retention of isotope after furosemide and after standing up
No rise in pressure
Antegrade nephrostogram (pressure–flow study, Whitaker test)
Obstruction

Fig. 50.7 Algorithm to exclude pelviureteral junction (PUJ) obstruction. Diagnostic path used to differentiate between significant PUJ obstruction and congenital ectasia of renal pelvis. *MAG3,* Mercaptoacetyltriglycine.

generally be left alone, and surgery is indicated only when function is clearly deteriorating.[22]

Gonadal Dysgenesis

The problems of intersex, gender identity, and micropenis are beyond the scope of this chapter and rarely encountered in adult practice. Patients will be met, however, with ESRD who are phenotypically female but are genotype XY and have mutations of *WT1* (Denys-Drash and Frasier syndromes). They have gonadal dysgenesis and must have their streak ovaries removed; otherwise, gonadoblastomas will develop.

URETERAL ABNORMALITIES

Duplex Ureters

Duplication of the ureter and the renal pelvis is a common anomaly, with an incidence of about 1 in 150 births; unilateral duplication is six times more frequent than bilateral. It is more common in girls. If duplication has been detected in a patient, the likelihood of another sibling with duplication rises to 1 in 8.

Pathogenesis

If the ureteral bud bifurcates after its origin from the mesonephric duct but arises at a normal site, an incomplete ureteral duplication with a Y ureter will develop.[7] Complete ureteral duplication occurs if there are two ureteral buds, one in the normal location and the other in a low position. The normal bud ends in a correct site on the trigone in the bladder and is nonrefluxing. The lower bud, representing the ureter of the lower pole of the kidney, ends in the bladder as a lateral orifice with a short submucosal tunnel. The lower pole ureter is therefore often associated with VUR, and scarring of the lower pole can result.

If there are two ureteral buds, one with a normal location and one with a high position, the upper ureter is incorporated into the developing bladder, ending more distally and medial to the normal one. Thus the upper pole ureter ends ectopically, and because of obstruction or dysplasia, there is often severe scarring of the upper pole moiety.

Clinical Manifestations

In most adult patients, ureteral reduplication is asymptomatic and causes no long-term problems. Children with ureteral duplication often have VUR. The spontaneous disappearance of reflux is less common in duplex ureters than in patients with a single ureter.[23] Duplex ureters are best diagnosed by CT urogram. PUJ obstruction of the ureter draining the lower pole of the kidney can occur.

Associated conditions, such as ectopic ureters and ureterocele (see later discussion), usually cause problems in early life and therefore have been addressed by adolescence. Upper pole scarring is associated with an ectopic ureter and lower pole scarring with VUR (Fig. 50.8A).

Ectopic Ureters

Ectopic ureters are almost always associated with ureteral reduplication, and 10% are bilateral. There is a female-to-male ratio of 7:1. The ectopic ureter comes from the upper pole and inserts into the bladder more distally and toward the bladder neck or opens into the upper urethra. In females, the ureter may end in the urethra, vagina, or vulva, and patients present with incontinence, UTIs, or a persistent vaginal discharge, particularly if the external sphincter is damaged, as during labor.

Ectopic ureters are rare in males and manifest as UTI. Usually, there is a single ureter associated with a dysplastic kidney, which ends in the posterior urethra, ejaculatory duct, seminal vesicle, or vas. Males are usually continent because the ureter is proximal to the external sphincter.

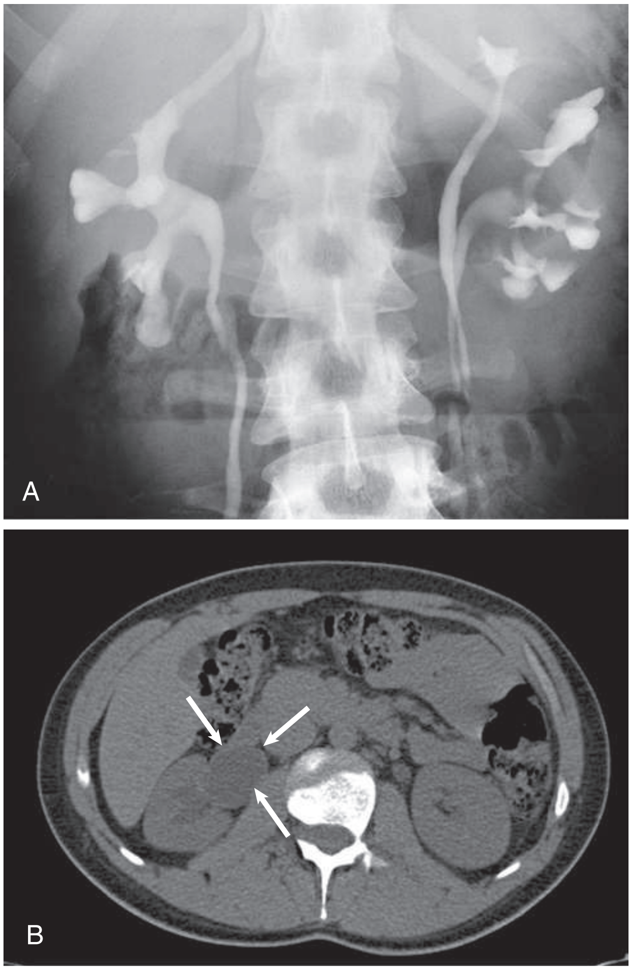


Fig. 50.8 Duplex kidney. (A) IVU shows a duplex left kidney. The lower pole is scarred and shows evidence of reflux damage. The two ureters enter the bladder separately, with the lower pole ureter in the abnormal location. The right kidney also shows features of reflux, with clubbing of the calyces and some scarring. (B) CT scan shows an isolated right-sided megaureter *(arrows).*

Ectopic ureters are best visualized by CT or MR urography. A voiding cystourethrogram shows reflux into the lower pole of the kidney in 50% of patients.

Ureterocele

Ureteroceles are cystic dilations of the terminal segments of the ureter and are caused by maldevelopment of the caudal ureter. Ureteroceles affect females more than males (4:1) and almost exclusively affect Caucasians, and 10% are bilateral. Ectopic ureters and ureters with ureteroceles frequently (80%) drain the upper pole and are often associated with dysplastic or nonfunctional renal tissue. These usually present in childhood with infection; when large, they can obstruct the bladder neck or even the contralateral ureter. In adults, ureteroceles typically manifest with stones in the lower ureter.

The treatment of simple ureteroceles is surgical excision with reimplantation of the ureter or endoscopic puncture if they subtend a well-functioning moiety. There are usually no medical sequelae.

Megaureter

Isolated dilation of the ureter does not necessarily imply obstruction. There are three broad groups of conditions with widely dilated ureters, as follows:

1. *Obstruction of the ureter itself.* This may be intrinsic (e.g., stone) or extrinsic (e.g., retroperitoneal fibrosis); it is not associated with reflux.
2. *Bladder outflow obstruction, with secondary ureteral obstruction.* Examples include a neuropathic bladder and posterior urethral valves; this may or may not be associated with reflux.
3. *A dilated but nonobstructed ureter.* This often occurs without reflux, and there can be normal renal function; this may be caused by an adynamic segment of the lower ureter (see Fig. 50.8B).

Pathogenesis

In the normal ureter, there is a characteristic helical orientation of muscle fibers. When the megaureter is secondary to bladder outflow obstruction, there is muscle hyperplasia and hypertrophy of the ureteral wall. In megaureters with no apparent cause, a variety of abnormalities of muscle orientation are described or there may be absence of muscle fibers at the proximal end of the undilated segment.

Electron microscopy shows an increase in collagen between the muscle bundles at the level of the obstructing segment. Obstruction appears to be caused by a failure of peristalsis through the distal ureteral segment.

Clinical Manifestations

Most cases of megaureter associated with obstruction present in childhood with severe infections, often complicated by septicemia. These patients have a high incidence of other congenital abnormalities. In less severe cases or with no obstruction, patients can present with abdominal pain, loin pain, hematuria, and UTI. Renal stones can form easily in the dilated systems. The exclusion of obstruction is often established only by an antegrade pressure-flow study (Whitaker test), in which a nephrostomy is placed in the renal pelvis and contrast material infused at 10 ml/min.[24]

Treatment

A definitive diagnosis must be made on whether an obstruction exists (see Fig. 50.7). The current view is that patients with asymptomatic nonobstructed disease should be managed conservatively, and most do well with this approach.

BLADDER AND OUTFLOW DISORDERS

Prune-Belly Syndrome

Prune-belly syndrome occurs in males and consists of absence of the muscles of the anterior abdominal wall, bizarre malformations of the urinary tract with gross dilation of the bladder and ureters, and bilateral undescended testes.[18,25,26] When the disorder is diagnosed early, renal outcome is related to the degree of renal dysplasia. There are incomplete forms of prune-belly syndrome (pseudo-prune). Rarely, a similar megacystis or megaureter may be seen in a male or female patient.

Pathogenesis

The incidence of prune-belly syndrome varies from 1 in 35,000 to 1 in 50,000 live births. Some familial cases have been reported demonstrating autosomal recessive inheritance; a mutation in *CHRM3*, a muscarinic acetylcholine receptor involved with parasympathetic-mediated detrusor contraction, has been identified in one family with prune-belly–like syndrome (pseudo-prune).[27] There is also evidence for a primary, localized arrest of mesenchymal development, supported by the lack of prostatic differentiation; the epithelial element in the prostate is absent or hypoplastic. Ultrastructure studies of the ureter show massive replacement of smooth muscle with fibrous and collagen tissue and the absence of nerve plexuses. An almost identical syndrome can result from fetal urethral obstruction, including urethral atresia.

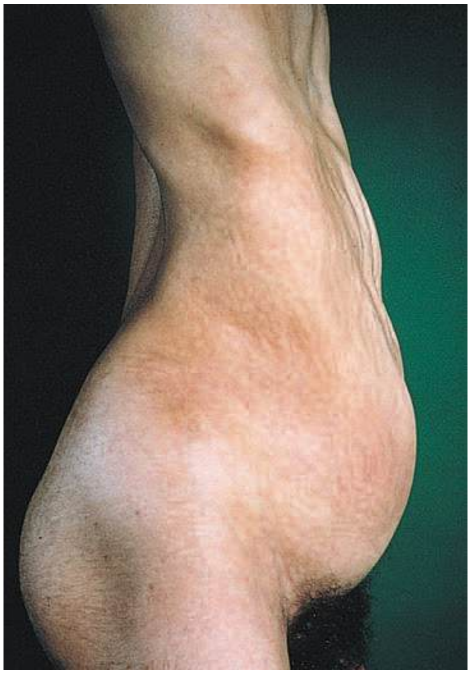


Fig. 50.9 Prune-belly syndrome. Note the lax abdominal musculature leading to a pot-bellied appearance. There is also marked thoracic cage deformity. (Courtesy Prof. C. R. J. Woodhouse, University College Hospital, London.)

Clinical Manifestations

The prognosis depends on the degree of renal dysplasia and injury. Three prune-belly groups can be distinguished. In group I (20%), complete urethral obstruction causes stillbirth or neonatal death. In group II (20%), acute, early presentation requires diversion and reconstruction. In group III (60%), good health and renal function continue despite urologic appearances.

There is complete absence or incomplete formation of the rectus abdominis and other muscles, which leads to the wrinkled abdominal wall of the prune infant (Fig. 50.9C). This gives way to a fairly smooth "pot belly" in later life (Fig. 50.10). Reconstructive surgery is not normally required. The patients grow up physically active and strong but cannot sit up directly from a supine position. Abnormalities of the thoracic cage, such as pectus excavatum, are common.

Although true outflow obstruction may be present, the gross and irregular dilation of the urinary tract characteristic of prune-belly syndrome is primarily caused by a developmental defect with a variable degree of smooth muscle aplasia leading to aperistaltic ureters (see Fig. 50.9A and B). Urodynamic studies are often difficult to interpret because of gross VUR, but typically there is a low-pressure bladder. With late manifestation, some patients have detrusor instability.

Differential Diagnosis

In severe cases of megacystis or megaureter with gross impairment of renal function (often with dysplastic kidneys), the differential diagnosis of prune-belly syndrome includes posterior urethral valves, renal dysplasia with or without multiple congenital defects, neuropathic bladder, and nephrogenic diabetes insipidus.

Natural History

Once any outflow obstruction is addressed, usually in infancy, the renal function should remain stable despite the frightening radiologic appearances. In prune-belly patients observed in our unit for up to 40 years,

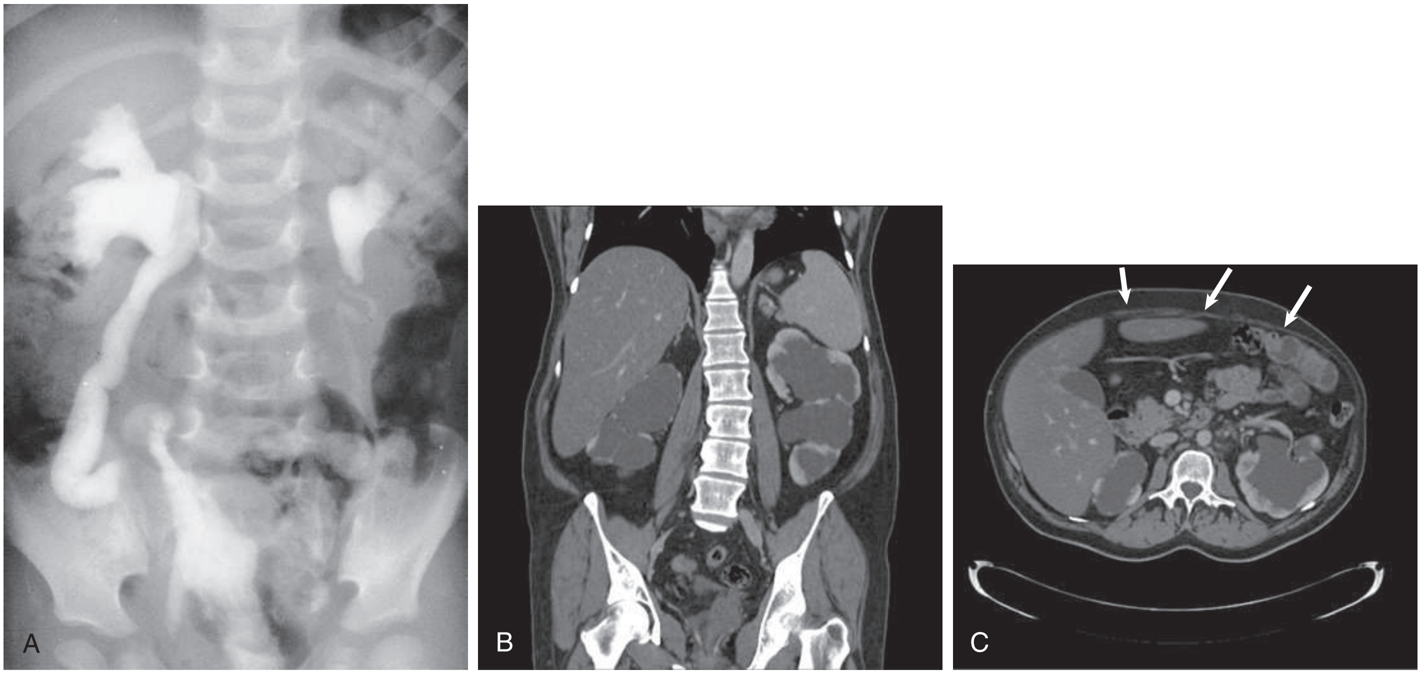


Fig. 50.10 **Prune-belly syndrome.** (A) Typical IVU appearance of a patient with prune-belly syndrome and good renal function. Often, the ureters are extremely dilated and tortuous. (B) CT urogram showing gross bilateral hydronephrosis. (C) Absence of anterior abdominal wall musculature *(arrows).*

renal deterioration and hypertension have been rare. In the small number who have progressed, recurrent infection, hypertension, and proteinuria have been warning signs of impending trouble. Renal scarring should be assessed by isotopic DMSA scintigraphy and renal function followed by serial isotopic GFR measurements. Lifelong attention to BP, UTIs, and stones is necessary.

Treatment

In all children with prune-belly syndrome, even with good renal function, a careful search for obstruction should begin with the urethra and work up to the PUJ. Often, however, no obstruction is found, and no surgery is required. In many other patients, the floppy bladder is not anatomically obstructed, but bladder emptying is improved by urethrotomy ("functional obstruction"). In infancy, there is debate about the need for reconstructive surgery. Certainly, a group of patients born with severely compromised renal function do require reconstruction after stabilization by early diversion.

The current view is that the testes should be brought down to the scrotum in infancy in the hope that earlier surgery will produce proper germ cell development and thus preserve fertility. Although men with prune-belly syndrome have azoospermia, and are by definition infertile, there are case reports of successful paternity using intracytoplasmic sperm injection.

Bladder Exstrophy (Ectopia Vesicae)

Classic exstrophy is the failure of the anterior abdominal wall and bladder to close. However, these defects range from epispadias of an otherwise normal penis to major cloacal abnormalities (Fig. 50.11). The condition occurs in 1 in 10,000 to 50,000 births. The male-to-female ratio is 2 : 1.

Pathogenesis

Failure of growth of the lower abdominal wall between the allantois and the urogenital membrane coupled with breakdown of the urogenital membrane leaves a small, open bladder plate, a low-placed umbilical root, and diastasis of the pubic bones (Fig. 50.12B). The genital tubercle is probably placed lower in these patients, and the cloacal membrane ruptures above it, leading to a penis with an open dorsal surface that is continuous with the bladder plate. A midline closure defect causes a failure of fusion of the lower anterior abdominal wall, including the symphysis pubis, lower urinary tract, and external genitalia. Reports of familial clustering and twin studies suggest an as yet undetermined genetic basis for the disorder.

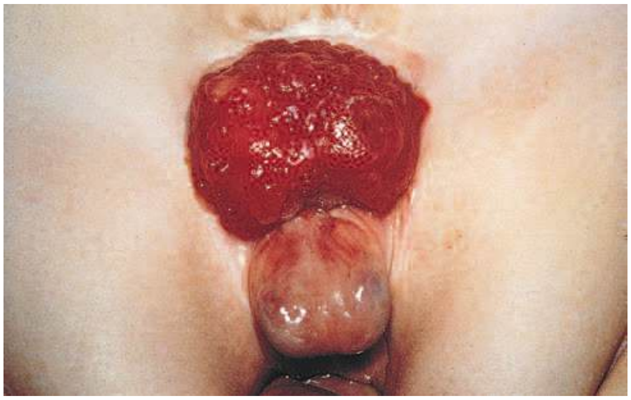


Fig. 50.11 **Bladder exstrophy.** The entire length of the penis is also open (epispadias). (Courtesy Prof. C. R. J. Woodhouse, University College Hospital, London.)

Clinical Manifestations

In severe cases, the bladder mucosa lies exposed on the lower abdominal wall, with the bladder neck and urethra laid open. The prostate and testes are normal. Most patients have normal kidneys at birth, although many reports do not record the state of the kidneys at birth. In one series, 33% had dilated ureters at presentation, but IVU was usually normal after diversion. In another series, however, one third of patients

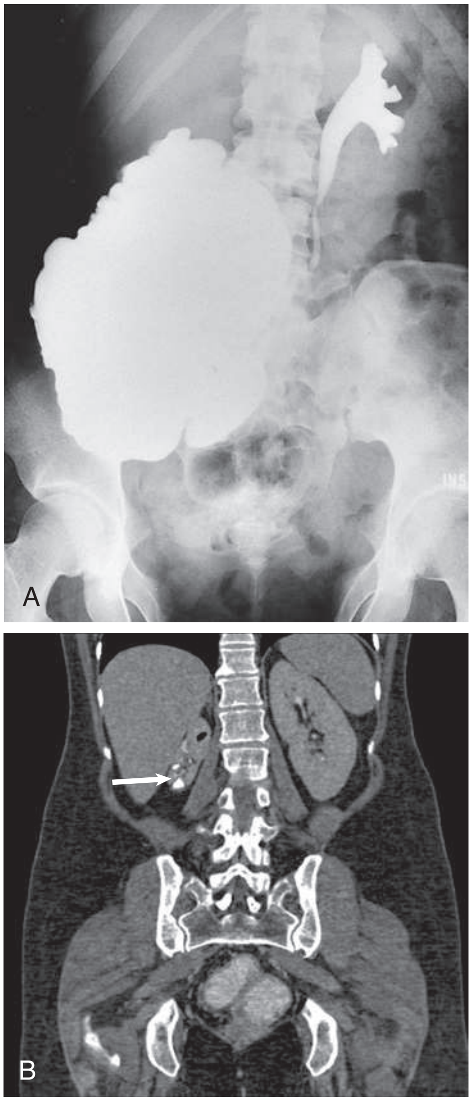


Fig. 50.12 **Cystography in bladder exstrophy.** (A) A 26-year-old woman with bladder exstrophy who has a continent Mitrofanoff system (see Fig. 52.18) with use of the colon to create a reservoir. There is reflux into the left kidney. Reflux also occurs into the right kidney, but the kidney is obscured by the full reservoir. Glomerular filtration rate is 130 ml/min. (B) MR scan of a patient with bladder exstrophy shows scarred, small left kidney with several renal calculi *(arrow)*. Note widely splayed symphysis pubis.

were said to have "unilateral renal agenesis."[28] Renal function may be preserved after the diversion, although reflux is common (see Fig. 50.12A).

Other congenital abnormalities are only rarely present. More severe cloacal abnormalities are associated with imperforate anus and high or low rectal atresia.

Natural History

Long-term renal outcome depends on the bladder. In a study with 12-year follow-up, the kidneys survive much better with a well-functioning bladder; 13% of those with a good bladder had significant renal damage compared with 82% with ileal conduits, 22% with nonrefluxing colonic conduits, and 33% with ureterosigmoidostomy.[29] Currently, the bladder is most commonly augmented (enterocystoplasty, ileocystoplasty, caecocystoplasty) or replaced by bowel (intestinal reservoir). In a study of 53 such patients monitored more than 10 years, renal function deteriorated (GFR decrease ≥20%) in only 10 patients.[30]

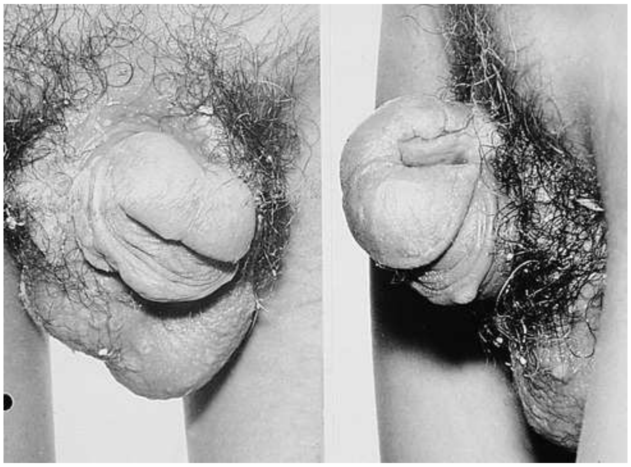


Fig. 50.13 **Epispadias.** Result of multiple surgeries to close the epispadias and to lengthen the penis. (Courtesy Prof. C. R. J. Woodhouse, University College Hospital, London.)

TABLE 50.3 **Causes of Neuropathic Bladder**

Site of Lesion	Causes
Cerebral	Cerebrovascular accident, cerebral palsy, encephalopathy, trauma, Parkinson disease, dementia
Spinal	Isolated (no other neurologic features), trauma, multiple sclerosis, compression, spina bifida, spinal dysraphism, tethered cord, sacral agenesis, sacral teratoma
Peripheral nerve	Pelvic surgery, diabetes

Treatment

When the infant is born, the three urologic treatment goals are to close the abdominal wall, establish urinary continence to preserve renal function, and reconstruct cosmetically acceptable genitalia. The aim of initial surgery is to convert the defect to a complete epispadias (Fig. 50.13). At 4 years of age, reconstruction of the bladder neck and correction of the epispadias can be performed. If the bladder is small, intestinal augmentation is required. Patients may be able to void, but many have to use catheters. Incontinence may be a long-term problem.

Neuropathic Bladder

In childhood, the most common cause of a neuropathic bladder is myelomeningocele, although with antenatal diagnosis and termination of affected pregnancies, it is becoming less common. A neuropathic bladder also may be seen without associated neurologic or other obvious causes (Table 50.3). The principal consequences are incontinence, infection, and reflux with upper tract dilation and subsequent renal failure. Early urodynamic assessment is essential (Fig. 50.14). Three different patterns of bladder behavior are seen: contractile, intermediate, and acontractile.

Contractile Behavior

An overactive detrusor (hyperreflexia) can produce some bladder emptying (incontinence). Unfortunately, 95% of patients have sphincter

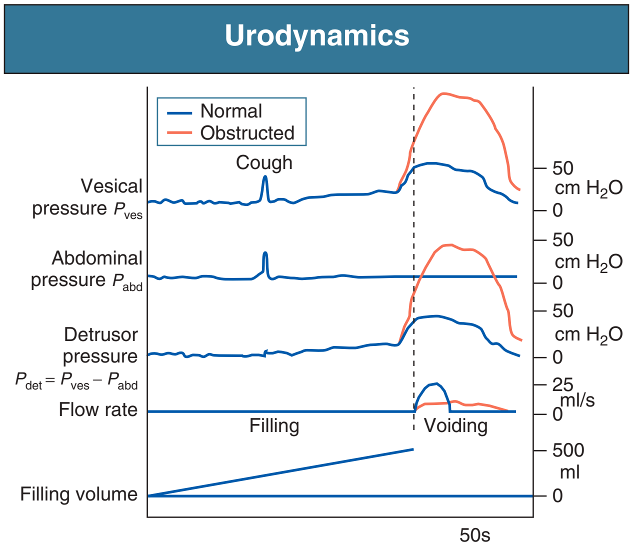


Fig. 50.14 Urodynamic assessment by cystometrography. The vesical pressure is measured simultaneously with the abdominal pressure through the rectum; the detrusor pressure is the difference. A cough is used as a marker to show that the system is working. During filling, the first desire to void is normally at a detrusor pressure of less than 10 cm H_2O. This point is noted. The voiding pressure should normally be less than 40 cm H_2O (and is lower in women). Detrusor instability is an unstable (spontaneous) contraction occurring with a detrusor pressure above 15 cm H_2O. Higher pressure can cause incontinence. In combination with radiologic imaging (videocystometrography), the following are recorded: bladder neck, closed or open; bladder pressure, end filling; voiding detrusor pressure; bladder stability; compliance; flow rate, maximum; sensation, first; volume, voided and residual. (Courtesy Prof. M. Craggs, University College London.)

dyssynergia (inability to relax the urethral sphincter), which results in no relaxation and incomplete emptying of the bladder. Patients with incomplete lesions may have some control of the distal sphincter and normal anal and sacral reflexes. Ironically, although this latter group has the least neurologic deficit, they have the worst bladder situation, generating high pressures and great risk for renal injury. The bladder becomes progressively hypertrophic, fibrotic, and poorly compliant. Botulinum toxin A can be injected into the bladder wall to improve compliance and reduce bladder pressure; it is increasingly being used in children with neuropathic bladders to delay or avoid the need for augmentation cystoplasty.

Intermediate Behavior

These patients have some detrusor activity, but not sufficient to empty the bladder. These intermediate bladders are poorly compliant, and patients have no voluntary control of their sphincters. Any rise in bladder pressure tends to cause incontinence, or the high intravesical pressures lead to renal injury.

Acontractile Behavior

About 25% of patients have no detrusor activity, and the bladder overflows when it is sufficiently full. This acontractile bladder is not usually associated with renal failure.

Myelodysplasia

Myelodysplasia refers to a group of neural tube anomalies that primarily affect the lumbar and sacral segment of the spinal cord and are the most common cause of neurogenic bladder dysfunction in children. *Spina bifida* reflects defective fusion of the posterior vertebral arches. *Meningocele* implies that the meninges extend beyond the confines of the vertebral canal with no neural elements contained inside. A *myelomeningocele* has neural tissue protruding with the meningocele. *Spinal dysraphism* (symptomatic spina bifida occulta) defines a group of structural anomalies of the caudal end of the spinal cord that do not result in an open vertebral canal but are associated with incomplete fusion of the posterior vertebral arches.

Sacral agenesis is a rare anomaly in which part or all of two or more vertebral bodies is absent. It occurs early in fetal development when there is failure of ossification of the lowest vertebral segments. The only known teratogen is insulin. Sacral agenesis occurs in 1% of children born to insulin-dependent mothers. Partial sacral agenesis can be associated with an anterior meningocele.

Pathogenesis

The neural tube normally forms as the neural folds close over and fuse, starting in the cervical region and progressing caudally. It is believed that the embryologic defect is an incomplete tubularization of the neural tube, with inadequate mesodermal invagination and subsequent arrest of vertebral arch formation.

The incidence of myelodysplasia varies from 1 to 5 in 1000 live births, but there are wide geographical variations. Monozygotic twins are often discordant for spina bifida, but siblings are at increased risk (1:10 to 1:20) and children of affected parents have a 4% chance of having a similarly affected child. Myelomeningocele accounts for more than 90% of myelodysplastic infants. Folic acid supplements taken during the first trimester reduce the incidence of myelodysplasia by 52%.

Clinical Manifestations

All causes of tethered cord can produce a variable neurologic deficit. During development, some children experience progressive neurologic disturbance with bladder dysfunction, bowel dysfunction, scoliosis, and a syndrome of pes cavus and limb growth failure.

Bladder dysfunction. Neuropathic bladder can be an isolated problem with abnormal urodynamic studies but a normal neurologic examination.

Bowel dysfunction. Bowel dysfunction is often present and needs to be treated accordingly. There may be severe constipation and overflow incontinence. The antegrade continent enterostomy procedure has been developed to improve management. The appendix is brought out to the abdominal surface, and thus the colon can be irrigated antegrade with saline.

Cognitive impairment. Patients with myelomeningocele may have some intellectual impairment, especially those who have required ventriculoperitoneal shunting for associated hydrocephalus. Manual dexterity also may be affected. These are crucial issues in long-term management.

Natural History

About 14% of patients have renal complications at birth and are at high risk in the next few years. Ultimately, about 50% will develop upper tract problems, although these can take up to 30 years to occur (Fig. 50.15). In one prospective study, renal outcome could be predicted by the urodynamic findings, with worst outcomes related to increased bladder wall thickness, degree of reflux, urethral pressures above 70 cm H_2O, and reduced bladder capacity. VUR occurs in 3% to 5% of newborns with detrusor hypertonicity or dyssynergia. Without treatment, this increases to 30% to 40% by age 5 years.[31]

Treatment

The management of the bladder depends on the urodynamic findings. In the 1970s, clean intermittent self-catheterization (CISC) was

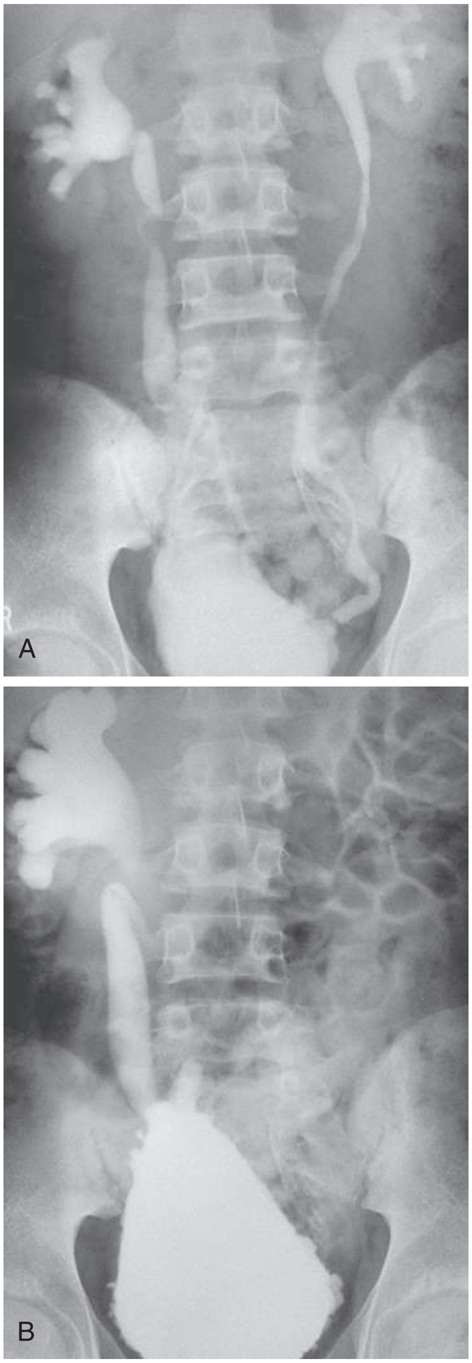


Fig. 50.15 **Sacral spina bifida with neuropathic bladder.** (A) IVU shows evidence of a previous hydronephrosis and subsequent scarring of the right kidney. The architecture of the left kidney is well preserved. (B) Micturating cystogram. The typical tapering, hypertrophied, trabeculated bladder gives the characteristic fir (pine) cone appearance. Note the gross reflux on the right side. This is probably helping to protect the left kidney by acting as a "pop-off" mechanism. This is analogous to the protection that can occur in boys with posterior urethral valves.

introduced,[32] but before that time, urinary diversion was the usual treatment. Currently, when reflux and hydroureter are present, the management is principally with CISC and antimuscarinic drugs that increase bladder compliance. With persisting symptoms related to bladder storage or hyperreflexia, bladder wall injection with botulinum toxin type A1 is offered. In the presence of deteriorating renal function or intractable symptoms, continent bladder augmentation or sometimes ileal conduit is required.[33]

Bladder Neck Obstruction

Congenital bladder neck obstruction is rare and is usually caused by a neuropathic bladder, posterior urethral valves, or an ectopic ureterocele.

Posterior Urethral Valves

Posterior urethral valves are the most common cause of severe subvesical obstruction in the male infant (but account for only 10% of neonatal hydronephrosis). As a result, bilateral hydronephrosis and megaureter occur. Obstruction is caused by a diaphragm that extends from the floor to the roof of the urethra at the apex of the prostate. Valves appear as mucosal folds in the posterior urethra below the verumontanum. There is dilation of the proximal urethra and bladder wall hypertrophy and trabeculation. Above the valves, the prostatic urethra dilates, undermining the bladder neck. The valves obstruct flow only in one direction, and therefore a catheter can be passed without difficulty.

Pathogenesis

The urethra develops in two parts: differentiation of the urogenital sinus part (posterior urethra) and tubularization of the urethral plate (anterior urethra). Early obstruction during renal development can result in severe renal dysplasia.

Clinical Manifestations

Most cases of posterior urethral valves are now detected antenatally on ultrasound as evidenced by bilateral hydronephrosis, dilated bladder, posterior urethra (keyhole sign), and, in severe cases, oligohydramnios. Infants present with a palpably distended bladder and enlarged kidneys, abnormal urine stream, or failure to thrive as a result of renal failure. At diagnosis, 30% to 52% of children also have VUR. Children with less severe disease present with poor stream, hematuria, incontinence, acute UTI, or renal failure. However, late presentation is also associated with worse outcome.[34]

Three abnormal features can help protect the kidney, reducing the high pressures generated during voiding: massive unilateral reflux, usually with ipsilateral renal dysplasia (thereby protecting the other kidney); large bladder diverticulum; and urinary extravasation, often with urinary ascites. These protective mechanisms are referred to as *pop-off mechanisms*[35] (see Fig. 50.15B). Ultrasound can show the bladder thickening, dilated system, and dilation of the posterior urethra. A specific diagnosis should be documented by videocystometrography (see Urodynamics).

Natural History

In the 1960s, 25% of children with posterior urethral valves died within the first 12 months, and 25% died later in childhood, including "renal death" (i.e., ESRD). By the late 1990s, early mortality was less than 5%, and after 15 years of follow-up, only 15% to 20% of patients had reached ESRD.[36]

The bladder may become stretched, resulting in poor emptying, or unstable, leading to poor compliance, unsuppressed detrusor contractions, and high storage pressure. Both situations are exaggerated by progressive polyuria. Such patients may have a daily urine volume of 5 liters. Urodynamic follow-up studies suggest that instability decreases with time; bladder capacity increases, but there are unsustained voiding contractions. The prognosis correlates with the nadir serum creatinine value once obstruction has been relieved. Despite adequate early treatment, CKD caused by renal dysplasia develops in many children.[33,37]

Treatment

All children have had transurethral resection of their valves in infancy. Bladder diversion should be avoided. Bladder instability and poor bladder compliance must be treated, regardless of whether symptoms result. Boys with substantial residual volumes can be managed by CISC, but compliance is often poor because of urethral discomfort or because previous urethral surgery has made the passage of catheters difficult. Compliance is a particular problem with adolescents who are continent and for whom renal failure is too abstract a concept. Continence often improves spontaneously at puberty but can be helped by imipramine. Deterioration in renal function will require further examination of urine flow rate and exclusion of urethral stricture.

Urethral Diverticulum

Urethral diverticulum usually occurs in boys and is rare. It may manifest with UTI, obstruction, or stones. The two types are anterior and posterior. The anterior type can be associated with anterior urethral valves and obstruction.

Other Congenital Causes of Bladder Outflow Obstruction

Urofacial Syndrome

Urofacial syndrome, or Ochoa syndrome, is a rare autosomal recessive disease characterized by facial grimacing when attempting to smile and failure of the urinary bladder to void completely, despite a lack of anatomic bladder outflow obstruction or overt neurologic damage. Patients present with enuresis and UTI and all the features of a neuropathic bladder together with dilated upper tracts. They are at risk for renal failure. Mutations of heparanase-2 *(HPSE2)* and leucine-rich repeats and immunoglobulin-like domains 2 *(LRIG2)* have been reported in urofacial syndrome, and the proteins they encode are expressed in the fetal bladder. It is proposed that they play an important role in the neural control of bladder function.[38] Urofacial syndrome is part of a spectrum of congenital bladder disorders that include non-neurogenic neurogenic bladder or Hinman syndrome.

GENERAL MANAGEMENT OF CONGENITAL RENAL TRACT ABNORMALITIES

The principles of management of congenital tract abnormalities are shown in Box 50.1. The most important part of the management is ensuring that the patient, family, and primary care physician know what can and must be done. First, they must understand the necessity of long-term follow-up at least annually. ESRD often occurs when a patient is lost to follow-up, often manifesting later with accelerated hypertension and rapid loss of renal function.

BOX 50.1 General Principles of Management of Congenital Renal Tract Abnormalities

- Educate and explain to encourage compliance
- Review urologic status
- Find cause of urinary tract obstruction and treat
- Control blood pressure
- Monitor renal function and proteinuria
- Treat acidosis
- Prevent bone disease
- Check for stones
- Institute clean intermittent self-catheterization for chronic urinary retention
- Maintain bladder storage pressure below 40 cm H_2O
- Maintain bladder volume below 400 ml

Clinical Evaluation

By the time the adolescent attends an adult clinic, it is assumed that the urinary tract is not obstructed and that further surgery is not required. Nevertheless, it is the responsibility of the nephrologists and urologists who care for these young people to review this aspect periodically.

Symptomatic UTI is common and must be treated promptly. Increase in frequency or severity of infections must lead to investigations to find the cause.[39] The BP must be monitored regularly and kept normal. Finally, renal function must be monitored, proteinuria assessed, and the cause of any deterioration identified. As in any renal condition, the remnant kidney function may decline inexorably, which is associated with increasing proteinuria and hypertension. As with other renal conditions, kidney function is usually stable when proteinuria is minimal or absent. Deterioration in the absence of proteinuria must alert the physician to the likelihood of obstruction or the adverse effect of a nephrotoxic drug.

The routine investigations performed to document the current situation act as a reference point for the future (Table 50.4). If the bladder empties completely with an adequate flow rate (15 ml/s), no problems should arise. If there is any doubt about the condition of the bladder, urodynamic investigations are necessary. If the clinical situation changes, further investigations are required. An increase in UTIs might suggest a stone or increase in residual urine. With an unexpected decline in renal function, obstruction again must be excluded.

The patient should keep a 24-hour urine volume diary every 6 to 12 months, recording the time of voiding and volume passed. It is best to ask patients to do this on 2 consecutive days, to determine the maximum bladder capacity and the total 24-hour urine volume. This should be done before urodynamic investigations, because results can be misleading if the bladder is not filled to capacity.

TABLE 50.4 Monitoring Patients With Congenital Renal Tract Abnormalities

Routine Investigations for Assessment of Clinical Status

Baseline Measurements	Reason for Test
Radiology	
CT KUB	Exclude stones
Ultrasound	
Ultrasound of kidneys	Baseline
Ultrasound of bladder after micturition	Assess residual volume
Urine flow rate	Ensure adequacy
Scintigraphy	
Glomerular filtration rate: ^{51}Cr-labeled EDTA	Baseline
Dynamic isotope scan: ^{99}Tc-labeled MAG3 or DTPA	Assess outflow obstruction/holdup
Static isotope scan: ^{99}Tc-labeled DMSA	Assess scarring and divided function
Biochemistry	
Urine protein-creatinine ratio	Baseline

^{51}*Cr,* Chromium-51; *CT,* computed tomography; *DMSA,* dimercaptosuccinic acid; *DTPA,* diethylenetriaminepentaacetic acid; *EDTA,* ethylenediaminetetraacetic acid; *KUB,* kidney, ureter, bladder; *MAG3,* mercaptoacetyltriglycine; ^{99}*Tc,* technetium-99.

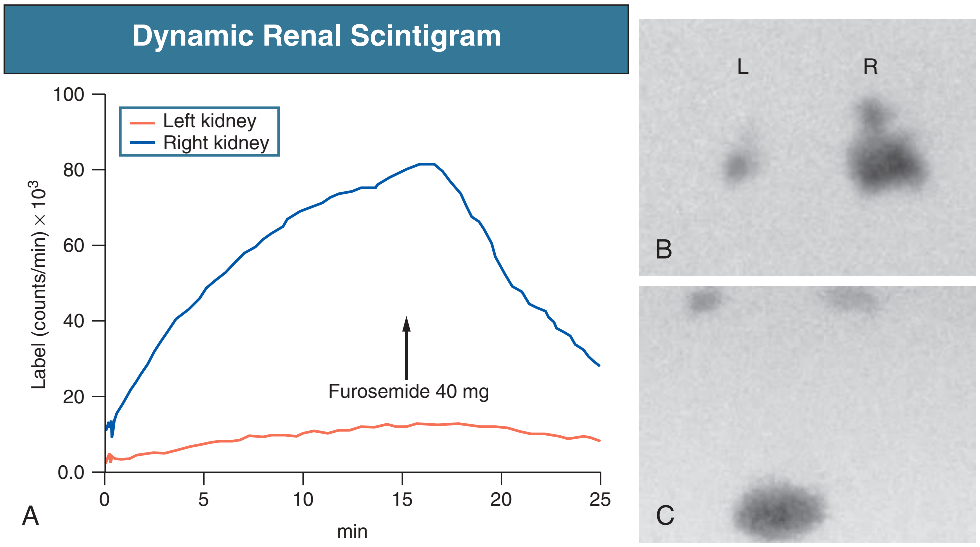


Fig. 50.16 Dynamic ^{99m}Tc-labeled MAG3 renal scintigram. (A) Time-activity curve showing accumulation of isotope in right kidney that washes out after furosemide, thus excluding significant obstruction. (B and C) Images from the same study showing holdup of isotope in dilated right *(R)* renal pelvis (B) that washes out into the bladder after furosemide (C), excluding significant obstruction.

Exclude Obstruction

Obstruction must always be excluded if there is a change in renal function. The possibility of obstruction may be raised by a routine ultrasound (see Fig. 50.7) and should be pursued with mercaptoacetyltriglycine (MAG3) scintigraphy to exclude obstruction (Fig. 50.16).

In patients with conduits, obstruction can be excluded by infusion of contrast material into the loop (loopogram) and demonstration of reflux up the ureter.

Rarely, in patients with large bladders or in transplant recipients, the kidney may become obstructed when the bladder reaches a certain volume. This can be investigated by filling the bladder by a catheter and performing ^{99m}Tc-labeled MAG3 scintigraphy, initially with the bladder full. If there is no excretion, the bladder volume can be reduced in 100-ml increments until there is flow down the ureter (Fig. 50.17).

Urodynamics

Any urodynamic investigation should start with a free urine flow rate. Provided the flow rate is normal and the bladder empties completely (leaving no residual volume on postmicturition ultrasound), it can be assumed that there is no significant bladder outflow obstruction.

Complete investigation of abnormalities of bladder and urethral function requires synchronous recordings of intravesical and intrarectal pressures taken during bladder filling and emptying (see Fig. 50.14). Combined with radiologic imaging, the study is known as *videocystometrography* (VCMG).

Surgical Correction of the Urinary Tract

A normal bladder acts as a low-pressure, good-volume urine reservoir that is continent, is sterile, and empties freely and completely. Any other form of urine reservoir aims to recreate such an environment. When this is not achieved in either a natural or a reconstructed bladder, complications such as sepsis and renal dysfunction can occur.

A variety of conduits and continent reservoirs have been developed to replace unusable bladders. Ileal conduit diversion has been most widely used for native kidneys, although deterioration in renal function frequently results from long-term complications, including urosepsis, renal calculi, and most often stenosis, leading to obstruction or reflux with ureteral dilation. There is an overall complication rate of 45%, but with a high index of suspicion and an aggressive diagnostic and therapeutic approach, many of these problems can be detected and treated early, with resultant good long-term function of native kidneys. Similar results may be obtained when renal transplantation is performed in these patients.[40] Other forms of urinary diversion that are continent and therefore more socially acceptable to patients are now widely used in general urologic practice and are being encountered in renal transplantation (Fig. 50.12A). These forms include augmented bladders draining through the urethra and augmented or intestinal bladders draining through continent stomas.

COMPLICATIONS

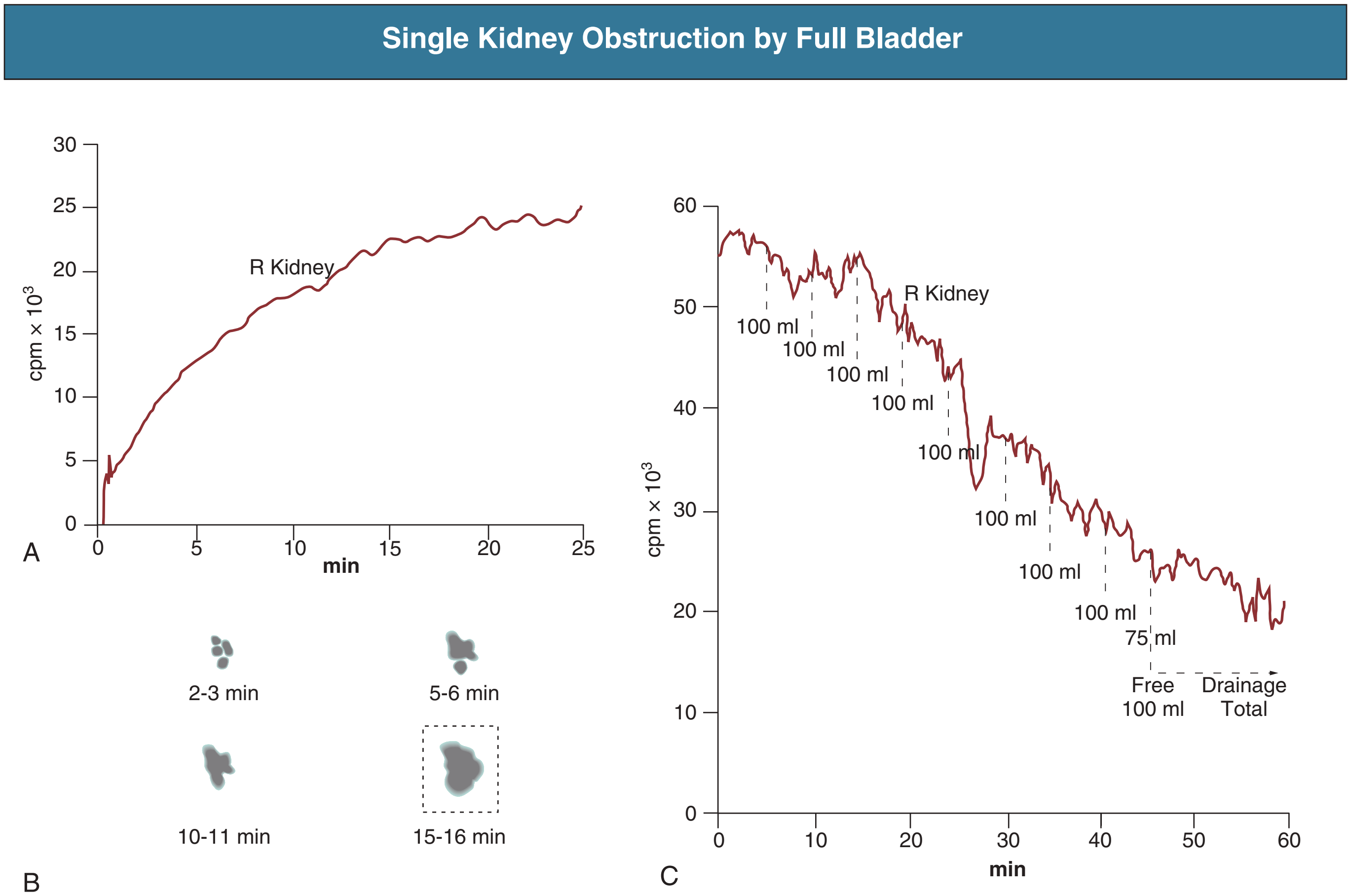
Urinary Tract Infections

Symptomatic UTIs are common.[39] Risk factors include stagnation of urine, stones, foreign bodies (stents, catheters), previous infections, and renal scarring. UTIs must be treated promptly after a urine culture specimen (midstream or catheter specimen) has been taken. Recurrent UTIs, particularly after a period of stability, must lead to further investigations to exclude stones or obstruction, including CT kidney, ureter, bladder (KUB), renal ultrasound, and postmicturition bladder ultrasound.

Asymptomatic UTIs often do not require treatment (except during pregnancy). For patients with urinary diversions, it is important to obtain a catheter specimen of urine because urine taken from a bag is invariably infected.

It is sometimes appropriate to give prophylactic antibiotics, such as trimethoprim or nitrofurantoin, to eradicate infection. Many patients think cranberry juice helps them; it reduces the incidence of *Escherichia coli* infection but will not treat a symptomatic infection. Nitrofurantoin should be avoided if GFR is below 50 ml/min, because it is renally excreted and toxic in renal failure. Quinolones should not be used for prophylaxis, if possible, because of the risk for inducing resistance. When foreign bodies such as stones remain, attempts to sterilize the urinary tract are unlikely to be successful.

If prophylactic antibiotics are no longer effective at preventing infection, it is advisable to stop all antibiotics and give the patient a supply of antibiotics to treat symptoms arising at home.



Single Kidney Obstruction by Full Bladder

Fig. 50.17 **Dynamic isotope scan (MAG3) starting with bladder full in a patient with a solitary right kidney.** (A) Rising curve of tracer accumulating in kidney and showing no excretion. *cpm,* Counts per minute. (B) Accumulation of isotope in hydronephrotic pelvis without excretion to bladder. (C) The 100-ml increments of fluid removed from bladder result in eventual free drainage of the kidney.

Glomerular Hyperfiltration

If renal function is declining with proteinuria and hypertension, glomerular hyperfiltration is likely, although all other causes of renal dysfunction must be excluded. Patients should be treated with RAS blockade with ACE inhibitors or angiotensin receptor blockers (ARBs).[4]

Proteinuria and Progressive Renal Failure

Can progression to ESRD be predicted, and does treatment with ACE inhibitors delay or prevent this?[4] We investigated this in a retrospective review of patients with scarred irregular kidneys caused by primary renal dysplasia or abnormal bladder function. All patients had at least 5 years of follow-up, and when ACE inhibitors were started, estimated GFR (eGFR) was below 60 ml/min/1.73 m^2 (mean, 41 ml/min), with mean proteinuria of 1.7 g/24 h. ESRD developed in 46% of patients but in none with proteinuria less than 0.5 g/24 h and in only 2 of 18 patients with eGFR above 50 ml/min. The renal outcome of the two groups was similar whether there was primary renal dysplasia or abnormal bladder function. There was a watershed GFR of 40 to 50 ml/min, above which ACE inhibitor treatment improved renal outcome.[4] The similar outcome of the two groups indicates that progressive renal failure in young men born with abnormal bladders is caused by intrinsic renal pathophysiologic processes, in contrast to the view that it is a result of poor bladder function.

Hypertension

Hypertension is common in the presence of scarred kidneys, but it is usually controlled easily with one or two drugs. Patients in whom CKD is secondary to obstruction tend to have volume contraction and therefore often have normal BP or only mild hypertension. ACE inhibitors or ARBs are preferred for patients with proteinuria and progressive renal failure. Diuretics should not be used if the patient is volume-contracted.

Stones

Stones that form in the presence of infected urine are typically magnesium ammonium phosphate (struvite) or calcium phosphate (hydroxyl apatite, carbonate apatite, calcium hydrogen phosphate [brushite], tricalcium phosphate [whitlockite]). These salts are poorly soluble in alkaline urine. In 90% of patients, the infecting organism is *Proteus* spp.,[41] but other urea-splitting organisms (including some staphylococci and *Pseudomonas* spp.) also generate ammonia.

Stones, usually calcium phosphate, are common in conduits because of the alkaline environment and occur in 5% to 30% of ileal conduits. Stones must be suspected if UTIs recur or become more frequent, if renal function suddenly deteriorates, or if there is an unexplained sterile pyuria.

Tubular Dysfunction

Patients whose renal failure is secondary to obstruction have significant tubular injury. This may cause problems, in particular with urinary concentration, acidification, and sodium reabsorption.

Polyuria

Nocturia is one of the most significant symptoms in the assessment of patients in whom obstruction or tubular dysfunction is suspected. Overfilling of the bladder or reservoir is an important cause of intermittent upper tract obstruction and deteriorating function. The 24-hour urine volume diary is a simple way to assess this.

Salt Depletion

Patients with tubular damage may have a salt-losing tendency. Patients typically have a cool periphery and constricted hand veins with no peripheral edema. Increasing salt intake can relieve cramps, improve renal function, and reduce hyperuricemia, but at the cost of increasing BP. With patients who are salt depleted, it is important to give sodium chloride because it is the chloride anion that is deficient and responsible for the reduction in circulating volume.

Acidosis

There is often a metabolic acidosis disproportionate to the degree of renal impairment. This is secondary both to a proximal tubular failure of bicarbonate reabsorption and a distal tubular failure to secrete hydrogen ions. It is our practice to give sufficient sodium bicarbonate to correct the serum bicarbonate into the normal range.

Bone Disease

In addition to the typical bone disease of progressive CKD, acidosis contributes significantly to osteomalacia. Growing children are particularly vulnerable to osteomalacia, and great care must be taken to correct acidosis and actively manage bone disease.

Urinary Diversions

Ureterosigmoidostomy

Fortunately, it is now rare to meet a patient who has a ureterosigmoidostomy, which was widely used as a technique for urinary diversion until the 1970s. The ureters were anastomosed directly into the sigmoid colon with no disruption of bowel continuity. This technique was most often used in patients with bladder exstrophy. Although patients start with normal renal function, there is frequently deterioration in function. In one series of 25 patients, significant renal damage occurred in 50%. Stones, infection, and ureteral strictures are common, and patients remain at risk for colonic carcinoma, with a 10% incidence of carcinoma at 20-year follow-up. However, this diversion is probably best known for the hyperchloremic, hypokalemic acidosis that occurs. Once the urine is in contact with the colonic mucosa, the urinary sodium exchanges for potassium and the chloride for bicarbonate, and large quantities of ammonium ions are produced by the action of the fecal bacteria on urinary ammonia. Ammonium ions are absorbed both with chloride and in exchange for sodium. The severe acidosis is caused by ammonium ion retention and stool loss of bicarbonate. Patients are managed with large doses of oral sodium bicarbonate, which is titrated to keep plasma bicarbonate in the normal range (>22 mmol/l).

Ileal Conduits

Unlike the sigmoidostomy, in which urine enters a reservoir, the ileal conduit is free flowing, with rapid urinary transit and no reservoir. Therefore metabolic complications are much less common, although again the bowel can exchange sodium and chloride for potassium and bicarbonate.[42,43] A number of other complications of ileal and colonic conduits can lead to progressive loss of renal function (Box 50.2).

BOX 50.2 Long-Term Complications of Urinary Diversion

- Pyelonephritis and scarring
- Calculi
- Obstruction
- Strictures
- Bladder mucus causing obstruction
- Cancer at intestinal-ureteral anastomosis
- Hyperchloremic acidosis
- Delayed linear growth in children
- Effects of intestinal loss from gastrointestinal tract (e.g., vitamin B_{12} deficiency)
- Complications related to abnormal pelvic anatomy (e.g., in pregnancy)
- Psychological and body image problems

Enterocystoplasty and Intestinal Urinary Reservoirs

In 53 patients with bladder exstrophy monitored more than 10 years with serial isotopic GFRs, renal function deteriorated (GFR decrease ≥20%) in only 10 (~20%).[30] Loss of function was caused principally by chronic urinary retention with or without infection in poorly compliant patients who did not catheterize regularly. Patients also must be checked regularly to ensure that anastomotic stenoses and high-pressure reservoirs do not occur. Stones are common and occur in up to 52% of patients.[44]

END-STAGE RENAL DISEASE AND TRANSPLANTATION

This group of patients presents two important problems if they develop ESRD. First, because of multiple abdominal surgeries, continuous ambulatory peritoneal dialysis (CAPD) is often impossible, although if there is any doubt and the patient is interested, CAPD should be attempted. Second, the bladder and urinary reservoir must be suitable for renal transplantation. If a bladder has just destroyed two good native kidneys, it is likely to do the same to a transplant kidney. Most patients will be maintained on hemodialysis, but it is frequently difficult to establish a good arteriovenous fistula because of chronic hypovolemia and venoconstriction. Patients receiving dialysis often continue to pass 1 liter or more of urine per 24 hours, and they also remain at risk for serious UTI and pyelonephritis.

Pretransplantation Assessment

Transplantation into the abnormal lower urinary tract requires careful evaluation and follow-up. Thorough preoperative assessment of bladder function is essential (Fig. 50.18). Patients considered to have normal bladders require at least postmicturition bladder ultrasound and urinary flow rate.

All patients with abnormal bladders or reservoir must have a full videocystometrogram to ensure that the bladder reservoir is large and adequately compliant. If the bladder is small or has not been used for some time, bladder cycling, which involves periodically filling and distending the bladder through a suprapubic catheter, may be required. A urodynamic study before transplantation indicated that poor bladder function, as shown by small bladder volumes, is a predictor of graft loss even in patients with previously normal bladder function.[45]

Intermittent self-catheterization is safe and effective for a patient with a poor flow rate who fails to empty the bladder. This, however, is possible only with a normal urethra and a cooperative patient. When

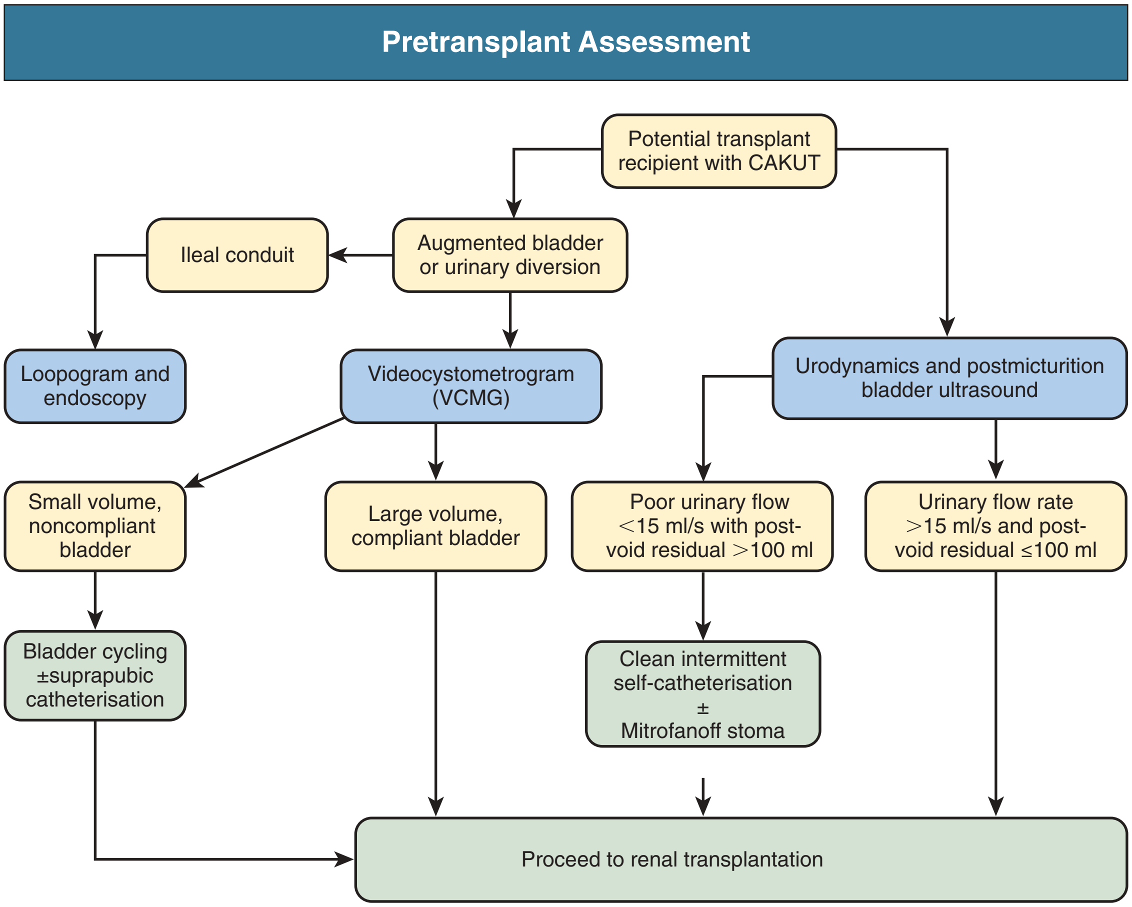

Pretransplant Assessment
Potential transplant recipient with CAKUT
Augmented bladder or urinary diversion
Ileal conduit
Loopogram and endoscopy
Videocystometrogram (VCMG)
Urodynamics and postmicturition bladder ultrasound
Small volume, noncompliant bladder
Large volume, compliant bladder
Poor urinary flow <15 ml/s with post-void residual >100 ml
Urinary flow rate >15 ml/s and post-void residual ≤100 ml
Bladder cycling ±suprapubic catheterisation
Clean intermittent self-catheterisation ± Mitrofanoff stoma
Proceed to renal transplantation

Fig. 50.18 Pretransplant assessment of patients with an abnormal lower urinary tract.

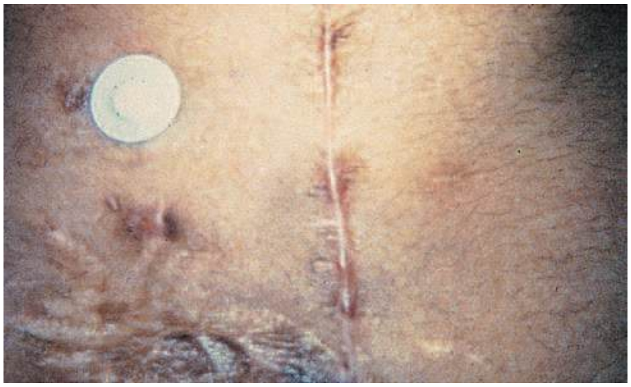


Fig. 50.19 Mitrofanoff stoma. This patient was born with bladder exstrophy and has had a successful renal transplant for 22 years. Her kidney is plumbed into a colonic reservoir, and she catheterizes herself through a continent Mitrofanoff stoma, which is covered by a small plaster in the photograph.

this is not practical, we attempt to establish suprapubic drainage through a continence stoma, such as a Mitrofanoff stoma (Fig. 50.19). If a conduit is to be used, a loopogram and endoscopy must ensure it is in good condition. We do not remove native kidneys unless they are causing recurrent UTI.

Transplant Outcome

In an 18-year experience, we performed transplantation in 65 patients with abnormal bladders, with a total of 72 renal transplants.[46] In 52 cases the ureters were transplanted into unaugmented bladders; in 20 cases, there was some form of augmentation or diversion. Results were compared with 59 transplants in 55 patients who had renal failure from renal dysplasia and whose bladder function was considered normal. There was no difference in actuarial graft survival in the two groups at 10 years (abnormal bladders, 66%; normal bladders, 61%), although longer follow-up showed an advantage for normal bladders, with a kidney half-life of 29 to 33 years compared with 15 years for the abnormal bladders. UTIs were relatively common in all patients but produced problems only in patients with abnormal bladders.

Management

A double-J ureteral stent should be placed routinely at the time of transplant surgery. Adequacy of urinary drainage must be assessed frequently, even when graft function seems to be good. Two months after transplantation, when the ureteral stent has been removed, we recommend performing a baseline postmicturition ultrasound of the transplant kidney and bladder, in addition to a dynamic ^{99m}Tc-MAG3 scintigraphy scan in patients with abnormal bladders.

Ultrasound and ^{99m}Tc-MAG3 scintigraphy are then repeated when clinically indicated. The protein-to-creatinine ratio is measured on a random urine sample at every outpatient visit. If there is renal dysfunction, imaging tests are repeated, and if there is a change from baseline, renal biopsy is performed to exclude an immunologic cause of graft dysfunction. If there is a documented deterioration in renal function in the absence of rejection or calcineurin inhibitor toxicity, the DMSA scan is repeated (to see whether new scarring has occurred) and the bladder reassessed urodynamically.[47]

Complications

UTIs must be detected and treated early, and recurrent UTIs may require long courses of antibiotics or even removal of the native tracts. Symptomatic UTIs are common in the first 3 months after transplantation (63%); fever and systemic symptoms occur in 39% of patients with normal bladders and 59% with abnormal bladders. UTI directly contributes to graft loss in patients with abnormal bladders but causes no consequences in those with normal bladders.[39] Prophylactic administration of antibiotics for the first 6 months reduces significantly the subsequent incidence of UTI. When UTIs recur, a cause must be sought with ultrasound of the kidneys and bladder. A CT KUB can be done to look for stones in native or transplant kidneys and the bladder or urinary diversion. If there is a residual volume after double micturition, the patient must be instructed to perform CISC. With these measures, good results are obtained.

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SELF-ASSESSMENT QUESTIONS

1. Which statement about unilateral renal agenesis is *false*?
   - **A.** It occurs in 1 in 10,000 births.
   - **B.** Typically, there is no ureter.
   - **C.** The fallopian tube may be absent in girls.
   - **D.** Renal ultrasound is recommended in first-degree relatives.
   - **E.** It can be part of a syndrome.
2. Which statement about prune-belly syndrome is *false*?
   - **A.** It usually occurs in males only.
   - **B.** The muscles of the anterior abdominal wall are absent.
   - **C.** Gross dilation of the bladder occurs, with normal ureters.
   - **D.** Males have bilateral undescended testes.
   - **E.** Patients are usually infertile.
3. Ureterosigmoidostomy may lead to all the following *except:*
   - **A.** Hyperchloremia
   - **B.** Hyperkalemia
   - **C.** Acidosis
   - **D.** Ammonium ion retention
   - **E.** Colonic carcinoma
4. Which of the following statements about posterior urethral valves is *false*?
   - **A.** They are usually detected antenatally.
   - **B.** Patients require urethral surgery.
   - **C.** Progressive renal failure is associated with proteinuria.
   - **D.** Posterior urethral valves may be confused with urofacial (Ochoa) syndrome.
   - **E.** Posterior urethral valves occur in males and females.
5. Which of the following statements about UTI in an augmented bladder is *false*?
   - **A.** The patient with UTI does not require treatment when asymptomatic.
   - **B.** UTI often causes calcium oxalate stones.
   - **C.** Recurrent UTIs should be investigated with ultrasound, including assessment of postvoid residual volume.
   - **D.** UTI may indicate poor bladder emptying.

51

Urinary Tract Infections in Adults

Thomas Hooton

DEFINITION

Urinary tract infection (UTI) in adults can be categorized into five groups: women with acute uncomplicated cystitis, women with recurrent cystitis, women with acute uncomplicated pyelonephritis, complicated UTI, and asymptomatic bacteriuria (Box 51.1).[1] Chapter 42 discusses UTI in pregnancy, and Chapter 61 describes vesicoureteral reflux (VUR) in children.

Complicated UTI is defined as UTI that increases the risk for serious complications or treatment failure. Patients with various conditions, such as those presented in Box 51.1, are at increased risk for complicated UTI. Complicated UTIs may require different pretreatment and post-treatment evaluation and type and duration of antimicrobial treatment than for uncomplicated UTI. On occasion, complicated UTIs are diagnosed only after a patient has a poor response to treatment.

EPIDEMIOLOGY

Acute uncomplicated UTIs are extremely common, with several million episodes of acute cystitis and at least 250,000 episodes of acute pyelonephritis occurring annually in the United States. The incidence of cystitis in sexually active young women is about 0.5 per 1 person-year.[2] Acute uncomplicated cystitis may recur in 27% to 44% of healthy women, even though they have a normal urinary tract.[3] The incidence of pyelonephritis in young women is about 3 per 1000 person-years.[4] The self-reported incidence of symptomatic UTI in postmenopausal women is about 10% per year.[5] The incidence of symptomatic UTI in adult men younger than 50 years is much lower than in women, ranging from 5 to 8 per 10,000 men annually.

Complicated UTIs occur in a wide range of settings (see Box 51.1). Nosocomial UTIs are a common type of complicated UTI and occur in 5% of admissions in the university tertiary care hospital setting; catheter-associated infections account for most of the infections. Catheter-associated bacteriuria is the most common source of gram-negative bacteremia in hospitalized patients.[6]

Asymptomatic bacteriuria is defined as the presence of two separate consecutive clean-voided urine specimens, both with 10^5 or more colony-forming units per milliliter (cfu/ml) of the same uropathogen in the absence of symptoms referable to the urinary tract.[7] Asymptomatic bacteriuria is found in about 5% of young adult women,[8] but rarely in men younger than 50. The prevalence increases up to 16% of ambulatory women and 19% of ambulatory men older than 70 and up to 50% of elderly women and 40% of elderly men who are institutionalized.[7] Asymptomatic bacteriuria may be persistent or transient and recurrent, and many patients have had previous symptomatic infection or develop symptomatic UTI soon after having asymptomatic bacteriuria. Asymptomatic bacteriuria is generally benign, although it may lead to serious complications in some clinical settings.

PATHOGENESIS

Uncomplicated Infection

Most uncomplicated UTIs in healthy women result when uropathogens (typically *Escherichia coli*) present in the rectal flora enter the bladder through the urethra after an interim phase of periurethral and distal urethral colonization. Colonizing uropathogens also may come from a sex partner's vagina, rectum, or penis. Hematogenous seeding of the urinary tract by potential uropathogens such as *Staphylococcus aureus* is the source of some UTIs, but this is more likely to occur in the setting of persistent bloodstream infection or urinary tract obstruction.

Many host behavioral, genetic, and biologic factors predispose healthy young women to uncomplicated UTI (Table 51.1).[2,9] Factors protecting individuals from UTI include the host's immune response; maintenance of normal vaginal flora, which protects against colonization with uropathogens; and removal of bladder bacteriuria by micturition.[10] Uropathogenic *E. coli,* the predominant pathogens in uncomplicated UTI, are a specific subset of extraintestinal pathogenic *E. coli* that have the potential for enhanced virulence[11] (see Table 51.1). P-fimbriated strains of *E. coli* are associated with acute uncomplicated pyelonephritis, and their adherence properties may stimulate epithelial and other cells to produce pro-inflammatory factors that stimulate the inflammatory response.[12] Other virulence determinants include adherence factors (type 1, S, and Dr fimbriae), toxins (hemolysin), immune evasion, iron acquisition (aerobactin), flagella, and serum resistance.[11,13] Bacterial virulence determinants associated with cystitis and asymptomatic bacteriuria have been less well characterized. Triggers for development of urinary symptoms are not entirely clear.

Factors affecting the large difference in UTI prevalence between men and women include the greater distance between the anus and the urethral meatus, the drier environment surrounding the male urethra, and the greater length of the male urethra. Risk factors associated with UTIs in healthy men include intercourse with an infected female partner, anal intercourse, and lack of circumcision, although these factors often are not present in men with UTI. Most uropathogenic strains infecting young men are highly virulent, suggesting that the urinary tract in healthy men is relatively resistant to infection.

TABLE 51.1 Factors Modulating Risk for Acute Uncomplicated Urinary Tract Infections in Women

Host Determinants	Uropathogen Determinants
Behavioral: Sexual intercourse, use of spermicidal products, recent antimicrobial use, suboptimal voiding habits	*Escherichia coli* virulence determinants: P, S, Dr, and type 1 fimbriae; hemolysin; aerobactin; serum resistance
Genetic: Innate and adaptive immune response, enhanced epithelial cell adherence, antibacterial factors in urine and bladder mucosa, nonsecretor of ABO blood group antigens, P1 blood group phenotype, reduced *CXCR1* expression, previous history of recurrent cystitis	
Biologic: Estrogen deficiency in postmenopausal women, glycosuria (including from SGLT-1 inhibitors)	

TABLE 51.2 Bacterial Etiology of Urinary Tract Infections

	URINARY TRACT INFECTION (%)	
Organisms	**Uncomplicated**	**Complicated**
Gram-Negative Organisms		
Escherichia coli	70-95	21-54
Proteus mirabilis	1-2	1-10
Klebsiella spp.	1-2	2-17
Citrobacter spp.	<1	5
Enterobacter spp.	<1	2-10
Pseudomonas aeruginosa	<1	2-19
Other	<1	6-20
Gram-Positive Organisms		
Coagulase-negative staphylococci (*Staphylococcus saprophyticus*)	5-20 or more	1-4
Enterococci	1-2	1-23
Group B streptococci	<1	1-4
Staphylococcus aureus	<1	1-2
Other	<1	2

(Data for complicating factors from Nicolle LE. A practical guide to the management of complicated urinary tract infection. *Drugs.* 1997;53:583-592.)

BOX 51.1 Categories of Urinary Tract Infection in Adults

- Acute uncomplicated cystitis in healthy women
- Recurrent acute uncomplicated cystitis in healthy women
- Acute uncomplicated pyelonephritis in healthy women
- Complicated urinary tract infection*
  - Male sex
  - Pregnancy
  - Poorly controlled diabetes mellitus
  - Obstruction or other structural factor: Urolithiasis, malignancies, ureteral and urethral strictures, bladder diverticula, renal cysts, fistulas, ileal conduits, other urinary diversions
  - Functional abnormality: Neurogenic bladder, vesicoureteral reflux
  - Foreign bodies: Indwelling catheter, ureteral stent, nephrostomy tube
  - Other conditions: Renal failure, renal transplantation, immunosuppression, multidrug-resistant uropathogens, health care–associated (includes hospital-acquired/LTCF-acquired) infection, prostatitis-related infection, upper tract infection in an adult other than a healthy woman, other functional or anatomic abnormality of urinary tract)
- Asymptomatic bacteriuria

(Data for complicating factors from Nicolle LE. A pactical guide to the management of complicated urinary tract infection. *Drugs.* 1997;53:583-592.)
*This is a selected list of complicating factors. Some factors complicate urinary tract infections through several mechanisms.

Complicated Infection

The initial steps leading to uncomplicated UTI discussed earlier probably also occur in most individuals who develop a complicated UTI. Factors that predispose individuals to complicated UTI generally do so by causing obstruction or stasis of urine flow, facilitating entry of uropathogens into the urinary tract by bypassing normal host defense mechanisms, providing a nidus for infection that is not readily treatable with antimicrobials, or compromising the host immune system (see Box 51.1).[1] UTIs are more likely to become complicated in the setting of impaired host defense, as occurs with indwelling catheter use, VUR, obstruction, neutropenia, and immune deficiencies. Diabetes mellitus is associated with several syndromes of complicated UTI, including renal and perirenal abscess, emphysematous pyelonephritis and cystitis, papillary necrosis, and xanthogranulomatous pyelonephritis.[14] Uropathogen virulence determinants are less important in the pathogenesis of complicated UTIs compared with uncomplicated UTIs. However, infection with multidrug-resistant uropathogens is more likely with complicated UTI.

ETIOLOGIC AGENTS

Uncomplicated upper and lower UTI are most often caused by *E. coli*, present in 70% to 95%, and *Staphylococcus saprophyticus*, present in 5% to more than 20%. Other organisms are less common (Table 51.2).[1] *S. saprophyticus* only rarely causes acute pyelonephritis.[15] Among otherwise healthy nonpregnant women, the isolation of lactobacilli, enterococci, group B streptococci, and coagulase-negative staphylococci other than *S. saprophyticus* most often represents contamination of the urine specimen[16] unless found in voided midstream urine in high counts and pure growth in symptomatic women.

A broader range of bacteria can cause complicated UTI, and many are resistant to broad-spectrum antimicrobial agents. Although *E. coli* is the most common, *Citrobacter* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, enterococci, and *S. aureus* account for a relatively higher proportion of cases compared with uncomplicated UTIs (see Table 51.2).[1] The proportion of infections caused by fungi, especially *Candida* spp., is increasing (see Chapter 53). Patients with chronic conditions, such as spinal cord injury and neurogenic bladder, are more likely to have polymicrobial and multidrug-resistant infections.

CLINICAL SYNDROMES

Acute Uncomplicated Cystitis in Young Women

Women with acute uncomplicated cystitis generally present with acute onset of dysuria, frequency, urgency, or suprapubic pain. Acute dysuria in a sexually active young woman is usually caused by acute cystitis; acute urethritis from *Chlamydia trachomatis, Neisseria gonorrhoeae,* or herpes simplex virus infections; or vaginitis caused by *Candida* spp. or *Trichomonas vaginalis*.[6] These three entities usually can be distinguished by the history, physical examination, and simple laboratory tests. Pyuria is present in almost all women with acute cystitis as well as in most women with urethritis caused by *N. gonorrhoeae* or *C. trachomatis,* and its absence strongly suggests an alternative diagnosis. Hematuria (microscopic or gross) is common in women with UTI but not in women with urethritis or vaginitis.

Definitive diagnosis of UTI requires the presence of significant bacteriuria, the traditional standard for which is 10^5 or more uropathogens per milliliter of voided midstream urine. Studies have shown, however, that up to half of women with cystitis have lower colony counts, which are missed with use of the traditional definition.[17,18] The Infectious Diseases Society of America (IDSA) consensus definition of cystitis is 10^3 cfu/ml or more uropathogens.[19] Urine cultures are generally not indicated in women with uncomplicated cystitis, because the patient's history has been shown to be highly reliable in establishing the diagnosis,[20] the causative organisms are predictable, and the culture results usually become available only after therapeutic decisions have been made.

E. coli in uncomplicated UTI is often resistant to sulfonamides and amoxicillin, and increasing resistance is also being observed for trimethoprim, TMP-SMX, and cotrimoxazole in outpatient urinary strains in the United States, Canada, and Europe.[21-23] In the United States, cotrimoxazole resistance rates among *E. coli* strains causing uncomplicated UTI range from 15% to 42% in different regions,[21] with a similar range among European countries and Brazil.[22] Many drug-resistant *E. coli* organisms are clonal and have been hypothesized to enter new environments by contaminated products ingested by community residents.[24] The prevalence of *E. coli* resistance to nitrofurantoin is generally less than 5%, although nitrofurantoin is inactive against *Proteus* spp. and some *Enterobacter* and *Klebsiella* spp. Fluoroquinolones remain active against most *E. coli* strains causing uncomplicated cystitis, although resistance is increasing in many areas of the world.[21,22] In a recent antimicrobial susceptibility study of more than 12 million *E. coli* isolates from U.S. outpatients, fluoroquinolone resistance increased from 3% to 17% over 10 years.[25] In addition, infections caused by extended-spectrum β-lactamase (ESBL)-producing strains are increasing in number, even in the setting of uncomplicated UTI.

Recommended management of acute uncomplicated cystitis is summarized in Fig. 51.1 and Table 51.3. Updated IDSA guidelines emphasize the importance of considering ecologic adverse effects of antimicrobial agents (i.e., selection for colonization or infection with multidrug-resistant organisms—so-called collateral damage) when selecting a treatment regimen.[26] Short-course regimens are recommended as first-line treatment for acute uncomplicated cystitis because of comparable efficacy, better compliance, lower cost, and fewer adverse effects than with longer regimens.[27] Given the benign nature of uncomplicated cystitis along with its high frequency, the IDSA guidelines give equal weight to the risk for ecologic adverse effects and drug effectiveness in the recommendations.

Nitrofurantoin is well tolerated and has good efficacy when given twice daily for 5 days, and it has a low propensity for ecologic adverse effects.[28] Despite concern about the high prevalence of resistance to TMP-SMX, this combination remains very effective and is inexpensive and well tolerated. Fosfomycin is also considered a first-line regimen because of its low propensity for ecologic adverse effects, even though it appears to be clinically inferior to TMP-SMX and fluoroquinolones.[26]

TABLE 51.3 Oral Antimicrobial Agents for Acute Uncomplicated Cystitis

Drug	Dose (mg)	Interval*	Comment
Nitrofurantoin			Less active against *Proteus* spp.
Monohydrate/macrocrystals	100	q12h	
Macrocrystals	50	q6h	
Trimethoprim-sulfamethoxazole (TMP-SMX)	160/800	q12h	If used in pregnancy (not approved use), avoid in first trimester.
Trimethoprim	100	q12h	If used in pregnancy (not approved use), avoid in first trimester.
Fosfomycin	3000	Single dose	Less effective than fluoroquinolone or TMP-SMX.
Pivmecillinam	400	q12h	Availability limited to some European countries; not available for use in North America. Associated with minimal resistance and propensity for collateral damage, but efficacy rates are lower than other agents.
Cefpodoxime proxetil	100	q12h	Comparable to TMP-SMX, inferior to ciprofloxacin in 3-day regimen[35]
Amoxicillin-clavulanate	500/125	q12h	Inferior to ciprofloxacin in 3-day regimen[34]
Amoxicillin	500	q12h	Used only when causative pathogen is known to be susceptible or for empiric treatment of mild cystitis in pregnancy
Fluoroquinolones			
Ciprofloxacin	250	q12h	Avoid fluoroquinolones if possible in pregnancy, nursing mothers, or persons younger than 18 years old. Although highly effective, should be considered second-line treatment to preserve their usefulness for other infections. Moreover, in the United States, the FDA has stated that the risks of systemic fluoroquinolone antibacterial drugs outweigh their benefits for uncomplicated cystitis.
Ciprofloxacin extended release	500	q24h	
Levofloxacin	250	q24h	
Ofloxacin	200	q12h	

*Duration of therapy depends on the clinical setting (see text and Fig. 51.1); *q6h, q12h, q24h,* every 6, 12, or 24 hours.
FDA, U.S. Food and Drug Administration.

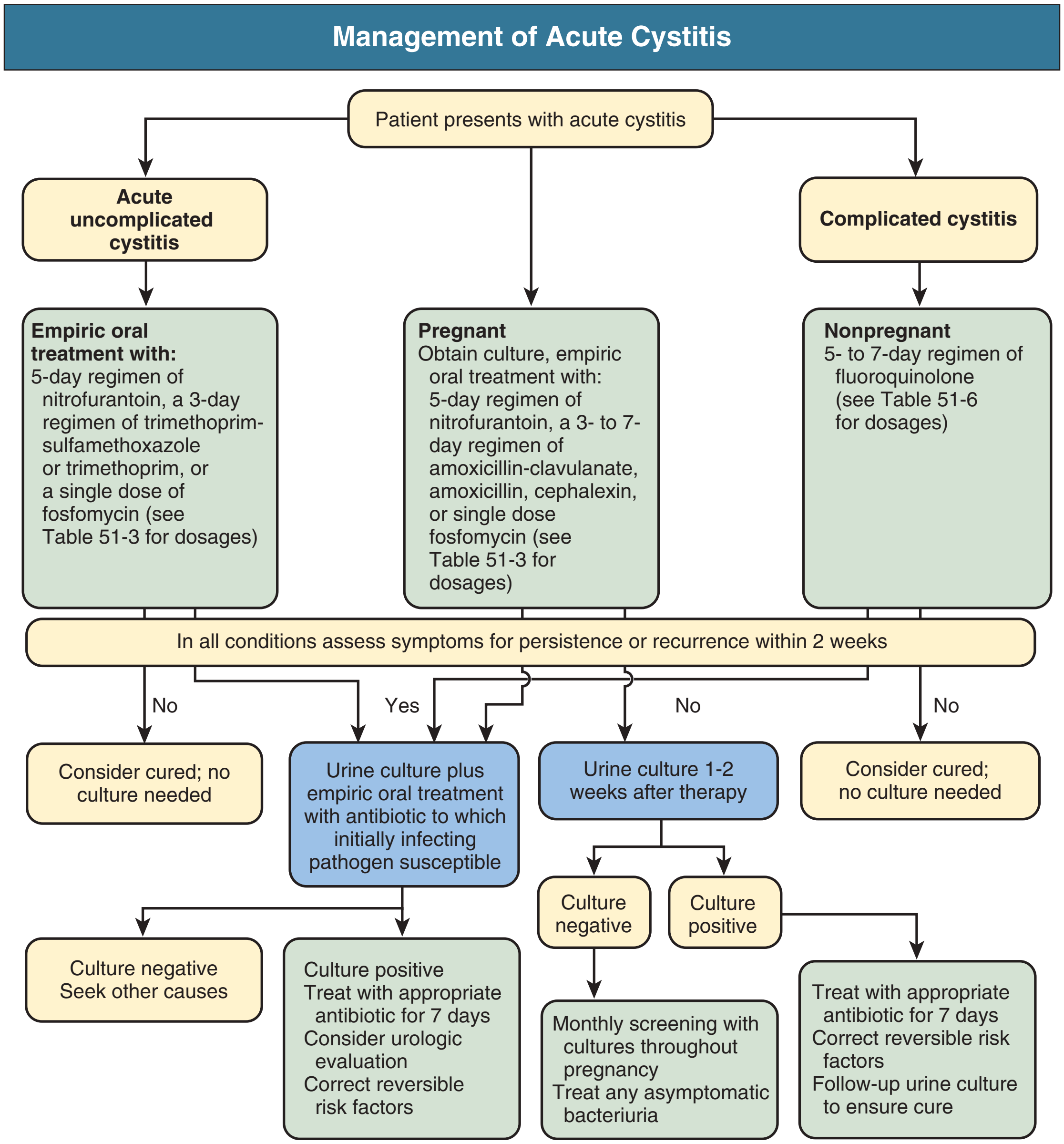
Management of Acute Cystitis
Patient presents with acute cystitis
Acute uncomplicated cystitis
Complicated cystitis
Empiric oral treatment with:
5-day regimen of nitrofurantoin, a 3-day regimen of trimethoprim-sulfamethoxazole or trimethoprim, or a single dose of fosfomycin (see Table 51-3 for dosages)
Pregnant
Obtain culture, empiric oral treatment with: 5-day regimen of nitrofurantoin, a 3- to 7-day regimen of amoxicillin-clavulanate, amoxicillin, cephalexin, or single dose fosfomycin (see Table 51-3 for dosages)
Nonpregnant
5- to 7-day regimen of fluoroquinolone (see Table 51-6 for dosages)
In all conditions assess symptoms for persistence or recurrence within 2 weeks
No
Yes
No
No
Consider cured; no culture needed
Urine culture plus empiric oral treatment with antibiotic to which initially infecting pathogen susceptible
Urine culture 1-2 weeks after therapy
Consider cured; no culture needed
Culture negative
Culture positive
Culture negative Seek other causes
Culture positive Treat with appropriate antibiotic for 7 days Consider urologic evaluation Correct reversible risk factors
Monthly screening with cultures throughout pregnancy Treat any asymptomatic bacteriuria
Treat with appropriate antibiotic for 7 days Correct reversible risk factors Follow-up urine culture to ensure cure

Fig. 51.1 Algorithm for management of acute cystitis.

Moreover, both nitrofurantoin and fosfomycin appear to have a role as therapeutic agents effective against ESBL *E. coli* UTIs.[29,30] Pivmecillinam, an extended gram-negative spectrum penicillin used only for treatment of UTI, is an appropriate choice for therapy in regions where it is available (availability limited to some European countries; not licensed and/or available for use in North America), because of minimal resistance and propensity for collateral damage, but efficacy rates are notably lower than with other recommended agents.[26] Pivmecillinam also may have a role in the treatment of ESBL-producing uropathogens.[32] The choice of an antimicrobial agent should be individualized based on the patient's allergy and compliance history, local practice patterns, prevalence of resistance in the local community (if known), availability, cost, and how comfortable the patient and provider are with increased risk for treatment failure associated with the use of an antimicrobial agent that may cause less collateral damage but is less effective than another drug.[26] If a first-line antimicrobial agent is not a good choice because of one or more of these factors, fluoroquinolones or β-lactams are reasonable alternatives, although it is preferable to minimize their use because of concerns about ecologic adverse effects.[26] Thus, although fluoroquinolones (3-day duration) are highly effective in the treatment of cystitis, many experts recommend that they be considered as second-line therapy for uncomplicated cystitis, to help preserve their usefulness in the treatment of other infections.[26] Moreover, in the United States, the Food and Drug Administration (FDA) has stated that the risks of systemic fluoroquinolone antibacterial drugs outweigh their benefits for uncomplicated cystitis.[31] In general, β-lactam antibiotics have been inferior to TMP-SMX or fluoroquinolones in regimens of the same duration.[36]

Although broad-spectrum oral β-lactams (e.g., cefixime, cefpodoxime, cefprozil, cefaclor, amoxicillin-clavulanate) demonstrate in vitro activity against most uropathogens causing uncomplicated cystitis, clinical data are sparse. Recent trials demonstrated that cure rates with 3-day regimens of amoxicillin-clavulanate[34] or cefpodoxime proxetil[35] were lower than a 3-day regimen of ciprofloxacin. Moreover, there are concerns about the possibility of ecologic adverse effects with oral broad-spectrum cephalosporins, as has been observed with parenteral cephalosporins, although again few data exist. Routine post-treatment cultures in women are not indicated unless the patient is symptomatic. If the patient remains symptomatic and has documented persistent infection, a longer course of therapy based on sensitivities, usually with a fluoroquinolone, should be used. The benefit of detecting and treating asymptomatic bacteriuria in healthy women has been demonstrated only in pregnancy and before urologic instrumentation or surgery.[7,37]

Recurrent Acute Uncomplicated Cystitis in Women

Much recurrent cystitis in healthy women is caused by persistence of the initially infecting strain in the fecal flora.[38] Experimental studies in mice also suggest that some same-strain recurrent UTIs may be caused by a latent reservoir of uropathogens in the bladder epithelium that persist after the initial UTI,[39] and indirect evidence indicates that this may occur in humans.[40] If the recurrence is within 1 or 2 weeks of treatment, an antimicrobial-resistant uropathogen should be considered, and a urine culture should be performed followed by treatment with an alternative regimen. It is reasonable to treat later recurrences the same as the original infection, although if the recurrence is within 6 months, one should consider a first-line drug other than the one used originally, especially if TMP-SMX was used, because of the likelihood of resistance.[16]

The goal of long-term management of recurrent cystitis should be to improve the quality of life while minimizing antimicrobial exposure.[16] Women with recurrent cystitis may benefit from behavioral modification (Fig. 51.2), such as avoiding spermicides, increasing fluid intake, and ensuring postcoital micturition, although the benefit of these practices has not been proven. Data on efficacy are sparse, but targeting the adherence mechanism of *Enterobacteriacea* with D-mannose powder is another antimicrobial-sparing modality used by some women to prevent UTI.[41] Although cranberry products are widely used by women as a preventive for recurrent UTI, randomized, placebo-controlled trials (RCTs) have shown no benefit from cranberry juice.[42] Women who do not want to try or who obtain no benefit from the preceding approaches should be offered antimicrobial prophylaxis.

Antimicrobial prophylaxis has been shown to reduce the risk for recurrent cystitis by approximately 95% (Table 51.4; see also Fig. 51.2).[43] Prophylaxis should be considered for women who experience three or more infections during a 12-month period or whenever the woman thinks her life is being adversely affected by frequent recurrences. Several approaches have been used, including continuous prophylaxis, postcoital prophylaxis, and intermittent self-treatment (which is really an early treatment method).[16] In postmenopausal women with recurrent UTI, intravaginal estradiol is effective, presumably by normalizing the vaginal flora, which reduces the risk for coliform colonization of the vagina.[38] This approach offers an alternative to antimicrobial strategies (see Fig. 51.2).

Many promising antimicrobial-sparing approaches are being developed to specifically target virulence pathways, which might prevent uropathogens from causing disease, without altering the gut commensal microbiota. Antivirulence therapeutics target processes that are critical for UTI pathogenesis but are not required for the essential processes of growth and cell division (targets of conventional antimicrobials).[13]

Acute Uncomplicated Pyelonephritis in Women

Acute pyelonephritis is suggested by fever (temperature ≥38° C), chills, flank pain, nausea and vomiting, and costovertebral angle tenderness. Cystitis symptoms are variably present. Symptoms may vary from a mild illness to a sepsis syndrome with or without shock and renal failure. Pyuria is almost always present, but leukocyte casts, specific for UTI, are infrequently seen. Gram stain of the urine sediment may aid in differentiating gram-positive and gram-negative infections, which can influence empiric therapy. A urine culture, which should be performed in all women with acute pyelonephritis, will have 10^4 cfu/ml or more of uropathogens in up to 95% of patients.[19]

On pathologic examination, the kidney shows a focal inflammatory reaction with neutrophil and monocyte infiltrates, tubular damage, and interstitial edema (Fig. 51.3). Although imaging studies are generally not performed, the infected kidney is often enlarged, and contrast-enhanced computed tomography (CT) shows decreased opacification of the affected parenchyma, typically in patchy, wedge-shaped, or linear patterns (Fig. 51.4).

The availability of effective oral antimicrobials, especially the fluoroquinolones, allows initial oral therapy in appropriate patients or, in those requiring parenteral therapy, the timely conversion from

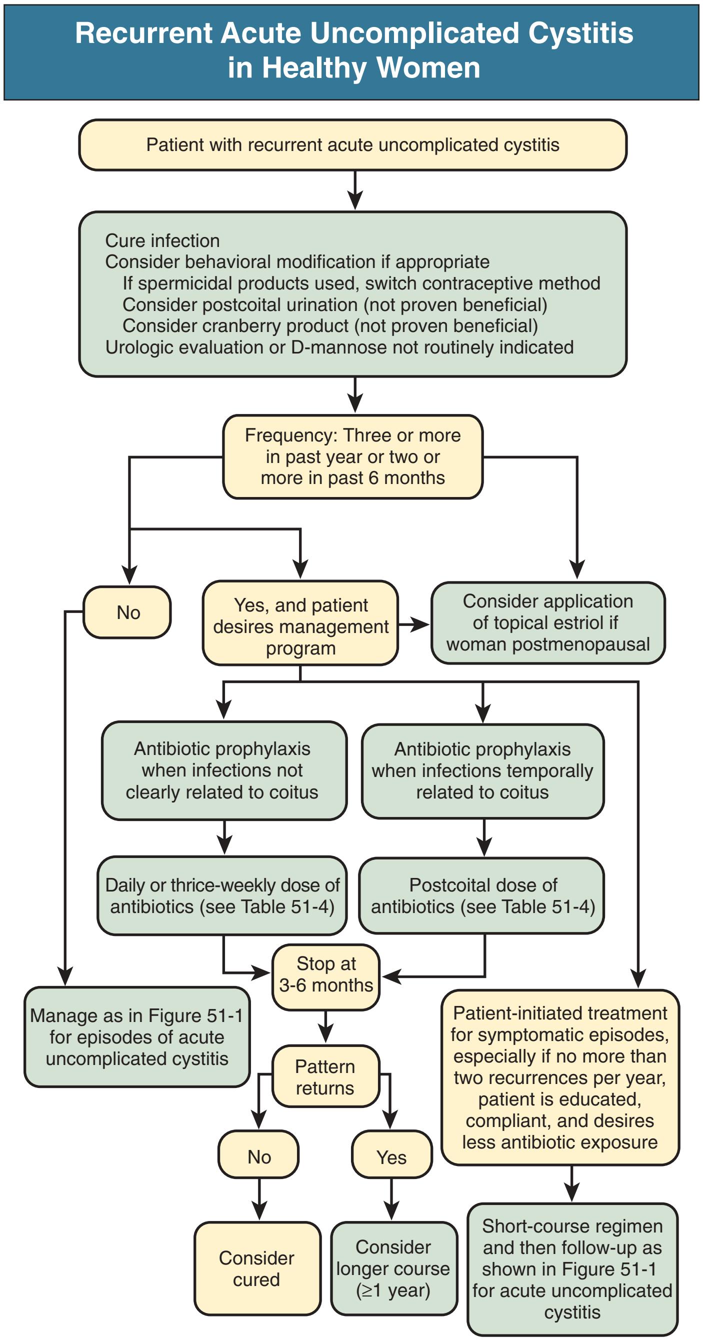
Recurrent Acute Uncomplicated Cystitis in Healthy Women
Patient with recurrent acute uncomplicated cystitis
Cure infection
Consider behavioral modification if appropriate
If spermicidal products used, switch contraceptive method
Consider postcoital urination (not proven beneficial)
Consider cranberry product (not proven beneficial)
Urologic evaluation or D-mannose not routinely indicated
Frequency: Three or more in past year or two or more in past 6 months
No
Yes, and patient desires management program
Consider application of topical estriol if woman postmenopausal
Antibiotic prophylaxis when infections not clearly related to coitus
Antibiotic prophylaxis when infections temporally related to coitus
Daily or thrice-weekly dose of antibiotics (see Table 51-4)
Postcoital dose of antibiotics (see Table 51-4)
Stop at 3-6 months
Manage as in Figure 51-1 for episodes of acute uncomplicated cystitis
Pattern returns
Patient-initiated treatment for symptomatic episodes, especially if no more than two recurrences per year, patient is educated, compliant, and desires less antibiotic exposure
No
Yes
Consider cured
Consider longer course (≥1 year)
Short-course regimen and then follow-up as shown in Figure 51-1 for acute uncomplicated cystitis

Fig. 51.2 Management strategies for recurrent acute uncomplicated cystitis.

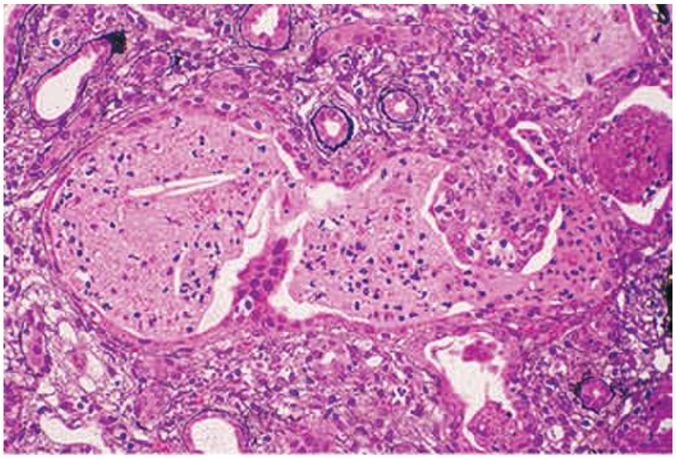

Fig. 51.3 Acute pyelonephritis. Renal tissue shows a dilated tubule with neutrophils enmeshed in proteinaceous debris ("pus casts") with adjacent interstitial inflammation. (Courtesy C. Alpers, University of Washington, Seattle, Wash.)

TABLE 51.4 Antimicrobial Prophylaxis Regimens for Women With Recurrent Acute Uncomplicated Cystitis*

Drug	Dose (mg)	Frequency
Continuous Prophylaxis		
Nitrofurantoin	50 or 100	Daily
TMP-SMX	40/200	Daily
TMP-SMX	40/200	Three times weekly
Trimethoprim	100	Daily
Cefaclor	250	Daily
Cefalexin (cephalexin)	125 or 250	Daily
Norfloxacin*	200	Other fluoroquinolones are likely to be as effective.[†]
Postcoital Prophylaxis		
Nitrofurantoin	50 or 100	Single dose
TMP-SMX	40/200	Single dose
TMP-SMX	80/400	Single dose
Cefalexin	250	Single dose
Ciprofloxacin*	125	Single dose
Norfloxacin*	200	Single dose
Ofloxacin*	100	Single dose

*See text and Fig. 51.2 for management strategy.

[†] Women should be cautioned about pregnancy when fluoroquinolones are being used. Fluoroquinolones are highly effective but not recommended, especially given the recent FDA warning that the risks of systemic fluoroquinolone antibacterial drugs outweigh their benefits for uncomplicated cystitis.

intravenous to oral therapy and reduced need for hospitalization. Indications for hospital admission include inability to maintain oral hydration or to take medications; uncertain social situation or concern about compliance; uncertainty about the diagnosis; and severe illness with high fevers, severe pain, and marked debility. Outpatient therapy is safe and effective for select patients who can be stabilized with parenteral fluids and antibiotics in an urgent care facility and sent home with oral antibiotics under close supervision. In one population-based study of acute pyelonephritis in adult women, only 7% were hospitalized.[4]

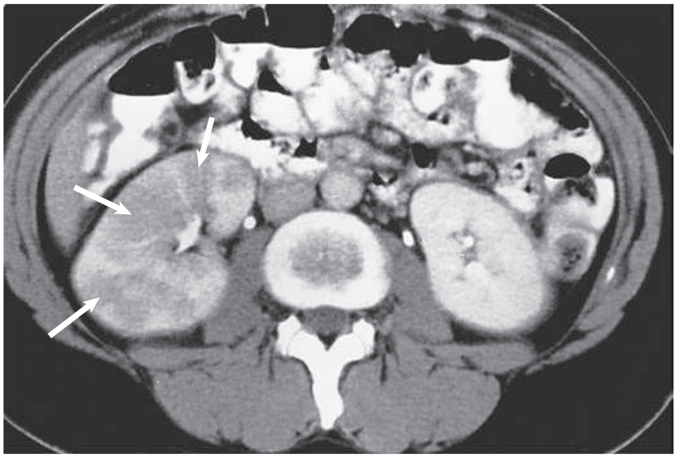

Fig. 51.4 Acute pyelonephritis. Contrast-enhanced CT scan shows areas of lower density caused by infection and edema *(arrows)*. (Courtesy W. Bush, University of Washington, Seattle, Wash.)

TABLE 51.5 Parenteral Regimens for Acute Uncomplicated Pyelonephritis and Complicated Urinary Tract Infection*

Drug	Dose (mg)	Interval
Ceftriaxone	1000-2000	q24h
Cefepime	1000-2000	q12h
Fluoroquinolones[†]		
Ciprofloxacin	200-400	q12h
Levofloxacin	250-750	q24h
Gentamicin[†] (± ampicillin)	3-5 mg/kg body weight 1 mg/kg body weight	q24h q8h
Ampicillin (+ gentamicin[†])	1000	q6h
Trimethoprim-sulfamethoxazole[†]	160/800	q12h
Aztreonam	1000	q8-12h
Piperacillin-tazobactam	3375	q6-8h
Imipenem-cilastatin[†,‡]	250-500	q6-8h
Meropenem[‡]	500	q8h
Ertapenem[‡]	1000	q24h
Ceftolozane/tazobactam	1500	q8h
Ceftazidime/avibactam	2500	q8h
Vancomycin§	1000	q12h

*Duration depends on clinical setting (see text and Fig. 51.5).

[†] Avoid, if possible, in pregnancy.

[‡] Recommended if ESBL Enterobacteriacea is suspected or known. Ertapenem is not indicated for suspected or known *Pseudomonas* infection.

§Recommended if methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected or known.

The management strategy for acute uncomplicated pyelonephritis is shown in Fig. 51.5. Many effective parenteral (Table 51.5) and oral (Table 51.6) regimens are available for patients with acute uncomplicated pyelonephritis. For outpatients, an oral fluoroquinolone should be used for initial empiric treatment of infection caused by gram-negative bacilli.[26,33] TMP-SMX or other agents can be used if the infecting strain is known to be susceptible. If enterococci are suspected from the Gram

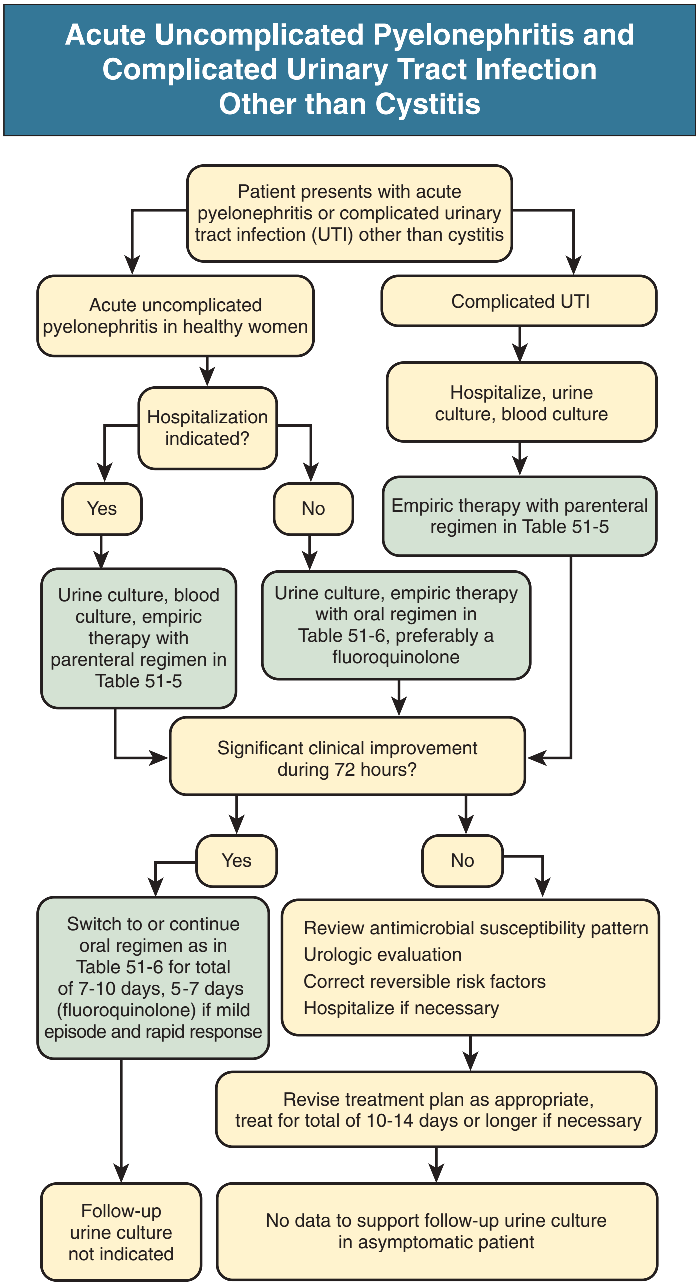
Acute Uncomplicated Pyelonephritis and Complicated Urinary Tract Infection Other than Cystitis
Patient presents with acute pyelonephritis or complicated urinary tract infection (UTI) other than cystitis
Acute uncomplicated pyelonephritis in healthy women
Complicated UTI
Hospitalization indicated?
Hospitalize, urine culture, blood culture
Yes
No
Empiric therapy with parenteral regimen in Table 51-5
Urine culture, blood culture, empiric therapy with parenteral regimen in Table 51-5
Urine culture, empiric therapy with oral regimen in Table 51-6, preferably a fluoroquinolone
Significant clinical improvement during 72 hours?
Yes
No
Switch to or continue oral regimen as in Table 51-6 for total of 7-10 days, 5-7 days (fluoroquinolone) if mild episode and rapid response
Review antimicrobial susceptibility pattern
Urologic evaluation
Correct reversible risk factors
Hospitalize if necessary
Revise treatment plan as appropriate, treat for total of 10-14 days or longer if necessary
Follow-up urine culture not indicated
No data to support follow-up urine culture in asymptomatic patient

Fig. 51.5 Management algorithm for acute uncomplicated pyelonephritis and complicated urinary tract infection other than cystitis.

stain, amoxicillin should be added to the treatment regimen until the causative organism is identified. Second- and third-generation cephalosporins also appear effective, although published data are sparse. Nitrofurantoin, fosfomycin, and pivmecillinam are not approved or recommended for the treatment of pyelonephritis. When antimicrobial resistance or intolerance of oral medications is a concern, one or more doses of a broad-spectrum parenteral antimicrobial is recommended until in vitro activity can be ensured.[26]

For hospitalized patients without evidence of gram-positive infection, ceftriaxone is effective and inexpensive. If enterococci are suspected based on the Gram stain, ampicillin plus gentamicin, ampicillin-sulbactam, and piperacillin-tazobactam are reasonable empiric choices. TMP-SMX should not be used alone for empiric therapy for pyelonephritis in areas with a high prevalence of resistance to this combination. Patients with acute uncomplicated pyelonephritis often can be switched to oral therapy after 24 to 48 hours, although longer durations of parenteral therapy are occasionally indicated in patients with continued high fever, severe flank pain, or persistent nausea and vomiting.

Treatment of acute uncomplicated pyelonephritis can be limited to 5 to 7 days for patients who have a rapid resolution of fever and symptoms soon after initiation of treatment. However, β-lactam regimens shorter than 14 days have been associated with unacceptably high failure rates in some studies.[33] One study demonstrated superiority of a 7-day ciprofloxacin regimen over a 14-day TMP-SMX regimen, with the difference accounted for entirely by the higher rate of resistance of the uropathogens to TMP-SMX.[15]

A recent study of patients with acute pyelonephritis presenting to emergency departments in the United States demonstrated that antimicrobial resistance prevalence (fluoroquinolone-resistant and ESBL-producing strains) is increasing and that such patients are often treated with empiric antimicrobial drugs that are inactive against the causative strains.[44] The authors conclude that in areas with high fluoroquinolone resistance rates, where ESBL-producing *Enterobacteriaceae* infections have emerged, or among persons with antimicrobial drug resistance risk factors, clinicians should consider empiric treatment with a carbapenem or another agent found to be active against these resistant strains.

Routine post-treatment urine cultures in asymptomatic patients are not cost-effective, but cultures should be performed if symptoms persist or recur. Recurrent infections are treated with a 7- to 14-day course of an antibiotic to which the organism is susceptible. Symptomatic patients who have persistent infection with the same strain as the initial infecting strain warrant at least 10 to 14 days of therapy with a different antibiotic, and complicating factors should be looked for and corrected if found.

Complicated Infections

Patients with complicated UTI may present with classic signs of cystitis and pyelonephritis but also may have vague or nonspecific symptoms, such as fatigue, irritability, nausea, headache, and abdominal or back pain. Acute cystitis in healthy individuals other than young women is more likely to involve occult renal or prostatic infection and may respond poorly to short-course therapy. Noninvasive tools to localize infections to the kidney or prostate are lacking, so clinical estimation of risk in a given patient is imprecise. Some patients, such as those who are diabetic or pregnant, warrant special attention because of the serious complications that can occur if treatment is inadequate. Urethritis must be excluded in dysuric sexually active men by a urethral Gram stain or a first-voided urine specimen wet-mount evaluation for urethral leukocytosis. Complicated UTI, as with uncomplicated infection, is generally associated with pyuria and bacteriuria, although these may be absent if the infection does not communicate with the collecting system.

Urine culture should always be performed in patients with suspected complicated UTI. The IDSA consensus definition of complicated UTI is 10^5 cfu/ml or more in the urine of women and 10^4 cfu/ml or more in men,[19] but lower counts in symptomatic persons, as demonstrated in patients with uncomplicated UTI, may well represent significant bacteriuria. This is especially true when the specimen is collected from a urinary catheter. Thus it is reasonable to use a colony count threshold of 10^3 cfu/ml of uropathogens to diagnose complicated UTI.

The wide variety of underlying conditions (see Box 51.1), diverse bacterial agents (see Table 51.2), and paucity of RCTs make generalizations about antimicrobial therapy difficult. Figs. 51.1 and 51.5 outline the management strategy for complicated cystitis and other complicated UTIs, respectively.

Correction of any underlying anatomic, functional, or metabolic defect must be attempted, because antibiotics alone may not be successful.[1]

TABLE 51.6 Oral Regimens for Acute Uncomplicated Pyelonephritis and Complicated Urinary Tract Infection*,†

Drug	Dose (mg)	Interval	Comment
Fluoroquinolones			Preferred for empiric treatment; avoid if possible in pregnancy, nursing mothers, or persons younger than 18 years of age.
Ciprofloxacin	500	q12h	
Ciprofloxacin extended release	1000	q24h	
Levofloxacin	250-750	q24h	
Trimethoprim-sulfamethoxazole	160/800	q12h	Use only when the causative pathogen is known to be susceptible. If used in pregnancy (not approved use), avoid in first trimester.
Cefpodoxime proxetil	200	q12h	Data are sparse; use only when the causative pathogen is known to be susceptible.
Amoxicillin-clavulanate	500/125 to 875/125	q12h	Use only when the causative pathogen is known to be susceptible or in addition to a broad-spectrum agent when empiric coverage against enterococci is desirable.

*A long-acting parenteral antibiotic should be given concomitantly if there are concerns about drug resistance.
†Duration depends on clinical setting (see text and Fig. 51.5).

For empiric therapy in patients with mild to moderate illness who can be treated with oral medication, the fluoroquinolones provide the broadest spectrum of antimicrobial activity, cover most expected pathogens, and achieve high levels in the urine and urinary tract tissue. An exception is moxifloxacin, which may not achieve sufficient concentrations in urine to be effective for complicated UTI. If the infecting pathogen is known to be susceptible, TMP-SMX or other agents are reasonable therapeutic choices. Nitrofurantoin and fosfomycin should be avoided except for cystitis in pregnancy, in which duration of treatment is 5 days or single-dose, respectively.

For initial treatment in more seriously ill, hospitalized patients, several parenteral antimicrobial agents are available (see Table 51.5). The broader spectrum agents shown in Table 51.5 are preferable for health care–associated infections. *S. aureus* is more common in complicated UTIs, and, if suspected, the therapeutic regimen should have activity against *S. aureus*. Studies show that a high proportion of *S. aureus* isolates, even in the community, are methicillin resistant (MRSA), so vancomycin should be included in the empiric treatment regimen if *S. aureus* is suspected. Potential concerns that must be considered in the management of complicated UTI include the increasing prevalence of resistance to fluoroquinolones in institutional settings and the frequency of enterococcal infections.

The antimicrobial regimen can be modified when the infecting strain has been identified and antimicrobial susceptibilities are known. Patients receiving parenteral therapy can be switched to oral treatment after clinical improvement. Few studies evaluate duration of treatment in populations with complicated UTIs. However, it is desirable to limit the duration of treatment, especially for milder infections, to reduce the selection pressure for drug-resistant flora. In one study, clinical and microbiologic success rates after treatment were almost identical in patients with acute pyelonephritis or complicated UTI treated with a 5-day course of levofloxacin or a 10-day course of ciprofloxacin.[45] These data suggest that a 5- to 10-day regimen is reasonable for most patients with complicated UTI, depending on their severity of illness and clinical response; shorter regimens, such as a 5-day regimen of a urinary fluoroquinolone, are likely to be sufficient in patients who are less severely ill, are infected with uropathogens susceptible to the antibiotic used, and have a rapid response to treatment. A recent large retrospective study of male veterans with UTI found no difference in recurrence rates with 7 days of treatment versus longer, with a trend toward more *Clostridium difficile* infections in those treated longer.[46] At least 10 to 14 days of therapy is recommended in patients who have a delayed response.

Routine post-treatment cultures are not indicated unless the patient is symptomatic, except in pregnant women (see Fig. 51.1). In men, early recurrence of UTI with the same species suggests a prostatic source of infection and warrants a 4- to 6-week regimen of either a fluoroquinolone (preferable) or TMP-SMX, depending on the antimicrobial susceptibility of the infecting strain.

Chronic Kidney Disease. Because of the wide variety of underlying diseases and comorbidities, prior instrumentation of the urinary tract, and differences in age and gender, the incidence of UTI in patients with chronic kidney disease (CKD) is not known.[47] Moreover, there are few data on urine concentrations of antimicrobials used for the treatment of UTI in patients with CKD.[48] Studies in animals suggest that (1) urine drug concentrations are necessary to sterilize urine, (2) effective tissue concentrations are necessary to treat pyelonephritis, and (3) serum concentrations of antimicrobials are correlated with the drug concentrations in renal tissue. Thus, for patients with CKD who have a therapeutic serum drug level and adequate perfusion of the renal parenchyma, the delivery of therapeutic concentrations of both the parenchyma and the urine should be adequate, but some oral agents for cystitis may not deliver adequate concentrations to the urine.[48] For patients with a low glomerular filtration rate (GFR) and pyelonephritis or cystitis, the agents listed in Tables 51.5 and 51.6 for pyelonephritis and complicated cystitis should be adequate to treat these infections if the organism is susceptible.[48]

As noted previously, however, β-lactams are not as effective as fluoroquinolones, even in patients with normal renal function.[33] For oral treatment, renal function (estimated GFR) adjusted doses of ciprofloxacin or levofloxacin, but not moxifloxacin, are recommended. Nitrofurantoin and sulfamethoxazole are not recommended in patients with reduced creatinine clearance, although trimethoprim concentrations appear to be adequate.[47] Likewise, according to the package insert, renal impairment significantly decreases the excretion of fosfomycin, which also should not be used in such patients.

Catheter-Associated Infections. Approximately 15% to 25% of patients in general hospitals have a urethral catheter inserted at some time during their stay, and approximately 5% to 10% of long-term care facility residents are managed with urethral catheterization, in some cases for years. The incidence of bacteriuria associated with indwelling catheters is 3% to 10% per day of catheterization, and the duration of catheterization is the most important risk factor for the development of catheter-associated bacteriuria.

Catheter-associated bacteriuria is the most common source of gram-negative bacteremia in hospitalized patients. Complications of long-term catheterization (≥30 days) include almost universal bacteriuria, often with multiple antibiotic-resistant flora, and (in addition to cystitis, pyelonephritis, and bacteremia, as seen with short-term catheterization) frequent febrile episodes, catheter obstruction, stone formation associated with urease-producing uropathogens, and local genitourinary infections. Other rare complications include fistula formation and bladder cancer. An increase in mortality risk has been reported with catheter-associated bacteriuria, but it is difficult to distinguish the role of the catheter because most deaths occur in patients who have severe underlying disease.

Most episodes of catheter-associated bacteriuria are asymptomatic and do not require routine screening or treatment because treatment does not reduce the complications of bacteriuria and can lead to antimicrobial resistance.[7] Moreover, the presence or absence of pyuria does not differentiate symptomatic from asymptomatic urinary infection.[7] Symptomatic UTIs, often caused by many multidrug-resistant uropathogens, warrant broad-spectrum therapy, as described previously. In a symptomatic catheterized patient, a urine culture specimen should be obtained from a freshly placed catheter if the catheter has been in place for a few days, because the catheter biofilm may result in spurious culture results. Moreover, clinical outcomes are improved if the catheter is replaced at the time of antimicrobial therapy.[49] Seven days is the recommended duration of antimicrobial treatment for patients who have prompt resolution of symptoms, and 10 to 14 days if response is delayed.[50]

Preventive measures are indicated to reduce the morbidity, mortality, and costs of catheter-associated infection. Effective strategies include avoidance of a catheter when possible and, when the catheter is necessary, sterile insertion, prompt removal, and strict adherence to a closed collecting system.[6,50] Bundling of preventive steps may be useful.[51,52] Meta-analyses have shown that rates of catheter-associated bacteriuria, at least in patients catheterized for less than 2 weeks, are higher in patients with an indwelling urethral catheter than in those with intermittent or suprapubic catheterization.[53] Likewise, condom catheterization is preferable to indwelling urethral catheterization in appropriately selected men.[54] Although highly effective in reducing catheter-associated UTI rates, prophylactic systemic antimicrobial agents are generally not recommended for routine use because of concerns about selection for antimicrobial resistance. Antimicrobial-coated catheters appear to be effective in reducing catheter-associated bacteriuria in patients catheterized for less than 2 weeks, but these have not been shown to be effective in reducing symptomatic infection.

Spinal Cord Injury. Spinal cord injury alters the dynamics of voiding and often requires the use of bladder drainage with catheters. The diagnosis of UTI in patients with spinal cord injuries is often problematic and is based on the combination of symptoms and signs (which are often nonspecific), pyuria, and significant bacteriuria. Uropathogens are usually present in quantities of 10^5 cfu/ml or more. Fluoroquinolones are the empiric oral agents of choice in patients with mild to moderate infection, although many uropathogens, even in the outpatient setting, are resistant to this class of antibiotic, and parenteral antibiotics may be needed.

Treatment of asymptomatic bacteriuria in patients with spinal cord injuries is not of proven benefit and increases the risk for infection with antimicrobial-resistant uropathogens.[7,55] Likewise, antibiotic prophylaxis is generally not recommended, although it may be considered for select outpatients with frequent symptomatic UTIs for whom there are no correctible risk factors. Recent studies have shown that use of a hydrophilic-coated catheter for intermittent catheterization is associated with a reduction in the incidence of symptomatic UTI in patients with spinal cord injury.[56]

Prostatitis. Prostatitis occurs in up to 25% of men during their lifetime, but it is caused by acute or chronic bacterial infection in a minority.[57] The most common organisms causing bacterial prostatitis are gram-negative bacilli, including *E. coli, Proteus* spp., *Klebsiella* spp., *P. aeruginosa,* and, less frequently, enterococci and *S. aureus*. The pathogenesis of prostatitis is believed to be related to reflux of infected urine from the urethra into the prostatic ducts. Prostatic calculi, commonly found in adult men, may provide a nidus for bacteria and protection from antibacterial agents.

Acute bacterial prostatitis is rare. Patients present with dysuria, frequency, urgency, obstructive voiding symptoms, fever, chills, and myalgias. The prostate is tender and swollen. Prostatic massage, as a diagnostic test, is contraindicated in men in whom the diagnosis of acute prostatitis is being considered because of the risk for precipitating bacteremia. The patient will usually have pyuria and a positive urine culture. Patients who are severely ill require hospitalization and parenteral antibiotics, but many patients can be treated in the outpatient setting with oral fluoroquinolones. The recommended duration of treatment is 14 to 30 days.[57] Rarely, abscess formation may occur.

Chronic bacterial prostatitis is characterized by recurrent UTIs with the same uropathogen with intervening asymptomatic periods. The prostate typically is normal to palpation during asymptomatic periods. Chronic bacterial prostatitis is characterized microscopically by the presence of 10 or more leukocytes per high-power field in expressed prostatic secretions or postmassage voided urine in the absence of significant pyuria in first-voided and midstream urine specimens, as well as a uropathogen colony count at least 10-fold higher in the expressed prostatic secretions or postmassage voided urine compared with the first-voided midstream urine. In addition, macrophage-laden fat droplets (oval fat bodies) are usually prominent in the prostatic secretions. These tests, however, are infrequently performed by urologists. Cure rates, which historically have been low, are 60% to 80% with the fluoroquinolones, which are the antibiotics of choice. The optimal duration of treatment is unknown, but 4 to 6 weeks is recommended by some authorities,[57] whereas others recommend up to 3 months. Some patients require long-term, low-dose suppressive therapy to prevent symptomatic UTIs. Surgical intervention is only rarely considered and is associated with high morbidity.

Renal Abscess. Renal cortical and corticomedullary abscesses and perirenal abscesses occur in 1 to 10 per 10,000 hospital admissions.[58] Patients usually present with fever, chills, back or abdominal pain, and costovertebral angle tenderness, but they may have no urinary symptoms or findings if the abscess does not communicate with the collecting system, as often occurs with a cortical abscess. Bacteremia may be primary (cortical abscess) or secondary (corticomedullary or perirenal). The clinical presentation may be insidious and nonspecific, especially with perirenal abscess, and the diagnosis may not be made until admission to a hospital or at autopsy. CT is recommended to establish the diagnosis and location of a renal or perirenal abscess (Fig. 51.6). Empiric antibiotic therapy should be broad and cover *S. aureus* and other uropathogens causing complicated UTI (see Fig. 51.5 and Table 51.5) and modified once urine culture results are known.

A *renal cortical abscess* (renal carbuncle) is usually caused by *S. aureus,* which reaches the kidney by hematogenous spread. Treatment with antibiotics is usually effective, and drainage is not required unless the patient is slow to respond. A *renal corticomedullary abscess,* in contrast, usually results from ascending UTI in association with an underlying urinary tract abnormality, such as obstructive uropathy or VUR,

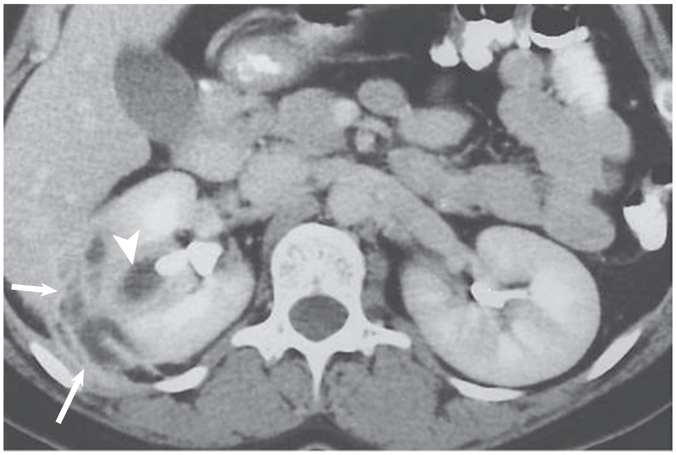

Fig. 51.6 Renal abscess. Contrast-enhanced CT scan shows an abscess in the medulla of the kidney *(arrowhead)* with penetration and extension into the perinephric space *(arrows)*. (Courtesy L. Towner.)

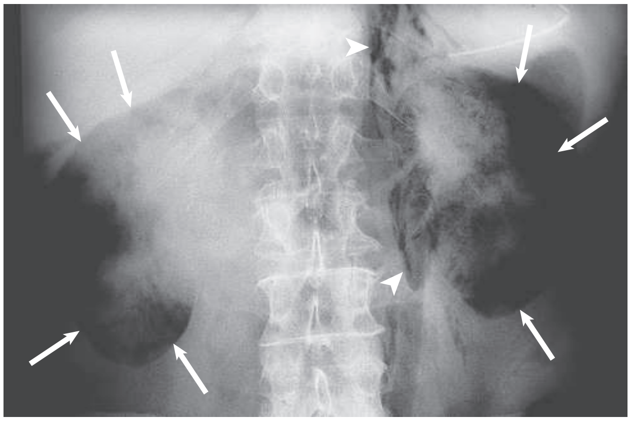

Fig. 51.7 Emphysematous pyelonephritis. A plain radiograph in this febrile patient with diabetes revealed diffuse gas formation throughout both kidneys *(outlined by arrows)* and gas dissecting in the left retroperitoneal space *(arrowheads)*. (Courtesy W. Bush, University of Washington, Seattle.)

and is usually caused by common uropathogenic species such as *E. coli* and other gram-negative bacilli. Such abscesses may extend deep into the renal parenchyma, perforate the renal capsule, and form a perirenal abscess. Treatment with antimicrobial agents without drainage may be effective if the abscess is small and if the underlying urinary tract abnormality can be corrected. Aspiration of the abscess may be necessary in some patients, and nephrectomy may occasionally be required in patients with diffuse renal involvement or with severe sepsis. Perirenal abscesses usually occur in the setting of obstruction or other complicating factors (see Box 51.1) and result from ruptured intrarenal abscesses, hematogenous spread, or spread from a contiguous infection. Causative uropathogens are those usually found in complicated UTIs (see Table 51.2), including *S. aureus* and enterococci; polymicrobial infections are common. Anaerobes or *Mycobacterium tuberculosis* may be causative (see Chapter 52). A previously high mortality rate has been lowered with earlier diagnosis and therapy. In contrast to the other types of renal abscesses, drainage of pus is the cornerstone of therapy and nephrectomy may be indicated.

Papillary Necrosis. More than half of patients who develop papillary necrosis have diabetes, almost always in conjunction with a UTI, but the condition also complicates sickle cell disease, analgesic abuse, and obstruction. Renal papillae are vulnerable to ischemia because of the sluggish blood flow in the vasa recta, and relatively modest ischemic insults may cause papillary necrosis. The clinical features are those typical of pyelonephritis. In addition, passage of sloughed papillae into the ureter may cause renal colic, renal impairment or failure, or obstruction with severe urosepsis. Papillary necrosis in the setting of pyelonephritis is associated with pyuria and a positive urine culture. Causative uropathogens are those typical of complicated UTI. CT is the preferred diagnostic procedure. Radiologic findings include an irregular papillary tip; dilated calyceal fornix; extension of contrast material into the parenchyma; and a separated crescent-shaped papilla surrounded by contrast, called the *ring sign* (see Fig. 49.8) Broad-spectrum antibiotics are indicated. Papillae obstructing the ureter may require removal with a cystoscopic ureteral basket or relief of obstruction by insertion of a ureteral stent.

Emphysematous Pyelonephritis. Emphysematous pyelonephritis is a fulminant, necrotizing, life-threatening variant of acute pyelonephritis caused by gas-forming organisms, including *E. coli, Klebsiella pneumoniae, P. aeruginosa,* and *Proteus mirabilis*.[59] Up to 90% of cases occur in diabetic patients, and obstruction may be present. Symptoms are suggestive of pyelonephritis, and there may be a flank mass. Dehydration and ketoacidosis are common. Pyuria and a positive urine culture are usually present. Gas is usually detected by a plain abdominal radiograph or ultrasound (Fig. 51.7). CT is the diagnostic modality of choice, however, because it can localize the gas better than ultrasound. Accurate localization of gas is important because gas also may form in an infected obstructed collecting system or renal abscess; although serious, these conditions do not carry the same poor prognosis and are managed differently. Parenteral broad-spectrum antibiotics and percutaneous catheter drainage with relief of obstruction may be adequate for less severely ill patients, but nephrectomy is warranted for those who are more severely ill and those less severely ill who do not respond to the preceding steps. Medical treatment is associated with mortality of 60% to 80%, which is lowered to 20% or less with surgical intervention (e.g., nephrectomy, percutaneous drainage).

Renal Malacoplakia. Malacoplakia is a chronic granulomatous disorder of unknown etiology involving the genitourinary, gastrointestinal, skin, and pulmonary systems.[60] It is characterized by an unusual inflammatory reaction to a variety of infections and is manifested by the accumulation of macrophages containing calcified bacterial debris called *Michaelis-Gutmann bodies* (Fig. 51.8). The underlying disorder appears to be a monocyte-macrophage bactericidal defect. The diagnosis is made by histologic examination of involved tissue. Genitourinary malacoplakia, most often involving the bladder, is usually associated with gram-negative UTI. Patients with renal malacoplakia generally have fever, flank pain, pyuria and hematuria, bacteriuria, and, if both kidneys are involved, impaired renal function. CT usually shows enlarged kidneys with areas of poor enhancement, and the condition may be indistinguishable from other infectious or neoplastic lesions. On occasion, the malacoplakia may extend through the renal capsule into the perinephric space, simulating a renal carcinoma (see Fig. 51.8). Treatment consists of therapy with a broad-spectrum antimicrobial, attempted correction of any underlying complicating conditions, and improvement of renal function. Nephrectomy is recommended for advanced unilateral disease. When the disease is bilateral or occurs in a transplanted kidney, the patient's prognosis is very poor.

Xanthogranulomatous Pyelonephritis. Xanthogranulomatous pyelonephritis is a poorly understood, uncommon but severe chronic destructive

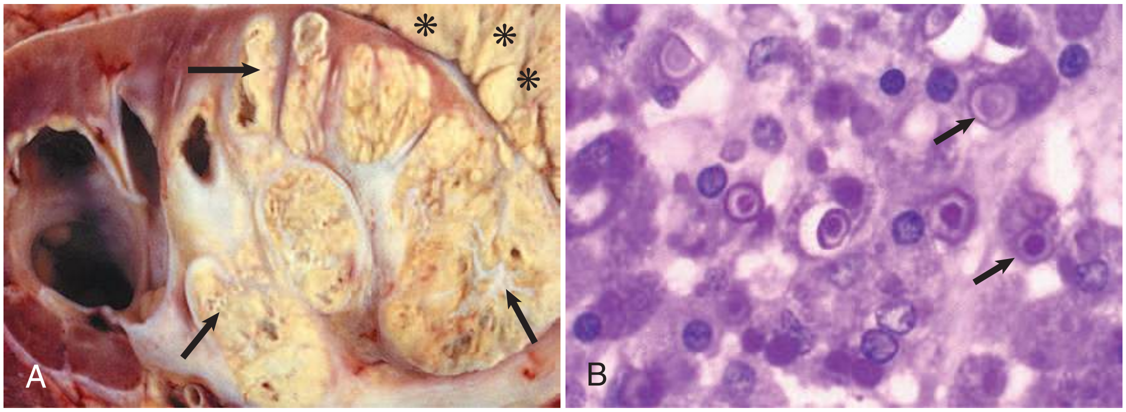

Fig. 51.8 Renal malacoplakia. (A) Malacoplakia involving most of the kidney *(arrows)* with extension through the capsule *(asterisks)*. A small portion of normal kidney is present associated with hydronephrosis secondary to obstruction by the malacoplakia. (B) The kidney tissue shows many macrophages containing intracytoplasmic inclusions (*arrows* identify two particularly well-demarcated macrophages with Michaelis-Gutmann bodies). (Courtesy L. Truong, Baylor College of Medicine, Houston, Tex, and N. Sheerin, Guy's Hospital, London.)

granulomatous inflammation of renal parenchyma associated with obstruction and infection of the urinary tract.[61] The renal parenchyma is replaced with a diffuse or segmental cellular infiltrate of foam cells, which are lipid-laden macrophages. The process also may extend beyond the renal capsule to the retroperitoneum. Its pathogenesis appears to be multifactorial, with infection complicating obstruction and leading to ischemia, tissue destruction, and accumulation of lipid deposits. Patients with xanthogranulomatous pyelonephritis are characteristically middle-aged women and have chronic symptoms such as flank pain, fever, chills, and malaise. Flank tenderness, a palpable mass, and irritative voiding symptoms are common. The urine culture is usually positive with *E. coli*, other gram-negative bacilli, or *S. aureus*. CT generally shows an enlarged nonfunctioning kidney, often the presence of calculi and low-density masses (xanthomatous tissue), and in some cases, involvement of adjacent structures (Fig. 51.9). It may be difficult to distinguish from neoplastic disease. Broad-spectrum antimicrobials are indicated, but total or partial nephrectomy is usually necessary for cure.

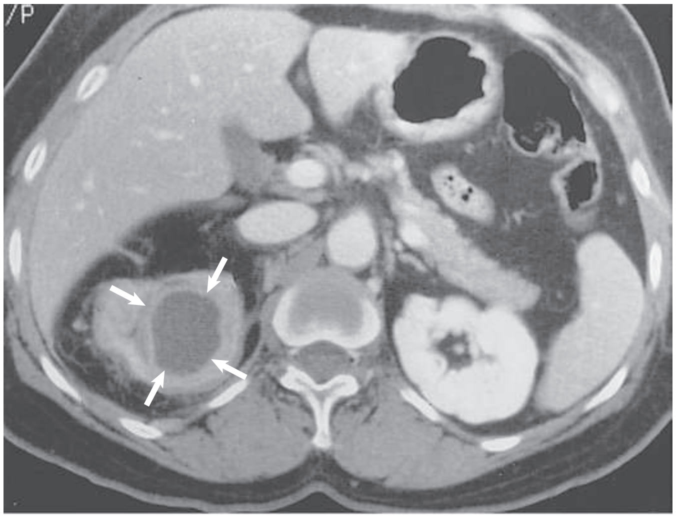

Fig. 51.9 Xanthogranulomatous pyelonephritis. Contrast-enhanced CT scan with the inflammatory mass outlined by *arrows*. Pathologic diagnosis confirmed xanthogranulomatous pyelonephritis. (Courtesy W. Bush, University of Washington, Seattle, Wash.)

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is common and generally benign.[7,37] Pyuria is often present, especially in elderly people, and is a predictor for subsequent symptomatic UTI in some groups. Causative uropathogens are the same as those causing UTIs in the same population. Screening for and treatment of asymptomatic bacteriuria is generally not warranted.[7] In young women with recurrent UTI, asymptomatic bacteriuria may be protective against symptomatic recurrence and treatment may increase the risk for such recurrences.[62] However, patients at high risk for serious complications warrant a more aggressive approach to diagnosis and treatment, including pregnant women and patients undergoing urologic surgery. Current management strategies in patients with a renal transplant, including long-term antimicrobial prophylaxis, help prevent both asymptomatic bacteriuria and symptomatic UTI. It is not clear, however, whether screening for or treatment of asymptomatic bacteriuria in such patients is worthwhile.[7] Some authorities advise treatment of asymptomatic bacteriuria found in patients with anatomic or functional abnormalities of the urinary tract, diabetic patients, and patients with urea-splitting bacteria (e.g., *P. mirabilis, Klebsiella* spp.).[37] Evidence-based guidelines for screening and treatment of asymptomatic bacteriuria in these populations are needed.

Asymptomatic bacteriuria in catheterized patients in hospitals and long-term care facilities, although thought to be generally benign, represents a large reservoir of antimicrobial-resistant urinary pathogens that increases the risk for cross-infection among catheterized patients and results in frequent inappropriate antimicrobial use.[50]

IMAGING OF THE URINARY TRACT

Urologic consultation and evaluation of the urinary tract should be considered in patients who present with symptoms or signs of obstruction, urolithiasis, flank mass, or urosepsis. Similarly, such an evaluation should be considered for those patients with presumptive uncomplicated or complicated UTI who have *not* had a satisfactory clinical response after 72 hours of treatment, to exclude complicating factors. A renal ultrasound can detect the size and contour of the kidneys and bladder, the presence of a renal mass or abscess, certain renal and ureteral calculi, hydronephrosis suggestive of obstructive uropathy, and elevated postvoid residual urine.[63] A plain abdominal radiograph (kidneys, ureters, bladder [KUB]) can identify radiopaque calculi along the genitourinary tract, especially proximal and distal ureteral stones that can be missed on ultrasound. However, renal ultrasound and KUB are less sensitive than CT for detection of many conditions in patients with complicated UTI. Thus any finding suggesting mass or complex fluid collection should prompt follow-up imaging with CT. CT offers fine anatomic detail and is thus the superior study for evaluation of focal inflammation, renal or perirenal abscess and masses, and both radio-opaque and radiolucent stones. However, CT also carries the greatest risk profile, exposing the patient to both intravenous contrast and ionizing radiation.[63] Non–contrast-enhanced spiral CT is a rapid, safe, and sensitive method for evaluating patients with suspected renal stones. Radionuclide imaging procedures have no role in the evaluation of adults with UTI, although they are very useful in children with pyelonephritis (see Chapter 61).

Excretory urography and cystoscopy in women with recurrent cystitis rarely demonstrate abnormalities or alter management[3] and therefore are not recommended. Likewise, imaging studies in young women with acute pyelonephritis are also generally not cost-effective and have a low diagnostic yield, although it is reasonable to obtain such studies after two episodes of pyelonephritis or if any complicating factor is present (see Box 51.1). Imaging studies and cystoscopy are probably unnecessary in a man who has had a single UTI with no obvious complicating factors and whose infection responds promptly to treatment.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following antimicrobials is *not* recommended for first-line use for uncomplicated cystitis by the Infectious Disease Society of America treatment guidelines?
   - **A.** Fosfomycin
   - **B.** Ciprofloxacin
   - **C.** Cotrimoxazole
   - **D.** Nitrofurantoin
2. What approach has not been shown to be effective in the management of recurrent cystitis in women?
   - **A.** Postcoital antimicrobial prophylaxis
   - **B.** Daily antimicrobial prophylaxis
   - **C.** Intermittent self-treatment
   - **D.** Periodic screening and treatment of asymptomatic bacteriuria
3. Which of the following antimicrobials should be *avoided* in the treatment of prostatitis?
   - **A.** Ciprofloxacin
   - **B.** Nitrofurantoin
   - **C.** Levofloxacin
   - **D.** Trimethoprim-sulfamethoxazole
4. In which of the following conditions is screening for and treatment of asymptomatic bacteriuria indicated?
   - **A.** Elderly men and women
   - **B.** Catheterized men and women
   - **C.** Pregnant women and patients undergoing urologic instrumentation
   - **D.** After treatment for acute pyelonephritis

52

Tuberculosis of the Urinary Tract

R. Kasi Visweswaran, K. P. Jayakumar

DEFINITION

Tuberculosis (TB) is a major global health problem. According to a recent report by the World Health Organization (WHO), there were nearly 9.6 million new cases in 2014, with 1.1 million deaths among HIV-negative and 0.39 million deaths among HIV-positive individuals attributed to TB.[1] Between 1999 and 2020, there will be an estimated 1 billion new cases of TB if control measures are not improved. In developed countries, TB commonly affects older individuals and immigrants from countries with high prevalence. The incidence of TB is 100 times greater in HIV-infected individuals, and TB is the most common fatal opportunistic infection in people with HIV.[2] TB also is more common in patients with chronic kidney disease (CKD) than those with normal kidney function, especially when associated with anatomic abnormalities or immunosuppression. In some endemic areas, TB has been reported to occur in up to 8.7% of patients on hemodialysis, 12.3% of renal allograft recipients,[3] and 9.3% of children with nephrotic syndrome.[4]

Genitourinary TB constitutes 9% of extrapulmonary TB. In HIV-negative patients[5] it is almost always secondary to a symptomatic or asymptomatic primary lesion in the lung. Renal involvement also may occur as a complication of miliary TB.

The incidence of multidrug-resistant (MDR TB) and extensively drug-resistant TB (XDR TB) is increasing. According to WHO estimates, there were 480,000 new cases of MDR TB worldwide and 190,000 deaths in 2014[1] and 9% of people with MDR TB also have XDR TB.

ETIOLOGY

The tubercle bacillus is a nonmotile, nonsporing, strictly aerobic straight or slightly curved rod-like bacillus that is weakly gram-positive and acid and alcohol-fast (Fig. 52.1). The cell wall has high concentration of waxy lipids (mainly mycolic acids) that make the organism resistant to acids, alkalis, antibiotics, osmotic agents, and intracellular events. The core of the cell wall is composed of peptidoglycan that is linked to galactofuran and arabinofuran, which is further linked to mycolic acid. The mycolyl transferase and lipoarabinomannan (LAM) is called antigen 85 of mycolic acid.[6] The most superficial layer consists of glycolipids and polypeptides (Fig. 52.2). The polypeptides are isolated and purified to make the skin testing antigen purified protein derivative. The following characteristics and composition of the lipid shell wall of mycobacteria have enabled their survival in the Earth for thousands of years and under adverse conditions (Table 52.1).

Whereas most TB, including genitourinary TB, is caused by *Mycobacterium tuberculosis,*[7] other mycobacteria may rarely cause clinical disease, especially in immunocompromised hosts. These include *M. avium-intracellulare*, *M. kansasii, M. bovis, M. fortuitum,* and *M. szulgai. M. chelonei abscessus* belong to the group of "rapid growers" among the atypical mycobacteria and cause abscesses after injection or percutaneous procedures, especially in patients with diabetes.[8]

PATHOGENESIS

The clinical and pathologic manifestations of TB depend on the virulence of the organism and the effectiveness of the host response. The host response may lead to complete containment of infection or result in an illness of varying severity.[9] Between-strain differences also may determine whether an infected person develops primary TB, reactivation TB, or a chronic asymptomatic infection. A low serum level of 25-hydroxyvitamin D also may compromise cell-mediated immunity and increase the risk for activation of latent TB.[10]

When an infected droplet with the size of 1 to 5 μm is deposited in the respiratory tract, tonsillar fossa, or gastrointestinal tract, a primary focus develops with the formation of a nonspecific, asymptomatic granuloma. The organisms from the primary focus drain to the regional lymph gland, causing its enlargement, resulting in the *primary complex*. This is often asymptomatic and self-limited.

Bacilli from the regional lymph node also may enter through the thoracic duct into the blood, resulting in silent dissemination to various sites, including the renal cortex (see Fig. 52.3). Here the bacilli elicit an inflammatory response, resulting in granuloma formation that may heal and form a scar, remain dormant for many years, or rupture into the proximal tubule of the nephron. The bacilli in the nephron are trapped at the level of the loop of Henle, where they multiply. The relatively poor blood flow, hypertonicity, and high ammonia concentration in the renal medulla impair the immune response and favor the formation of medullary granulomas. These granulomas (tuberculomas), which contain macrophages, may undergo coagulative necrosis, forming cavities filled with cheese-like caseous material (Fig. 52.4) that occasionally rupture into the calyx.

The renal medulla is the most common site of involvement of clinical renal TB and is usually unilateral. When this caseous focus ruptures into the collecting system, cavities and ulcers are formed, and involvement of renal papillae may lead to sloughing and papillary necrosis. Healing in the kidney occurs by fibrosis and scarring, resulting in strictures and obstruction. Calcification commences intracellularly because of the accumulation of phosphate ions from the disintegration of nucleoproteins and entry of calcium ions from cell membrane damage. These dystrophic calcific lesions may harbor live or dormant mycobacteria, and such dystrophic lesions are considered active disease and not signs of healing. Dystrophic calcification of damaged structures may result in a nonfunctioning kidney called *putty* or *cement* kidney. Spread of TB to contiguous structures may occur; ureteritis is common and may result in strictures and obstructive uropathy (Fig. 52.5).

The bladder may develop hyperemia near the ureteral orifice, followed by superficial ulcers and granulomatous changes involving all layers (pancystitis). Healing by fibrosis at the ureteral orifice results in a refluxing "golf-hole" ureter. Extensive fibrosis of the bladder wall results in a thick, small-capacity bladder called *thimble* bladder (Fig. 52.6). Bladder infection also may rarely result from instillation of bacillus Calmette-Guérin (BCG) in the bladder as part of treatment of superficial bladder carcinomas.

Involvement of the genital tract is also common. As many as 70% to 80% of men with TB of the urinary tract have epididymitis, prostatitis, seminal vesiculitis, orchitis, or cold abscesses (gradual pus accumulation with no signs of acute inflammation). In women, genital tract involvement is less common, but, if present, usually presents as salpingitis, often diagnosed during investigation for infertility.

TB can be transmitted from the donor to recipient through renal transplantation, and the risk can be minimized by thorough screening of the donor.[11]

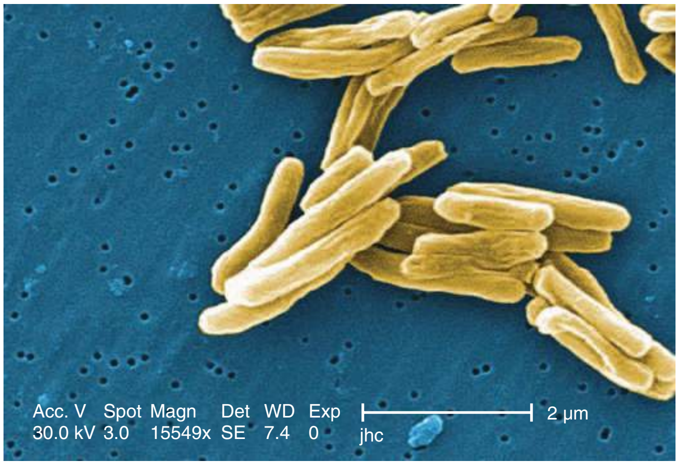
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Fig. 52.1 Scanning electron microscopy of *Mycobacterium tuberculosis*. The bacillus is a straight or slightly curved rod about 2 to 4 µm long and 0.3 to 0.5 µm wide. (high magnification, 15,549×). (Courtesy Ray Butler MS, CDC. Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention. Atlanta, GA.)

CLINICAL MANIFESTATIONS

Urinary tract TB may be asymptomatic or may mimic other disorders. Patients may present with constitutional symptoms or symptoms related

TABLE 52.1 Cell Wall Characteristics Enabling Organisms to Survive Under Adverse Conditions

Composition of Cell Wall	Factors for Survival
Mycolic acid	Resist proteolysis and uptake into phagolysosomes
Lipoarabinomannan (LAM)	Detected by CD1 T cells
Muramyl dipeptide	Stimulate T cell response (granuloma formation)
Glycolipids	Inhibit macrophage function
Inert lipids and surface proteins	Dormant survival inside phagocytes

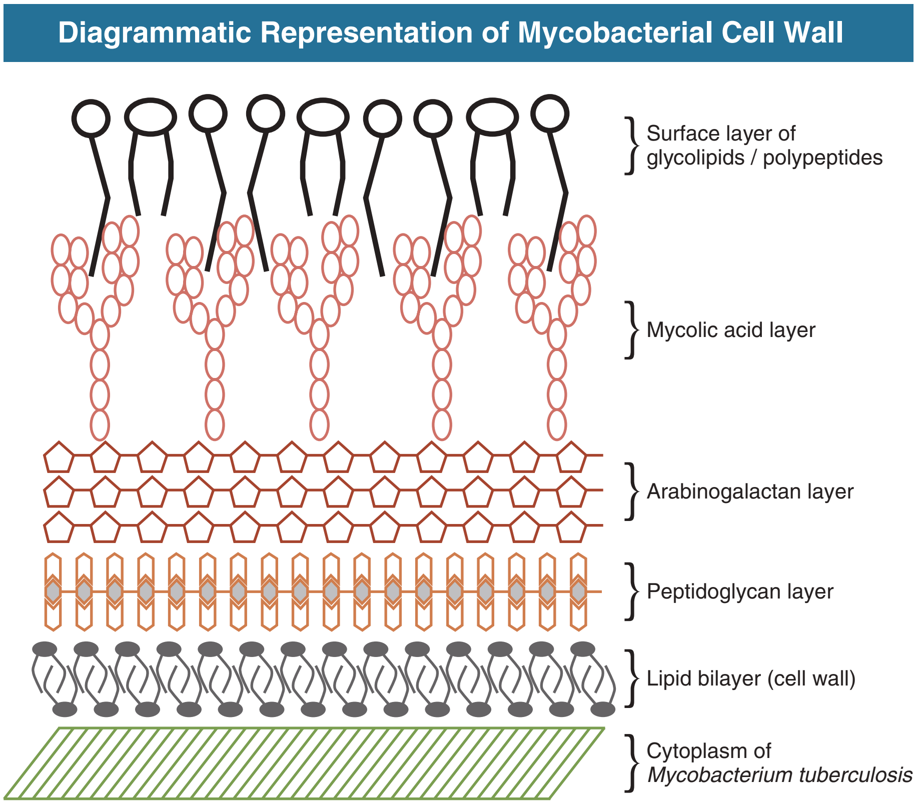
Diagrammatic Representation of Mycobacterial Cell Wall
Surface layer of glycolipids / polypeptides
Mycolic acid layer
Arabinogalactan layer
Peptidoglycan layer
Lipid bilayer (cell wall)
Cytoplasm of *Mycobacterium tuberculosis*

Fig. 52.2 Diagrammatic representation of mycobacterial cell wall.

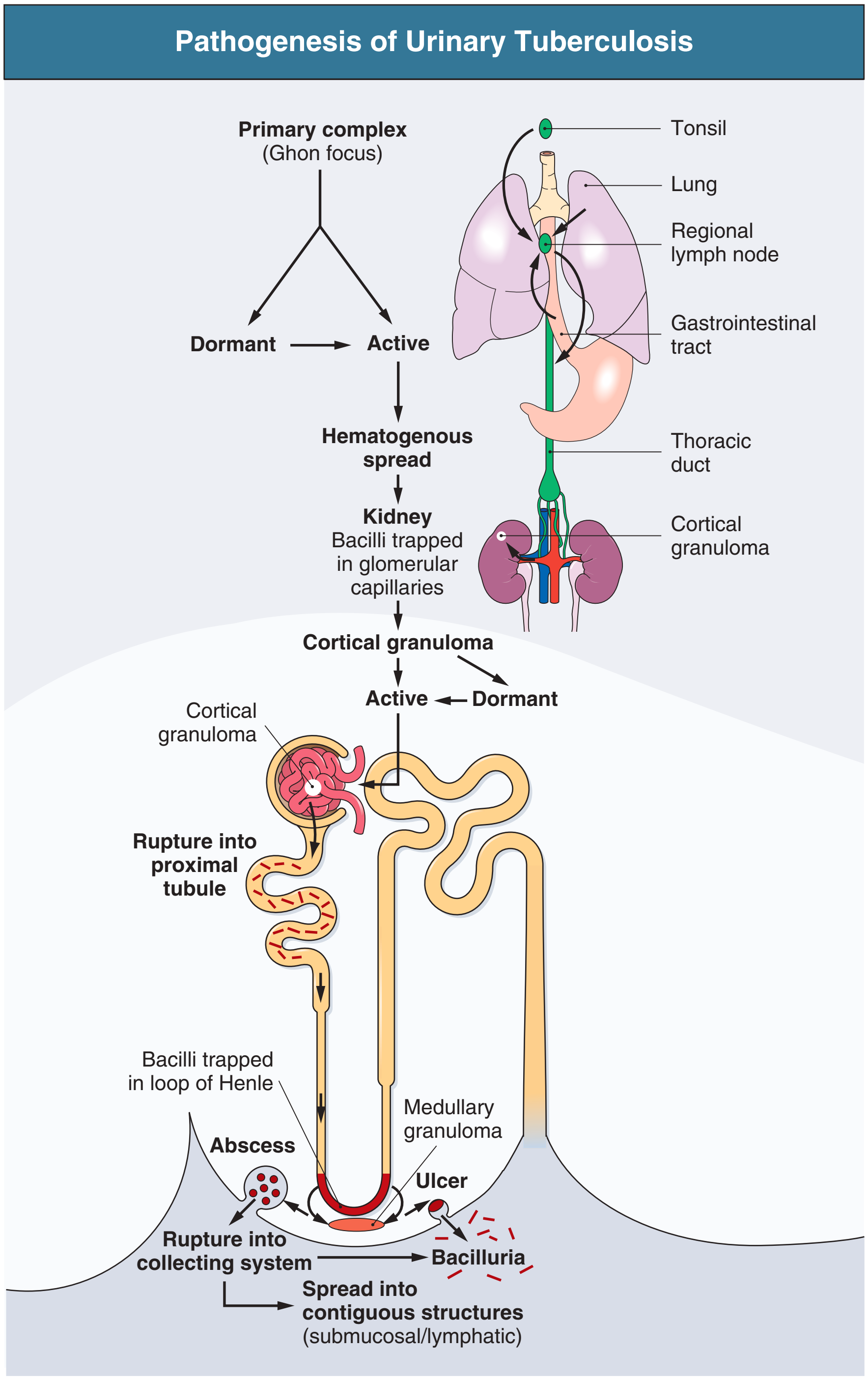
Pathogenesis of Urinary Tuberculosis
Primary complex
(Ghon focus)
Dormant
Active
Hematogenous spread
Kidney
Bacilli trapped in glomerular capillaries
Cortical granuloma
Active
Dormant
Tonsil
Lung
Regional lymph node
Gastrointestinal tract
Thoracic duct
Cortical granuloma
Cortical granuloma
Rupture into proximal tubule
Bacilli trapped in loop of Henle
Medullary granuloma
Abscess
Ulcer
Rupture into collecting system
Bacilluria
Spread into contiguous structures
(submucosal/lymphatic)

Fig. 52.3 Pathogenesis of urinary tuberculosis.

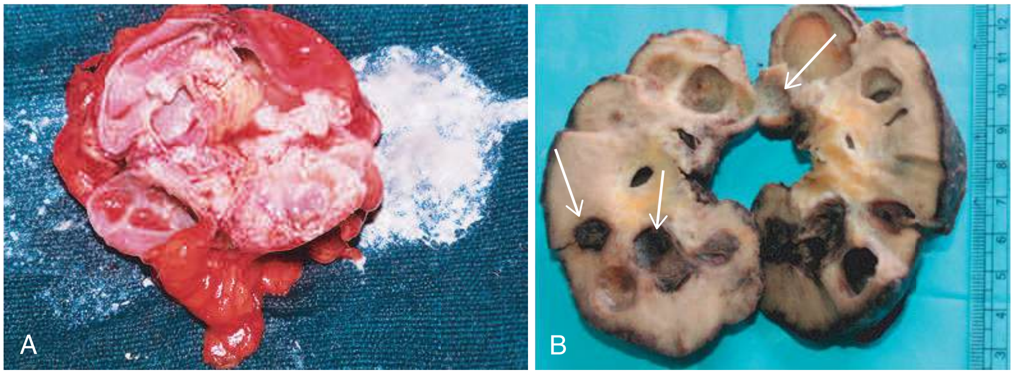

Fig. 52.4 Renal tuberculosis. (A) Cut section of kidney shows areas of cavitation and caseation necrosis (white chalky material). (B) Cavitating lesions *(arrows)* are caused by tuberculosis in cut section of kidney (autopsy). (**B,** Courtesy Department of Pathology, Amrita Institute of Medical Sciences, Kochi, Kerala, India.)

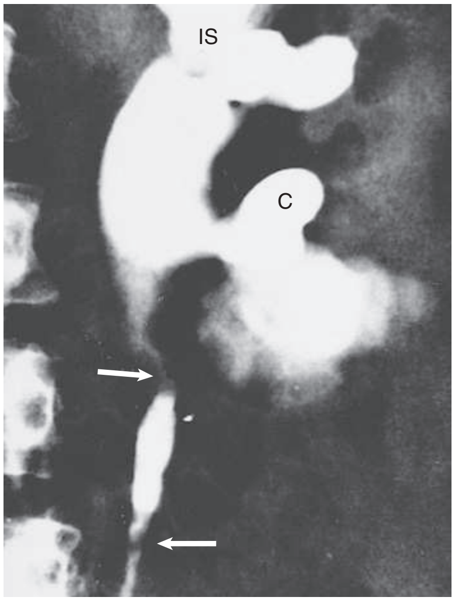

Fig. 52.5 **Multiple ureteral strictures.** Strictures *(arrows)* associated with dilated ureter, infundibular stenosis *(IS),* and caliectasis *(C)* are seen in this intravenous urogram. (Courtesy Professor K. Sasidharan, Kasturba Medical College, Manipal, India.)

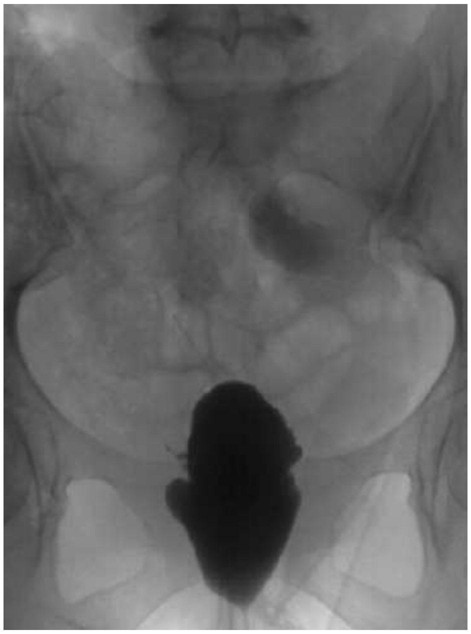

Fig. 52.6 **Thimble bladder.** Cystogram shows small-capacity bladder.

to the lower urinary tract, abdomen, or genitalia (Table 52.2).[12] A high index of suspicion enables early diagnosis. Most patients are 20 to 40 years of age, with a male-to-female ratio of 2 : 1. Because active genitourinary TB manifests 5 to 15 years after primary infection, it is relatively rare in children. Risk factors for TB include close contact with sputum smear–positive individuals, social deprivation, neglect, immunosuppression, HIV infection, diabetes mellitus, CKD, vitamin D deficiency, and other debilitating illnesses.

Asymptomatic Presentations

Almost 25% of patients have no clinical or laboratory evidence of any abnormality, and the diagnosis of urinary TB is made on investigation for other diseases, during surgery, or at autopsy. Another 25% have asymptomatic urinary abnormalities, usually persistent asymptomatic pyuria or hematuria. In patients with persistent pyuria, conventional urine cultures do not yield any growth, and the urine is usually acidic (acid-sterile pyuria). Renal calcification may be asymptomatic and detected as an incidental finding on investigations.

Lower Urinary Tract Symptoms

Of the patients who are symptomatic, lower urinary tract symptoms, such as frequency, urgency, dysuria, nocturia, frank pyuria, or hematuria, occur in more than 75% of patients with TB. Increased urinary frequency is an early symptom and results from inflammation of the bladder. The defect in the urinary concentrating mechanism explains the nocturia. Recurrent bouts of painless gross macroscopic hematuria should alert the clinician to the possible diagnosis of urinary TB, although glomerular diseases such as immunoglobulin A (IgA) nephropathy also should be considered. Macroscopic hematuria in urinary TB is a result of bleeding from the ulcerating lesions, inflammation of the urothelium, or rupture of a blood vessel in the vicinity of a cavity. Episodes of frank pyuria also may be a manifestation of renal TB and indicate either secondary bacterial infection or drainage of a caseous focus into the collecting system. In advanced disease, frequency and urgency of micturition related to reduced bladder capacity, incomplete emptying, increased susceptibility to infection and secondary vesicoureteral reflux (VUR) may also occur.

TABLE 52.2 Clinical Features of Urinary Tuberculosis

Features	Frequency (%)	Symptoms
Asymptomatic	25	Detected during autopsy, surgery, or investigations for other diseases
Asymptomatic urinary abnormalities	25	Persistent pyuria, microscopic abnormalities, hematuria
Lower urinary tract symptoms (most common)	40	Frequency, urgency, dysuria, incontinence, nocturia, suprapubic pain, perineal pain
Male genital tract involvement	75	Epididymitis, hemospermia, infertility, reduced semen volume
Female genital tract involvement	<5	Amenorrhea, infertility, vaginal bleeding, pelvic pain
Constitutional symptoms	<20	Fever, reduced appetite, anorexia, weight loss, night sweats
Miscellaneous	—	Urolithiasis, hypertension, acute kidney injury, chronic kidney disease, abdominal colic, abdominal mass

Proteinuria and Nephrotic Syndrome

Long-standing renal TB may result in mild tubular proteinuria (<1 g/24 h) in about 50% or more than 1 g/24 h in 15% of patients. In rare instances when nephrotic proteinuria occurs, it could be due to mesangioproliferative glomerulonephritis or secondary amyloidosis resulting from accumulation of SAA protein.

Low Glomerular Filtration Rate

Some patients with urinary TB present with reduced glomerular filtration rate (GFR), pyuria, microscopic hematuria, and proteinuria, but the urine cultures for mycobacteria are repeatedly negative. These patients respond favorably to antituberculous chemotherapy combined with corticosteroids. The kidneys are of normal size and show noncaseating granulomas, diffuse interstitial nephritis, or caseating granulomas containing the bacilli in 75% of the biopsy samples.[13]

Pain

Colicky pain may occur as a presenting manifestation of urinary TB when it is associated with stone, blood clot, sloughed papilla, or other causes of acute obstruction. Obstruction of the upper tract may be associated with dull aching pain in the loin. Severe suprapubic pain with backache and dysuria suggests acute tuberculous cystitis. Patients with TB cystitis may show worsening of symptoms such as frequency and urgency after initiation of antituberculous treatment because of fibrosis and bladder wall contraction. This should not be mistaken for nonresponsiveness to therapy because it is part of the healing process.

Stone Formation

Nephrolithiasis may occur in 7% to 18% of patients. Secondary infection with *Escherichia coli* may be seen in 20% to 50% of patients.

Genital Involvement

In men, the most common genital involvement is epididymitis that manifests with scrotal discomfort, mass, cold abscess, or asymptomatic. When the cold abscess ruptures, a nonhealing posterior scrotal sinus discharging caseous material may form. Thickening of the vas deferens may result in a “beaded” texture. TB of the prostate may manifest with lower urinary tract symptoms and perineal pain. The prostate may be hard or boggy. Penile and urethral TB may manifest with strictures, fistulas, ulcers, or papulonecrotic skin lesions. Hemospermia, reduction of semen volume, and infertility are other manifestations of genital involvement. Direct spread of *M. tuberculosis* to a sexual partner is also possible.

Only 5% of women with renal TB also have genital TB. The major manifestation of genital involvement in women is infertility resulting from adherent salpingitis. Secondary amenorrhea, vaginal bleeding, and pelvic pain caused by inflammation may occur.

Other Manifestations

Anemia is seen in less than 20% of patients with nonmiliary disease, but the frequency is higher in those with CKD stages 3 to 5. A few patients may develop nephrogenic diabetes insipidus or renal tubular acidosis. Hyporeninemic hypoaldosteronism may result from the tubulointerstitial injury secondary to obstructive uropathy.[14,15] Renal function is usually normal, but CKD stages 3 to 5 may develop if both kidneys are extensively damaged.

Hypertension is unusual in renal TB, but intimal proliferation of vessels near inflamed areas may lead to segmental ischemia and renin release.[16] In patients with a nonfunctioning kidney, nephrectomy may help improve the hypertension. Relief of any obstruction also may help lower the blood pressure.

Constitutional symptoms, such as fever, weight loss, night sweats, fatigue, and anorexia, occur in less than 20% of patients and indicate active infection in other organs or secondary bacterial infection of the urinary tract. All patients who present with constitutional symptoms must be carefully examined to identify pulmonary, lymph node, or skeletal TB. The chest radiograph may show evidence of active or healed tuberculous lesions in more than half of cases. Rarely, hypercalcemia may be present because of increased synthesis of calcitriol in the granulomas.

PATHOLOGY

Urinary TB may present as a miliary or ulcerocavernous pathologic process. The miliary form of TB is rare and is seen particularly in immunosuppressed individuals. The gross appearance of the kidney is characteristic; the cortex is studded with yellowish white, hard, pinhead-sized nodules that on microscopy show several coalescent granulomas with central caseation.

In the more common ulcerocavernous form, the kidneys will initially appear normal or show yellow nodules on the outer surface. On cut section, granulomas and ulcers in the renal pyramid or medullary cavities may be seen. Larger cavities filled with caseous material communicating with the collecting system also may occur (see Fig. 52.4A and B). Other gross findings include multiple ulcers in the infundibular region of the calyces, calyceal stenosis with caliectasis, ulcers or strictures of the ureter with hydronephrosis, pyonephrosis, subcapsular collections, and perinephric abscesses. The bladder may show ulcers or be grossly fibrotic and contracted (thimble bladder) (see Fig. 52.6)

In early disease, neutrophilic infiltration with phagocytosis of the bacilli may be seen. Subsequent histologic features depend on the virulence of the organism and the cell-mediated immunity. With an effective cell-mediated response, granulomas are seen, characterized by the presence of macrophages with engulfed bacilli surrounded by epithelioid cells and Langhans giant cells (Fig. 52.7). There is often a cuff of lymphocytes and plasma cells surrounding the lesion. Healing occurs by fibrosis and scarring. In those with a less effective immune response, caseating necrosis is characterized by amorphous, cheese-like eosinophilic material replacing the normal tissue architecture. The presence of caseous necrosis generally implies that the lesion is active. Later, this may calcify. Dystrophic calcification suggests activity rather than healing.

Kidneys also may be enlarged from amyloidosis. In tuberculous interstitial nephritis, interstitial granuloma formation associated with normal-sized kidneys and negative urine cultures is seen.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A high index of suspicion is necessary to diagnose genitourinary TB. Elderly patients, those recently exposed to infection,

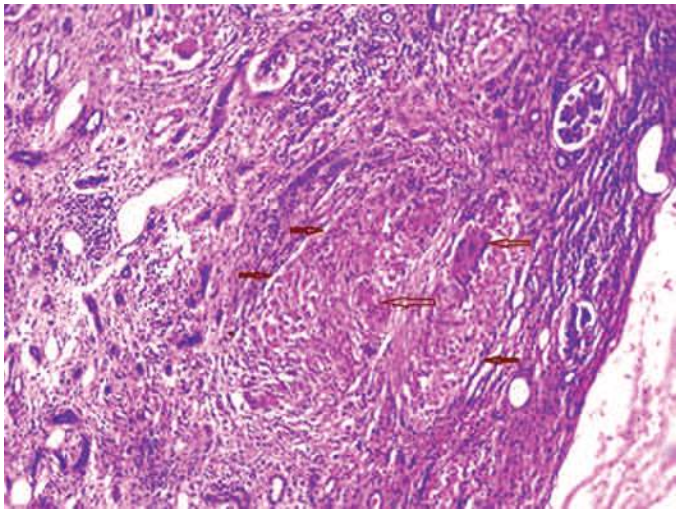

Fig. 52.7 Needle biopsy sample showing granuloma formation and Langhans giant cell in the kidney. Section from renal biopsy showing outline of evolving granuloma *(bold short arrows)* and multinucleated Langhans giant cell *(open arrows)* (Courtesy Department of Pathology, Government Medical college, Kottayam, India.)

immunocompromised individuals, and patients with TB elsewhere are at high risk. Suspicion also may occur if there is sterile pyuria, which is present in 50% of patients. The tuberculin test (Mantoux test) is useful for proving infection (or prior immunization with BCG), but not necessarily disease. A positive test response only suggests prior exposure to the antigen and does not indicate active infection. A negative test response in the absence of an immunosuppressed state helps rule out tuberculous infection in countries with high TB burden. Patients with stage 4 or 5 CKD, and after transplantation, particularly in the setting of malnutrition, may display anergy and have a false-negative result.[17] *M. tuberculosis*–specific enzyme-linked immunospot (ELISPOT) assay is useful for rapid confirmation of diagnosis.

Isolation of *M. tuberculosis* by urine culture is the definitive diagnostic test. Fully voided early-morning urine samples for 3 to 5 consecutive days are cultured on two standard solid mycobacterial culture media: egg-based Lowenstein-Jensen and agar-based Middlebrook 7H10. These transparent media enable earlier visualization of microcolonies, which grow by 6 to 12 weeks. Sensitivity tests are performed to choose the optimum chemotherapeutic agents. However, this may take an additional 6 to 12 weeks. Any tissue specimen submitted for mycobacterial culture should be macerated with sterile sand by a mortar and pestle before inoculation. Direct demonstration of acid-fast bacilli (AFB) in urine by Ziehl-Nielsen stain is not reliable for diagnosis because *Mycobacterium smegmatis,* a saprophyte, may be easily mistaken for *M. tuberculosis*.

Rapid methods for diagnosis of TB are increasingly available. With use of the radiometric broth method for AFB isolation, a positive growth can be obtained in about 9 days. Serologic tests with the soluble antigen fluorescent antibody test and polymerase chain reaction (PCR) can be used for early diagnosis of TB.[18] ELISPOT assays to monitor cellular immune response are used as in vitro diagnostic tests. They help accurately detect *M. tuberculosis* antigen–specific T cells and provide qualitative and quantitative information. The test results are unaffected by prior tuberculin testing or low CD4 counts.[19] Another reliable and simple test using whole blood is based on quantifying the interferon-γ (IFN-γ) released from the white blood cells that have been exposed to some of the mycobacterial antigens. Whole-blood IFN-γ release assays, available, for example, as the QuantiFERON test, have been approved by the U.S. Food and Drug Administration as an aid for diagnosing latent and active tuberculous infection replacing the conventional tuberculin skin testing[20] with greater than 95% sensitivity and 90% specificity. The availability of the result in 24 hours is the main advantage and has led to its widespread use.[21] Detection of LAM in urine using the lateral flow assay is a simple and rapid test for the detection of TB in patients with advanced HIV infection with a CD4 T lymphocyte count less than 200 cells/µl. The results are available in 30 minutes. A cartridge-based, rapid, and reliable automated test endorsed by the WHO to identify targeted nucleic acid sequences in the *M. tuberculosis* genome (Xpert MTB/RIF) is also available.[22] This test has a pooled sensitivity of 98% and specificity of 99%. In sputum AFB-positive cases, the sensitivity was 100%. This test detects the DNA sequences specific for *M. tuberculosis* and rifampin resistance by PCR, and results can be generated in 2 hours.[22] Ultrasound-guided fine-needle aspiration cytology is useful as a diagnostic tool in defining the granulomatous nature of the lesion in patients with positive urine culture. Histologic diagnosis is made by identifying the pathologic triad of caseating necrosis, loose aggregates of epithelioid histiocytes, and Langhans giant cells.

Plain radiographs of the chest and spine show active or healed tuberculous lesions in 60% to 70% patients with TB of urinary tract. Imaging the renal area may reveal extensive dystrophic calcification in advanced renal TB (Fig. 52.8). Sometimes, thick, wavy, puffy, cotton-like dense calcification resembling a cumulus cloud may be seen. Other abnormalities, such as minimal erosion of the tip of the calyx with spasticity, incomplete filling, distortion, infundibular stenosis, hydrocalicosis, multiple ureteral strictures, hydronephrosis, hydroureter, or nonvisualization of the kidney may be seen in the excretory urogram in 70% to 90%. The renal pelvis, which may be dilated initially, may eventually be obliterated, leading to a distorted appearance called *hiked-up pelvis* (Kerr kink sign). Irregularities or multiple strictures lead to a beaded or corkscrew appearance of the ureter or hydronephrosis. Later, thickening and straightening of the whole ureter may occur ("pipestem" ureter). The bladder may appear irregular and fibrosed, and VUR may occur. Antegrade or retrograde pyelography can identify the number, length, or site of ureteral strictures and assist in placement of a ureteric stent across the stenotic segment.

High-resolution ultrasound is useful to rule out obstruction and study the parenchyma closely. The earliest finding is mucosal thickening and calyceal irregularity followed by granulomas, small abscesses, or calcification[23] (Figs. 52.9 and 52.10).

Computed tomography (CT) is the most sensitive method for identifying renal parenchymal scarring, calcification, and cavitary lesions (Fig. 52.11). Cortical thinning is a common CT finding and may be either focal or global. These imaging modalities are helpful in follow-up of patients with cavities or mass lesions in the kidney. Cystoscopy under general anesthesia helps visualize the mucosal lesions, the golf-hole ureteral orifice, or the efflux of white toothpaste-like caseous material. Biopsy is avoided during the acute stage because of the risk for dissemination of TB.

Differential Diagnosis

TB mimics numerous diseases. Chronic nonspecific urinary tract infections may be confused with renal TB, especially because secondary bacterial infection may complicate 20% of cases of renal TB. Absence of response to usual antibiotics should raise suspicion of urinary TB. Conditions causing recurrent painless hematuria, such as IgA nephropathy (see Chapter 23) and schistosomiasis (see Chapter 54), are often misdiagnosed as TB in endemic areas. In interstitial cystitis, lower urinary

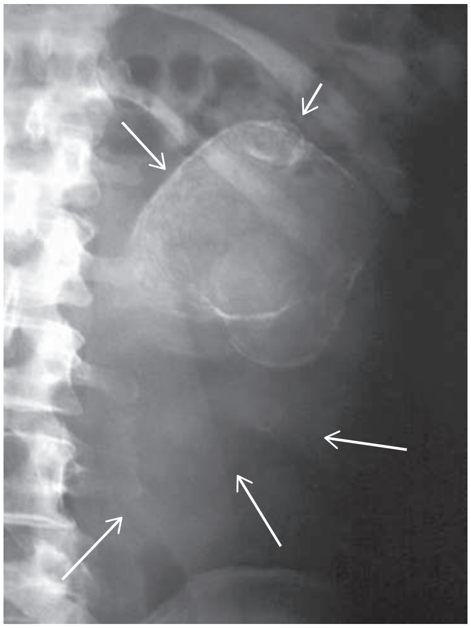

Fig. 52.8 Renal calcification. Plain radiograph shows calcification in the upper half of the left kidney. *Arrows* outline the kidney.

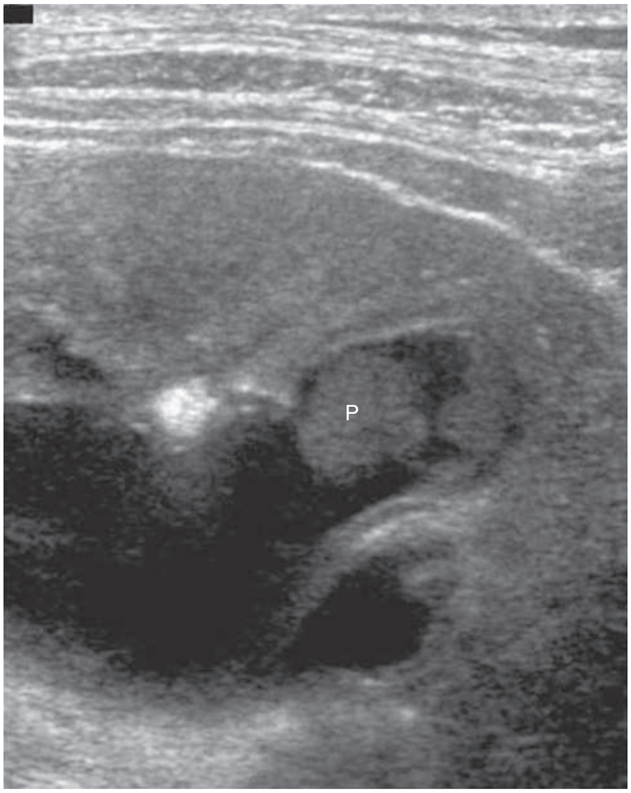

Fig. 52.9 Necrosed papilla. High-resolution ultrasound scan of the kidney shows a sloughed, necrosed papilla *(P)* in the calyx. (From reference 23, with permission of the American Institute of Ultrasound in Medicine.)

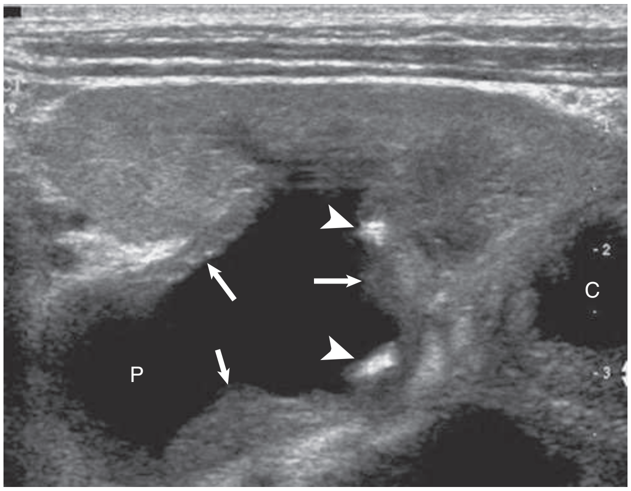

Fig. 52.10 Thickened mucosa and calcifications. High-resolution transverse ultrasound scan of kidney shows mucosal thickening *(arrows)* of calyces and the pelvis *(P)*. There are calcifications of the wall of the calyx and pelvis *(arrowheads)*. A parenchymal cavity *(C)* is also shown. (From reference 23, with permission of the American Institute of Ultrasound in Medicine.)

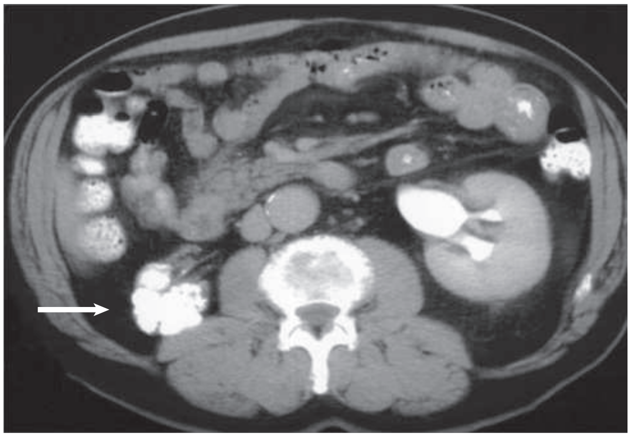

Fig. 52.11 Calcified kidney. Contrast-enhanced CT image shows contracted calcified right kidney *(arrow)* and normal opposite side.

tract symptoms similar to tuberculous cystitis may occur, but the urinalysis does not show gross pyuria, and cultures for AFB are negative. On radiologic examination, chronic pyelonephritis, renal papillary necrosis, medullary sponge kidney, calyceal diverticulum, renal carcinoma, xanthogranulomatous pyelonephritis, and multiple small renal calculi need to be differentiated from TB. In a few reported cases of pseudotuberculous pyelonephritis, caseating granulomas resembling TB were observed in the renal parenchyma, but no mycobacteria or other microorganisms were detected in the renal tissue or urine culture.[24]

NATURAL HISTORY

The prognosis of genitourinary TB depends on host resistance and the load and virulence of the organism. In many cases, foci in the urinary tract remain dormant indefinitely. Progression occurs through formation of tuberculous granuloma, caseation, ulceration, and dystrophic calcification. Most manifestations result from complications of these processes, which can be prevented by timely chemotherapy and appropriate surgical intervention when indicated. The bacterial burden is lesser in genitourinary TB compared with pulmonary cavitary lesions, and hence treatment is easier. However, the problems with MDR and XDR TB remain challenges for the clinician. With the advent of effective chemotherapeutic measures, the frequency of long-term sequelae of TB has decreased significantly.

TREATMENT

Genitourinary TB is usually amenable to medical treatment. Many antituberculous drugs reach the kidneys, urinary tract, urine, and cavitating lesions in high concentration, and there are fewer organisms in the renal lesions compared with cavitating lung lesions. A wide variety of antituberculous agents are available (Table 52.3).

A short-course regimen is recommended.[25] Treatment is started with daily rifampin 600 mg, isoniazid 300 mg, and Pyrazinamide 25 mg/Kg body weight in the morning. Unless the culture sensitivity indicates otherwise, pyrazinamide is discontinued after 2 months and isoniazid and rifampin are continued for another 4 months. If the patient is very sick with irritative bladder symptoms, streptomycin in daily doses of 1 g may be added during the first 2 months. However, if the patient is older than 40 years, the daily dose of streptomycin is reduced to 0.5 to 0.75 g with periodic monitoring for ototoxicity and vestibular toxicity.

If the probability of drug resistance is high, ethambutol in daily doses of 800 to 1200 mg also may be used in the first 2 months. Longer courses of antituberculous treatment ranging from 9 months to 2 years are indicated under the following circumstances:

- Patients not tolerating pyrazinamide.
- Those responding slowly to a standard regimen.
- Miliary TB.
- Central nervous system disease.

TABLE 52.3 Antituberculous Drugs[*]

Dosage, Actions, and Side Effects

Drug	Dose Form	Dosage	Mode of Action	Dose Modification GFR (50-10 ml/min)
Isoniazid (INH)[†]	Tablet 100 mg, 300 mg	PO: 5 mg/kg/day (max: 300 mg/day)	Bactericidal for groups I and II Interferes with mycolic acid synthesis	Nil
Rifampin (rifampicin)[†]	Tablet/capsule 150 mg, 300 mg, 450 mg	PO: 10 mg/kg/day (max: 600 mg/day)	Bactericidal for groups I, II, and III Interferes with protein synthesis by inhibiting RNA polymerase	Nil
Pyrazinamide[†]	Tablet 400 mg, 500 mg	PO: 25 mg/kg/day (max: 2 g/day)	Bactericidal for semidormant *Mycoplasma tuberculosis*	Nil
Ethambutol	Tablet 100 mg, 400 mg	PO: 15-25 mg/kg (max: 2.5 g/day)	Bacteriostatic Bactericidal in high concentrations Inhibits cell wall synthesis	75%[‡]
Streptomycin	Injection 1 g, 0.75 g	IM: 15-25 mg/kg/day (max 1 g) Age >60 y: 75% dose	Bactericidal Inhibit protein synthesis	50%[‡]
Amikacin	IM/IV: Ampoules 500 mg, 1000 mg	15 mg/kg/day (max: 1 g/day)	Bactericidal Inhibit protein synthesis	50%[‡]
Levofloxacin	PO/IV: PO: Tablet— 250, 500, 750 mg IV: Ampoule—500-750 mg	750-1000 mg/day	Bactericidal Inhibit protein synthesis—DNA gyrase	50%[‡] (500-750 mg q36h)
Moxifloxacin	PO/IV: PO—Tablet 400 mg IV— Infusion 400 mg in 100 ml	400 mg/day	Bactericidal	Nil
Capreomycin	IM/IV: 1-g vial	15 g/kg/day (max 1 g/day) On 5-7 days/wk	Strongly bactericidal Inhibits protein synthesis	75%
Ethionamide	PO	15-25 mg/kg/day (max 1 g/day in 2 divided doses)	Weakly bactericidal Blocks mycolic acid synthesis	Nil
Cycloserine	PO	15-25 mg/kg/day	Bacteriostatic	50%[‡]

[*] The main drugs are listed with dosage form, dosage, mode of action, side effects, and dose modifications in those with low glomerular filtration rate. *M. tuberculosis* exists as three subpopulations. Group I is extracellular, occurs mainly in cavitating lesions, and responds to streptomycin, isoniazid, and rifampin. Group II resides intracellularly in macrophages, replicates slowly, and responds to pyrazinamide, isoniazid, or rifampin. Group III organisms exist within closed caseous lesions, survive better in neutral pH, replicate slowly, and respond best to rifampin.

[†] Prescribed dose to be given after hemodialysis.

[‡] Dose reduction and / or increasing dosing intervals.

GFR, Glomerular filtration rate; *GI*, gastrointestinal; *HD,* hemodialysis; *IM,* intramuscular *IV,* intravenous, *MDR TB,* multidrug-resistant TB; *PO,* orally, *QTc,* corrected QT interval on electrocardiogram; *TB,* tuberculosis; *TDM,* therapeutic drug monitoring.

Dose Modification GFR (<10 ml/min)	Side Effects	Remarks
66%	Hypersensitivity Peripheral neuritis Hepatitis	Administer pyridoxine 50 mg/day.
Nil	Febrile reactions Acute interstitial nephritis Hepatitis	Dose adjustment when using calcineurin inhibitors or oral contraceptives. May be used in pregnancy and lactation.
50%[‡]	Hyperuricemia Hepatotoxicity Photosensitivity	Primary hepatic metabolism. Monitor liver functions and uric acid.
Avoid or 50%[‡]	Optic neuritis (monitor for color vision)	Primarily renal excretion. May be used during pregnancy and lactation.
25%[‡]	Ototoxicity Vestibulotoxicity Hypokalemia Hypomagnesemia	Therapeutic drug monitoring advised. Peak level for efficacy. Trough level for toxicity.
25%[‡]	Ototoxicity Vestibulotoxicity Hypokalemia Hypomagnesemia	Cleared by hemodialysis. Supplement dose after HD or give regular full dose after dialysis. Avoid coadministration of loop diuretics. TDM recommended.
25%[‡] (250-500 mg q48h)	Severe upper GI symptoms Prolonged QTc Arthralgia Tendon rupture	Hepatic and renal elimination. Used in liver disease. More effective than ciprofloxacin and ofloxacin.
Nil	Severe upper GI symptoms Prolonged QTc Arthralgia Tendon rupture	Not removed by HD.
25%[‡]	Nephrotoxicity Ototoxicity Hypokalemia Hypomagnesemia Hepatotoxicity when combined with other anti TB drugs	Used only for MDR TB.
50%	Hepatotoxic Severe GI symptoms Hypothyroidism Gynecomastia	Not to be combined with cycloserine.
25%[‡]	Neurotoxicity, seizures, peripheral neuropathy	Maintain peak level <35 μg/ml. Cleared by dialysis. Avoid in pregnancy and lactation.

- Children with multisite involvement.
- Patients with HIV. The choice of drugs and duration of treatment for those with HIV/AIDS is essentially the same as for immunocompetent patients. In view of the drug interaction between antiretroviral drugs and rifampin, rifabutin may be used in place of rifampin. Another strategy is to delay initiation of antiretroviral therapy by 4 to 8 weeks after starting antituberculous therapy with a view to prevent immune reconstitution syndrome.

Fixed-dose combinations of anti-TB drugs incorporating two or more drugs in the same tablet may facilitate compliance and adequate dosing while minimizing the risk for medication errors and drug resistance.

During treatment, healing by fibrosis may lead to obstruction of one or both ureters, with hydroneprhrosis, parenchymal damage, and renal failure. Dehydration or salt depletion may occur from tubulointerstitial damage or adrenal involvement. Allergic interstitial nephritis may occur in patients receiving intermittent rifampin therapy. Nanoparticle-based drug delivery systems being developed may result in even more successful treatment of TB.[26]

Surgical Treatment

The role of surgical treatment in patients with urinary TB is limited. For ureteral strictures, timely introduction of stents across the narrow segment may avoid the need for major surgical procedures. Two broad types of surgical treatments are considered.

Reconstructive surgery involves the correction of obstruction to the ureter by pyeloplasty, ureteroureterostomy, correction of reflux by ureteral reimplantation, and increasing the bladder capacity by augmentation cystoplasty, which involves anastomosis of an isolated segment of bowel to the contracted bladder.

Ablative surgery involves removal of the diseased parts together with the infected material containing the dormant organisms. The need for removal of a unilateral nonfunctioning kidney is controversial. Because prolonged antituberculous treatment for 18 to 24 months effectively sterilizes caseous and calcified lesions in the tuberculous kidney, nephrectomy is advocated only in patients with secondary sepsis, pain, bleeding, uncontrollable hypertension, "putty kidney," or continued positive urinary cultures. Tuberculous abscesses can be aspirated under ultrasound or CT guidance and antituberculous drugs directly instilled into the cavity.

Treatment Regimens in Special Situations

Women During Pregnancy and Lactation

Most antituberculous drugs are safe for use during pregnancy. However, streptomycin is ototoxic to the fetus and must be avoided. If a four-drug schedule is indicated, streptomycin is replaced by ethambutol. There is no contraindication to the use of these drugs during breastfeeding, and it is not necessary to isolate the baby from the mother. The baby should receive BCG immunization and isoniazid prophylaxis. Because rifampin can reduce the efficacy of oral contraceptives, women taking these agents together should be advised to take a higher dose of estrogen or use alternative methods of contraception.

Patients With Liver Disease

The usual short-term (6-month) chemotherapy regimen can be used in patients with liver disorders if there is no evidence of chronic liver disease, hepatitis virus carrier state, history of acute hepatitis, or excessive alcohol consumption. In chronic liver disease, isoniazid and two of the nonhepatotoxic drugs (streptomycin and ethambutol) can be used for 8 to 12 months. If rifampin is used, liver function should be closely monitored. Pyrazinamide is contraindicated. In those with acute hepatitis unrelated to TB or its therapy, it would be safer to defer chemotherapy until the acute hepatitis has resolved. If immediate treatment of TB during acute hepatitis is mandatory, streptomycin plus ethambutol for 3 months followed by isoniazid and rifampin for 6 months is advised.

Patients With Chronic Kidney Disease

In patients with CKD, isoniazid, rifampin, and pyrazinamide, which are eliminated by the biliary route, can be given in normal dosages. Because streptomycin and ethambutol are excreted by the kidney, dosage modification of these drugs is necessary when GFR is reduced. Streptomycin 15 mg/kg is administered every 48 to 72 hours for a GFR of 10 to 50 ml/min and every 72 to 96 hours for a GFR of less than 10 ml/min to maintain a therapeutic peak level of 20 to 30 μg/ml. Patients taking streptomycin who have a sense of fullness of the ear, have tinnitus, or are older than 45 years should have an audiogram to detect ototoxicity early. For ethambutol, the dose is administered every 24 to 36 hours if GFR is 10 to 50 ml/min and every 48 hours if GFR is less than 10 ml/min. Monthly questioning for symptoms of visual dysfunction (alterations in visual fields, acuity, blue-green vision) with early referral for ophthalmic examination may identify ethambutol toxicity early, with potential reversibility.

Renal Allograft Recipients

A modified treatment regimen is recommended for patients with renal allograft, with adjusted doses of isoniazid and ethambutol for 18 months, combined with ofloxacin 200 mg twice daily for the first 9 months and pyrazinamide 750 mg twice daily for the first 3 months.[27] Rifampin should be avoided in patients receiving a calcineurin inhibitor (CNI) because enzyme induction will make it more difficult to maintain adequate CNI blood levels. If rifampin is used in those receiving a non–CNI-based immunosuppressive regimen, the maintenance dose of prednisolone should be doubled.

Acquired Immunodeficiency Syndrome

Short-term chemotherapy is sufficient for patients with AIDS. If the follow-up cultures are positive, prolonged therapy for up to 2 years may be needed based on antibiotic sensitivity.

Patients Who Fail Treatment

Failure to show clinical or radiologic improvement with treatment may signify poor compliance, inadequate regimen and dosage, incorrect diagnosis, MDR TB, XDR TB, delayed response, or the paradoxical reaction known as *immune reconstitution inflammatory syndrome*. This syndrome is characterized by unexpected worsening of symptoms or appearance of new lesions, including lymphadenopathy, serosal effusions, and pleural infiltrates. This syndrome is more common in those receiving antiretroviral treatment for coexisting HIV and TB infections.[28]

Patient Monitoring

After 2 months of intensive chemotherapy, urine is cultured for *M. tuberculosis* for 3 consecutive days. If cultures remain positive, sensitivity testing is done and treatment modified accordingly. After completion of treatment, all patients should provide three consecutive early-morning samples of urine for *M. tuberculosis* culture, and this is repeated after 3 months and 1 year. Intravenous urography or ultrasound is repeated at the end of 2 months and at the completion of treatment to detect any evidence of obstruction. In cases of renal calcification, the patient should be evaluated yearly by three early morning samples of urine for culture of mycobacteria and by plain radiography of the abdomen for up to 10 years, because calcification may harbor *M. tuberculosis* and may progress to destruction of the kidney.

Considerable progress has been made in the areas of TB diagnostics, antituberculous drugs, and vaccines during the last decade. New antituberculous agents and several vaccines are in various phases of clinical trials. For example, nanoparticle-based drug delivery systems are being developed and have potential to improve TB treatment and control because of their superior solubility and bioavailability.[25] The "End TB" strategy of the WHO that is targeting global reductions in the number of new TB cases and TB deaths by 90% and 95%, respectively, between 2015 and 2035.

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SELF-ASSESSMENT QUESTIONS

1. All of the following are features of immune reconstitution inflammatory syndrome (IRIS) *except*:
   - **A.** Development of new lesion
   - **B.** Worsening of symptoms
   - **C.** Severity inversely proportional to the load of organisms
   - **D.** Common in multidrug-resistant tuberculosis (MDR TB)
   - **E.** Common in patients with simultaneous treatment of coexisting HIV infection
2. The following antituberculous drugs act as bactericidal agents when used in therapeutic doses *except*:
   - **A.** Rifampicin
   - **B.** Isoniazid
   - **C.** Amikacin
   - **D.** Ethambutol
   - **E.** Pyrazinamide
3. The following symptoms point to suspicion of renal TB *except:*
   - **A.** Recurrent painless macroscopic hematuria
   - **B.** Acid, sterile pyuria
   - **C.** Sterility in women/epididymitis in men
   - **D.** Lack of constitutional symptoms
   - **E.** Icterus
4. Which of the following antituberculous drug combinations require dose modifications in patients with renal failure?
   - **A.** Isoniazid and rifampin
   - **B.** Streptomycin and ethambutol
   - **C.** Pyrazinamide and rifampin
   - **D.** Isoniazid and pyrazinamide
5. The drug uniformly effective against all three groups of *Mycobacterium tuberculosis*—group I (extracellular), group II (intracellular), and group III (closed caseous lesions) —is:
   - **A.** Isoniazid
   - **B.** Rifampicin
   - **C.** Pyrazinamide
   - **D.** Ethambutol
   - **E** Streptomycin

53

Fungal Infections of the Urinary Tract

Carol A. Kauffman

Funguria is a frequent finding in hospitalized patients. Almost always, the organisms found in urine are *Candida* spp., although several other yeasts and, less often, molds and endemic fungi, also can be found (Table 53.1). Candiduria is not a symptom, a sign, or a disease, but frequently it is a perplexing phenomenon for the physician to address. In reality, most patients with candiduria are asymptomatic and have colonization of the bladder or an indwelling urinary catheter. The most difficult diagnostic problem is determining when *infection,* rather than colonization, is present. Diagnostic tests to define whether candiduria is related to colonization or infection have not been standardized; similarly, diagnostic studies to localize the site of infection to either the bladder or the kidneys are not well established. In contrast to the situation with candiduria, growth in urine of organisms such as *Blastomyces dermatitidis, Aspergillus* spp., and *Cryptococcus neoformans* almost always reflects disseminated infection. This chapter outlines an approach to the diagnosis and treatment of candiduria and other, less common fungal urinary tract infections (UTIs).

CANDIDA

Epidemiology

Candida spp. are common inhabitants of the perineum but are not found in urine in appreciable numbers in healthy hosts. However, a variety of predisposing factors allow these commensals to grow in the urine and in some cases to invade the bladder or the upper urinary tract and cause infection. These factors are more frequently encountered in hospitalized patients, especially those in the intensive care unit (ICU).[1] In a cross-sectional survey of positive urine cultures obtained from hospitalized patients, *Candida* spp. were found in almost 10% of specimens and were the third most common microorganism isolated from urine.[2]

Risk factors for candiduria, but not specifically for *Candida* UTI, include increased age, female gender, antibiotic use, urinary drainage devices, prior surgical procedures, and diabetes mellitus[3-5] (Table 53.2). In the largest surveillance study, urinary drainage devices, mostly indwelling urethral catheters, were present in 83% of patients who had candiduria.[3] In a multicenter study of patients in an ICU setting, independent risk factors associated with candiduria were age over 65, female gender, diabetes mellitus, prior antibiotic use, mechanical ventilation, parenteral nutrition, and length of hospital stay before ICU admission.[4] A case-controlled study that compared candiduria caused by *Candida glabrata* with that from *Candida albicans* found that *C. glabrata* was more common in patients with diabetes and in those who had received prior treatment with fluconazole.[5] Most patients in these studies had colonization and not infection with *Candida*.

Prospective controlled studies assessing risk factors for well-documented *Candida* UTI have not been performed because firm diagnostic criteria have not been established. However, clinical experience suggests that UTI is more common in diabetic patients and those with urinary tract obstruction.

Pathogenesis

Candida can cause urinary tract disease by either the hematogenous or the ascending route. This contrasts with most bacterial UTIs, in which infection ascends from bladder to the collecting system of the kidney. The pathogenesis of hematogenous seeding of *Candida* to the kidney has been studied with animal models.[6] Multiple microabscesses develop throughout the cortex, with the yeasts penetrating through the glomeruli into the proximal tubules, where they are shed into the urine (Fig. 53.1). Healthy animals eventually clear the infection, but immunocompromised animals do not. Consistent with the experimental studies, renal microabscesses have been identified at autopsy in most patients with invasive candidiasis. For ascending infection with *Candida,* obstruction is an important factor in many patients. Virulence factors of *Candida,* such as those that control adherence and biofilm formation, are also likely relevant, but have not been studied in the context of *Candida* UTI.[6,7]

A unique syndrome seen early after kidney transplantation is graft site candidiasis, which appears to result from contamination of the donor kidney during the harvest procedure.[8] Arteritis with aneurysm formation and rupture can result from direct fungal invasion into the arterial wall. Most patients lose the graft, and mortality is high.

Microbiology

C. albicans accounts for 50% to 70% of all *Candida* urinary isolates, and *C. glabrata* for about 20% of isolates.[3] *Candida tropicalis* and *Candida parapsilosis* are less common, and other species are rarely isolated. Certain populations of patients have a predominance of *C. glabrata*. Older adults frequently have *C. glabrata* isolated from urine, but urine cultures from neonates rarely yield *C. glabrata*. In a prospective survey of candiduria in renal transplant recipients at one transplant center, *C. glabrata* represented 53% and *C. albicans* only 35% of isolates.[9]

For therapeutic reasons it is important to know the species causing candiduria. Resistance to fluconazole, the primary agent used for the treatment of *Candida* UTIs, is common among isolates of *C. glabrata* and in all isolates of *Candida krusei.* In contrast, almost all isolates of *C. albicans, C. tropicalis,* and *C. parapsilosis* are susceptible to fluconazole.

Clinical Manifestations

Most patients with candiduria are asymptomatic, and, indeed, most do not have infection. A large prospective surveillance study of patients

TABLE 53.1 Fungal Genitourinary Tract Infections

Fungal Infection	Prostate	Bladder	Kidney
Candidiasis	++	++++	++++
Cryptococcosis	++	+/−	+++
Blastomycosis	+++	+	++
Histoplasmosis	+	+/−	++
Coccidioidomycosis	+	+/−	++
Aspergillosis	+/−	+/−	++
Mucormycosis	+/−	+/−	++

Shown is the relative frequency of the site of infection for various fungal organisms.

TABLE 53.2 Risk Factors for Candiduria

Type	Risk Factors
Renal (hematogenous)	Neutropenia, recent surgery, central venous catheter, parenteral nutrition, antibiotics, dialysis
Lower urinary tract	Indwelling bladder catheter, older age, female, diabetes, obstruction, antibiotics, urinary tract instrumentation
Upper urinary tract	Older age, diabetes, antibiotics, obstruction, urinary tract instrumentation (e.g., nephrostomy tube, ureteral stent)

with candiduria noted that less than 5% of patients with candiduria had any symptoms suggesting UTI.[3] When patients have symptomatic cystitis or pyelonephritis, symptoms are indistinguishable from those noted with bacterial infections. Cystitis is manifested by dysuria, frequency, urgency, and suprapubic discomfort; patients with upper tract infection can manifest with fever, chills, and flank pain. Urinary tract obstruction occurs from formation of a bezoar or fungal ball in the bladder or the collecting system.

Patients who have had seeding of the renal parenchyma during an episode of candidemia manifest the symptoms and signs associated with invasive candidiasis and not UTI. Chills, fever, hypotension, and other manifestations of sepsis are often noted in patients who are candidemic.

Diagnosis

Major diagnostic difficulties are encountered in trying to differentiate contamination of a urine specimen from colonization of the bladder or an indwelling urethral catheter from invasive infection of the bladder or kidney.[10] Contamination is most easily differentiated by simply repeating the urine culture a day or two later to determine if candiduria persists. It may be necessary to obtain the second urine specimen by sterile bladder catheterization if the patient is unable to accomplish a clean-catch collection. In those patients who have an indwelling urethral catheter, the catheter should be replaced and a second urine specimen collected the next day. For either of these circumstances, if the repeated culture yields no yeasts, no further diagnostic studies or therapeutic interventions are needed.

Distinguishing colonization from infection is not straightforward. Compared with bacterial UTIs, in which the diagnosis is based on appropriate symptoms combined with the findings of pyuria and quantitative bacterial counts, no studies have established the importance of quantitative urine cultures or pyuria for the diagnosis of *Candida* UTI.[11]

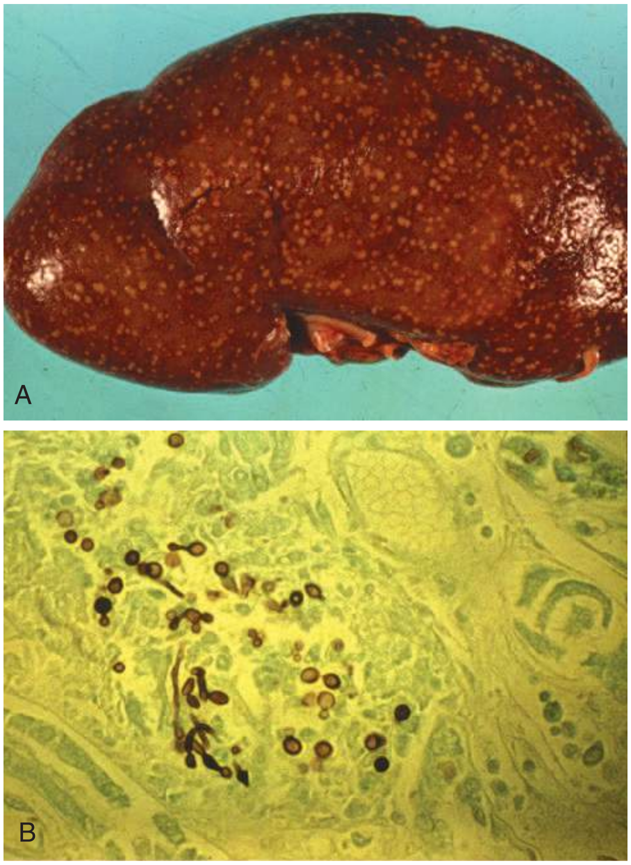

Fig. 53.1 Hematogenous renal candidiasis. (A) Multiple small abscesses are grossly obvious throughout the kidney. (B) Histopathologic demonstration of a microabscess caused by *Candida albicans* in the cortex of the kidney (methenamine silver stain; yeast shown in *gray-brown color*). Magnification 100x.

The role of quantitative urine cultures to differentiate upper tract infection from bladder colonization was assessed by investigators in the 1970s and unfortunately showed broad ranges of colony counts for both colonization and infection.[11] In patients who did not have indwelling catheters, documented renal infection was found with colony counts as low as 10^4 yeast colony-forming units per milliliter (cfu/ml). For patients who had indwelling catheters, colony counts between 2×10^4 and 10^5 cfu/ml or more were noted and there was no correlation with biopsy-proven renal infection. A murine model of hematogenous renal candidiasis noted that renal involvement could be seen with any concentration of *Candida* in the urine.[12]

The techniques routinely used in most clinical laboratories for the detection of bacteria will also detect *Candida* in urine. However, *C. glabrata* grows more slowly than other species and more slowly than bacteria, and colonies may not appear for 48 hours, which is often after routine cultures of urine have been discarded. Laboratories should be notified if *C. glabrata* is a likely pathogen.

Pyuria is often not a helpful diagnostic criterion for infection in patients with candiduria. Concomitant bacteriuria is frequently noted in patients with candiduria and may be responsible for pyuria. In patients who have an indwelling bladder catheter, pyuria is routinely noted, regardless of whether infection is present. In patients who do not have an indwelling bladder catheter or bacteriuria, the presence of pyuria is helpful.

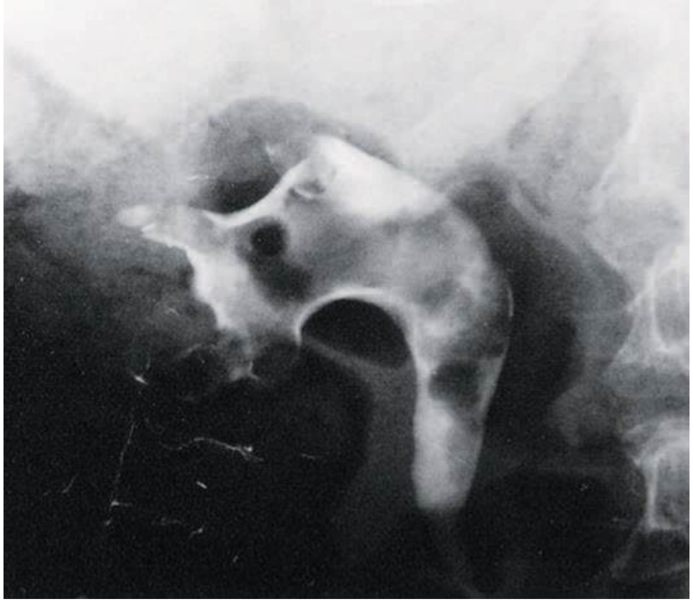

Fig. 53.2 **Fungal hydronephrosis.** Several fungus balls *(dark round "holes" in the contrast dye)* in the ureter and pelvis of the right kidney causing hydronephrosis.

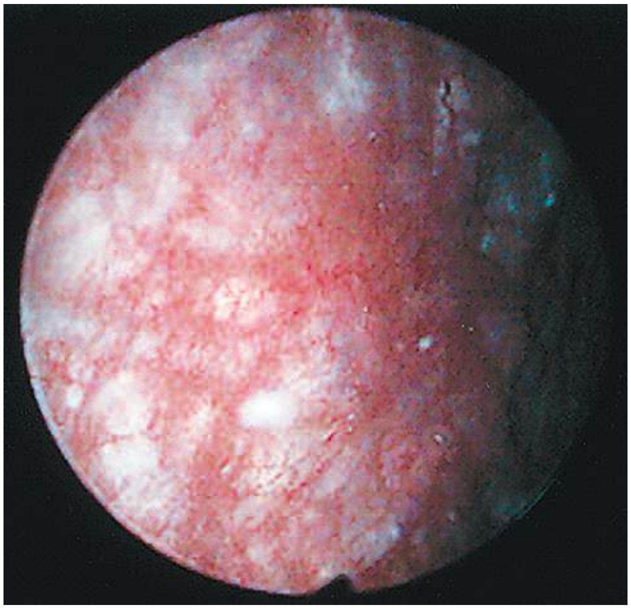

Fig. 53.3 ***Candida*** **cystitis.** Cystoscopic appearance of extensive cystitis caused by *Candida krusei.*

Imaging procedures, including abdominal ultrasound and computed tomography (CT), are essential to document obstruction at any level in the urinary tract and determine the presence of fungus balls in bladder or kidney (Fig. 53.2). In some patients, it is helpful to perform cystoscopy and biopsy of the bladder wall to determine whether inflammation is present and evaluate the extent of invasion (Fig. 53.3).

Treatment With Systemic Antifungal Agents

Most patients who have candiduria do not need treatment with an antifungal agent. For patients who are asymptomatic, treatment should be given only to those who are at high risk for development of candidemia or in whom the presence of candiduria, regardless of symptoms, is likely to represent disseminated infection.[13] The guidelines for the management of candidiasis published by the Infectious Diseases Society of America recommend treatment for patients about to undergo urologic procedures, infants with very low birth weight, and neutropenic patients[13] (Table 53.3). Patients who have candiduria and who are to undergo a urologic procedure are at increased risk for development of candidemia and should be treated with an antifungal agent a few days before and after the procedure. Candiduria in neutropenic patients and in infants with very low birth weight has a high probability of representing disseminated candidiasis; thus these groups also should be treated with an antifungal drug. Asymptomatic candiduria in the renal transplant patient does not warrant systemic antifungal treatment unless obstruction is present or symptoms suggestive of local or systemic infection develop.

In non–high-risk patients who have asymptomatic candiduria, removal of an indwelling urinary catheter will eradicate candiduria in many patients.[3] If catheterization cannot be discontinued, the existing catheter should be removed and a new one inserted. This will often eradicate candiduria transiently, but it is highly likely that the organisms will return within a short time. It is not known if a suprapubic catheter is less likely to be colonized than an indwelling urethral catheter. Relief of obstruction, whether it is present in the upper or lower urinary tract, is essential for the long-term eradication of *Candida* from the urinary tract.

Patients who have symptoms suggestive of cystitis or pyelonephritis, and in whom bacteria as well as *Candida* are found in the urine culture specimen, should be treated initially with an antibacterial agent. If no bacteria are present, treatment with an antifungal drug is appropriate. Eradication of the organism with antifungal therapy is more likely if the indwelling catheter is also removed.[14] Oral fluconazole, which is an azole antifungal agent and is excreted as active drug in the urine, is the agent of choice (see Table 53.3). A loading dose of 400 mg should be given, followed by 200 mg daily for 14 days.[13,15] Fluconazole does not effectively treat *C. krusei* infections, and many *C. glabrata* infections also do not respond to fluconazole.

The possibility of drug-drug interactions should be evaluated before fluconazole is prescribed. Phenytoin, warfarin, cyclosporine, tacrolimus, and sulfonylurea agents are a few of the drugs for which serum concentrations will increase and may reach toxic levels after the addition of fluconazole. Azoles should be used with caution in patients on drugs that prolong the QTc interval.

The other available azole agents, itraconazole, voriconazole, posaconazole, and isavuconazole are not excreted into the urine as active drug. Whether tissue concentrations might be high enough to treat invasive kidney or bladder infections is not known, but there is little clinical experience to suggest that they will be effective.[15]

Intravenous amphotericin B deoxycholate is effective in treating *Candida* UTIs but should be reserved for patients who have upper tract infection or for whom fluconazole therapy has failed, which will be predominantly those who have *C. glabrata* infection. Because of its inherent nephrotoxicity, intravenous amphotericin B must be used judiciously in patients who have renal dysfunction. The recommended dosage is 0.3 to 0.6 mg/kg/day for 1 to 7 days, although this may be extended to 2 weeks for those who have complicated upper tract infection.[13] The dose used depends on renal function and number of days infusions will be given; for example, some clinicians have had success with 0.3 mg/kg/day for 3 days, whereas others use a single dose of 0.6 mg/kg. Infusion-related side effects are seen in some patients, even when low dosages are used, and can include rigors, fever, nausea, vomiting, and headache.

Lipid formulations of amphotericin B are not recommended for treatment of fungal UTIs. The decreased nephrotoxicity that results

TABLE 53.3 **Treatment Recommendations for Candiduria and *Candida* Urinary Tract Infections**

Infection	Treatment	Other/Alternative Therapy
Asymptomatic candiduria	No treatment indicated except: Urologic surgery	Treat a few days before and after the procedure with: Fluconazole 200-400 mg/day *or* Amphotericin B 0.3-0.6 mg/kg/day
	Low-birth-weight infant	Treat as for disseminated candidiasis/candidemia with fluconazole 12 mg/kg/day[13]
	Neutropenic patient	Treat as for disseminated candidiasis/candidemia with an echinocandin or fluconazole[13]
Cystitis	Preferred: PO fluconazole 200 mg/day × 14 days*	Alternatives include: Amphotericin B 0.3-0.6 mg/kg/day × 1-7 days Flucytosine 25 mg/kg q6h × 7-10 days†
Pyelonephritis	Preferred: PO fluconazole 200-400 mg/day × 14 days	Alternatives include: Amphotericin B 0.3-0.6 mg/kg/day × 1-7 days with or without flucytosine, 25 mg/kg q6h Flucytosine 25 mg/kg q6h × 14 days
Renal (hematogenous)	Treat as for disseminated candidiasis/candidemia with an echinocandin or fluconazole	—
Fungus balls	Surgical removal *plus* Fluconazole 200-400 mg/day until resolved	Alternatives include: Surgical removal *plus* Amphotericin B 0.3-0.6 mg/kg/day with or without flucytosine 25 mg/kg q6h Irrigation through nephrostomy tube with amphotericin B 25-50 mg in 200-500 ml sterile water
Prostatitis Epididymo-orchitis	Surgical drainage *plus* Fluconazole 400 mg/day until resolution noted on imaging studies	Alternatives include: Surgical drainage *plus* Amphotericin B 0.3-0.6 mg/kg/day

*Fluconazole dosage in renal failure: creatinine clearance (Cr Cl) 20-50 ml/min, reduce dose by 50%; CrCl <20 ml/min, reduce dose by 75%.
†Flucytosine dosage in renal failure: CrCl 20-40 ml/min, reduce dose to 25 mg/kg q12h; CrCl <20 ml/min, reduce dose to 25 mg/kg q24h.
PO, Orally; *q6h,* every 6 hours.

from the addition of the lipid component likely also precludes the drug's effectiveness by failing to achieve adequate levels in the urinary tract.[15]

One of the few uses of flucytosine is for the treatment of *Candida* UTIs. Flucytosine, which is excreted into the urine in high concentrations as active drug, should be used only when fluconazole is not tolerated or the organism is fluconazole resistant. The usual dosage of flucytosine in patients who have normal creatinine clearance is 25 mg/kg orally every 6 hours for 7 to 10 days.[15] Most species of *Candida,* with the exception of *C. krusei,* are susceptible to flucytosine, but resistance emerges quickly when this agent is used alone. Serious adverse effects of flucytosine include bone marrow suppression and hepatotoxicity. These effects are dose related, and the risk increases greatly with renal failure (see Table 53.3).

The echinocandins (caspofungin, micafungin, and anidulafungin) have minimal or no excretion into the urine as active drug. The tissue concentrations achieved with these agents may be adequate to treat invasive *Candida* infections of the bladder or kidney, but clinical data are limited.[16-18] Therefore echinocandins currently cannot be recommended for the treatment of *Candida* UTIs.

Local Antifungal Administration

Continuous bladder infusion of amphotericin B 50 mg in 1 liter of sterile water through a triple-lumen catheter is sometimes used to treat *Candida* bladder infection. Bladder irrigation clears candiduria more quickly than systemic antifungal agents.[19] However, the effect is brief, and recolonization occurs within 1 to 2 weeks. Amphotericin B bladder irrigation is rarely required as a strategy given the need for catheter placement and the availability of more convenient treatment options.[20] The one exception might be lower tract infection with azole-resistant *C. krusei* or *C. glabrata*.

In the patient with kidney obstruction caused by a fungus ball, irrigation through a percutaneous nephrostomy tube with amphotericin B is recommended, in addition to systemic antifungal therapy with fluconazole.[13] Absorption of amphotericin B does not occur, and direct infusion is not nephrotoxic. Surgical or endoscopic removal of the fungus ball is essential to eradicate the infection.

Localized *Candida* Infections

Prostatitis and prostatic abscess caused by *Candida* spp. manifest with symptoms that are similar to those of bacterial prostatic infection. The initial manifestation may be urinary retention; physical examination reveals a tender prostate, and imaging can show either discrete abscesses or diffuse inflammation. Treatment is drainage if an abscess is present, and fluconazole, which achieves excellent concentrations in the prostate for several months until the infection has resolved.[21] Epididymo-orchitis is less common and usually manifests as a tender scrotal mass. Surgical drainage or orchiectomy is required, along with fluconazole therapy until resolution has occurred.

OTHER YEASTS

C. neoformans infection in immunosuppressed hosts, especially patients with AIDS, is a systemic illness with involvement of many organs, including the genitourinary (GU) tract. In autopsy series, kidney involvement has been noted in 25% to 50% of patients who died of cryptococcosis, but symptoms rarely are referable to the GU tract. The prostate is frequently infected and can be a reservoir for persistent *C. neoformans* infection. Isolated prostatitis and epididymo-orchitis have been reported in the absence of systemic cryptococcosis.[22] The diagnosis is usually made at the time of biopsy of a mass or nodule; granulomatous inflammation is typically seen. Treatment of localized GU tract cryptococcal infection is fluconazole 400 mg/day for 6 to 12 months.

Saccharomyces cerevisiae has been described rarely as a cause of UTI. The manifestation is the same as for *Candida* spp. In clinical microbiology laboratories that do not identify yeasts in urine to the species level, this organism will not be differentiated from *Candida*. *S. cerevisiae* is often resistant to fluconazole, and successful treatment may require amphotericin B.

ASPERGILLUS AND OTHER MOLDS

The urinary tract is an uncommon site of infection with molds. However, individual case reports have noted GU infections caused by a variety of molds, including the Mucorales (e.g., *Rhizopus, Mucor*), *Aspergillus*, *Penicillium*, and *Paecilomyces*.[23] The most common mold infection is aspergillosis. Hematogenous spread to the kidney with invasive disease in immunosuppressed patients results in numerous renal microabscesses and infarcts. This may be an incidental finding in light of massive dissemination at autopsy. Patients who have symptomatic UTI usually present with urinary tract obstruction from masses of fungal elements causing fungal balls, which can be visualized on CT scan or ultrasound. Treatment is surgical removal of the obstructing mass, often nephrectomy, and systemic antifungal therapy for the specific mold. Mortality is extremely high.

ENDEMIC FUNGI

All of the major endemic mycoses have been reported to infect the GU tract. For all of these organisms, infection is by hematogenous spread to the GU tract. For upper tract infection, treatment is the same as that for disseminated infection. The treatment of focal infection, which is more likely to involve the lower GU tract, often requires surgical removal of the infected tissue, as well as antifungal therapy.

B. dermatitidis has the greatest propensity to cause symptomatic infection. In patients with disseminated blastomycosis, involvement of the GU tract occurs in as many as a third of cases and usually manifests as prostate or epididymal infection.[24] In most patients, this involvement is discovered incidentally when urine cultures yield the organism or a biopsy is performed for a prostatic or epididymal mass.

Symptomatic GU tract involvement with histoplasmosis is uncommon. However, at autopsy, kidney lesions are often found in patients who have disseminated histoplasmosis.[25] Patients are usually asymptomatic in regard to urinary symptoms. Individual cases of testicular abscesses, epididymitis, and prostate nodules have been reported.

Coccidioidomycosis rarely causes symptomatic UTI. However, autopsy series of cases of disseminated coccidioidomycosis have noted kidney involvement in more than 50% of cases.[26] The finding of *Coccidioides* spp. in the urine in such patients is not uncommon. Localized infection, manifesting as abscesses or mass lesions of the epididymis or prostate, also occurs in patients with disseminated coccidioidomycosis.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following *Candida* spp. is isolated *most* often in patients with candiduria?
   A. *C. glabrata*
   B. *C. parapsilosis*
   C. *C. albicans*
   D. *C. krusei*
   E. *C. tropicalis*
2. The presence of pyuria is a helpful diagnostic test for *Candida* UTI when there is:
   A. An indwelling bladder catheter in a symptomatic patient
   B. An indwelling bladder catheter in an asymptomatic patient
   C. Concomitant bacteriuria and candiduria in an asymptomatic patient
   D. Concomitant bacteriuria and candiduria in a symptomatic patient
   E. No indwelling bladder catheter and no bacteriuria
3. The dose of which of the following antifungal agents used to treat fungal UTI should be reduced in patients who have a creatinine clearance below 40 to 50 ml/min?
   A. Amphotericin B
   B. Flucytosine
   C. Caspofungin
   D. Liposomal amphotericin B
   E. Voriconazole
4. The antifungal agent of choice for treating a *Candida albicans* UTI is
   A. Amphotericin B
   B. Fluconazole
   C. Flucytosine
   D. Voriconazole
   E. Caspofungin

54

The Kidney in Schistosomiasis

Rashad S. Barsoum, Tarek S. Fayad

Schistosomiasis is a parasitic disease usually acquired by teenagers, often leading to complications that may extend into the fourth and fifth decades of life. It was known to the ancient Egyptians as "the bloody urine disease"[1] and is also known as *bilharziasis* in honor of its discoverer, Theodor Bilharz, the German physician who practiced in Egypt in the 1850s.

The life cycle of the parasite is shown in Fig. 54.1. Infection is acquired through contact with contaminated waters in ponds and slow-flowing canals. Cercariae enter through the skin or mucous membranes and migrate through the lymphatics and blood circulation into the portal or perivesical venous system, where they mature into sexually differentiated adult worms and live in almost continuous copulation. Females leave the males only to lay eggs, and, traveling against the blood flow, reach the rectal or bladder mucosa. The ova are driven out by visceral contraction during defecation or urination. Contact with fresh water within a couple of days allows the eggs to hatch, releasing miracidia, which infect specific snails. In this intermediate host, the organisms mature asexually into cercariae, which are eventually released, searching for their definitive host, usually humans and occasionally apes and cattle. The snail demography defines the endemicity and frequency of schistosomiasis in different geographic regions, and is largely influenced by climatic factors such as temperature and humidity.[2]

About 200 million inhabitants of 78 countries on five continents are infected, and an additional 600 million are at risk. Of the infected persons, 60% are symptomatic, 10% have serious sequelae, and 1% die of the disease each year, mainly in China, the Philippines, Egypt, Brazil, northern Senegal, and Uganda. These numbers reflect the outcome of a significant decline in prevalence during the second half of the past century, as a result of mass treatment with tartar emetic during the 1960s, the extensive use of praziquantel during the 1980s, and its use in a World Health Organization–sponsored global mass treatment program starting in the late 1990s. The latter had already captured 90% of the target population by 2016 and resulted in eradication of schistosomiasis from Japan and the Lesser Antilles islands; transmission was halted in Tunisia and significantly reduced in China, Egypt, Morocco, Saudi Arabia, Brazil, Venezuela, and Puerto Rico. However, certain schistosomal strains—up to 82% in Senegal—are resistant to praziquantel. Such strains are responsible for incremental prevalence in several countries, and even spread to adjacent geographical regions in East and West Africa.

Of seven species that affect humans, three are responsible for almost all major morbidity from the disease: *Schistosoma haematobium* throughout Africa and adjacent regions; *Schistosoma mansoni* in Africa, South America, and the Caribbean; and *Schistosoma japonicum* in the Far East (Fig. 54.2). The other four human-pathogenic schistosomal species (*Schistosoma intercalatum, Schistosoma mekongi, Schistosoma guineensis,* and *Schistosoma mattheei*) have a patchy distribution in certain geographical locations, hence their limited impact on the global epidemiology of schistosomiasis.

S. haematobium affects the urinary tract, whereas *S. mansoni* and *S. japonicum* affect the colon and rectum, ultimately reaching the liver and inducing periportal fibrosis. Sporadically, all three species cause metastatic lesions when ova are driven by the bloodstream to the lungs, brain, spinal cord, heart muscle, eyes, and other sites.[3] Overall morbidity is variable and depends on the virulence of the infective strains, host resistance, environmental factors, and standards of primary medical care. For example, chronic lower urinary tract disease among infected subjects is reported to vary from 2% in Nigeria in the west of Africa to 52% in Tanzania in the east.[4]

PATHOGENESIS

Schistosomes cause morbidity through two major mechanisms: (1) local reactions around the ova deposited in different tissues and (2) systemic effects attributed to the host's response to circulating antigens released from the worms or the ova (Fig. 54.3).[4,5]

The local reaction is a cell-mediated immune response to soluble egg antigens diffusing out of trapped ova through micropores in the eggshell. The initial response is innate, being driven by tissue macrophages, and involves natural killer cells, neutrophils, and complement. This response is followed by a specific immune response orchestrated by T helper (Th) lymphocytes.

The schistosomal granuloma is composed of mononuclear cells, eosinophils, neutrophils, basophils, and fibroblasts, which are recruited and activated by a variety of Th lymphokines as well as specific chemoattractants of parasitic origin (Fig. 54.4). These cells are involved in the elimination of the parasite by direct phagocytosis (monocytes), lymphocytotoxicity (T lymphocytes), antibody-dependent cytotoxicity (eosinophils), and antibody- and complement-dependent cytotoxicity (neutrophils). Later, the granuloma is modulated by gradual switching from Th1 to Th2 activation, largely mediated by a change in the monokine profile that favors release of interleukin (IL)-4, which is associated with a phenotypic change of the committed tissue macrophages. At this stage, the intensity of the inflammatory reaction is reduced, and progressive fibrosis is induced largely through the release of IL-4, IL-5, IL-10, somatostatin, and transforming growth factor β. Further on, tolerance to the parasite is achieved by an established population of regulatory T cells, which develop under the combined influence of host- and parasite-derived mediators. With the final extinction of the inflammatory reaction, granulomas in the bladder, lower ureters, and seminal vessels heal with dystrophic calcification.[6,7]

The systemic immune response is primarily a humoral reaction to circulating schistosomal antigens, which originate mainly from the

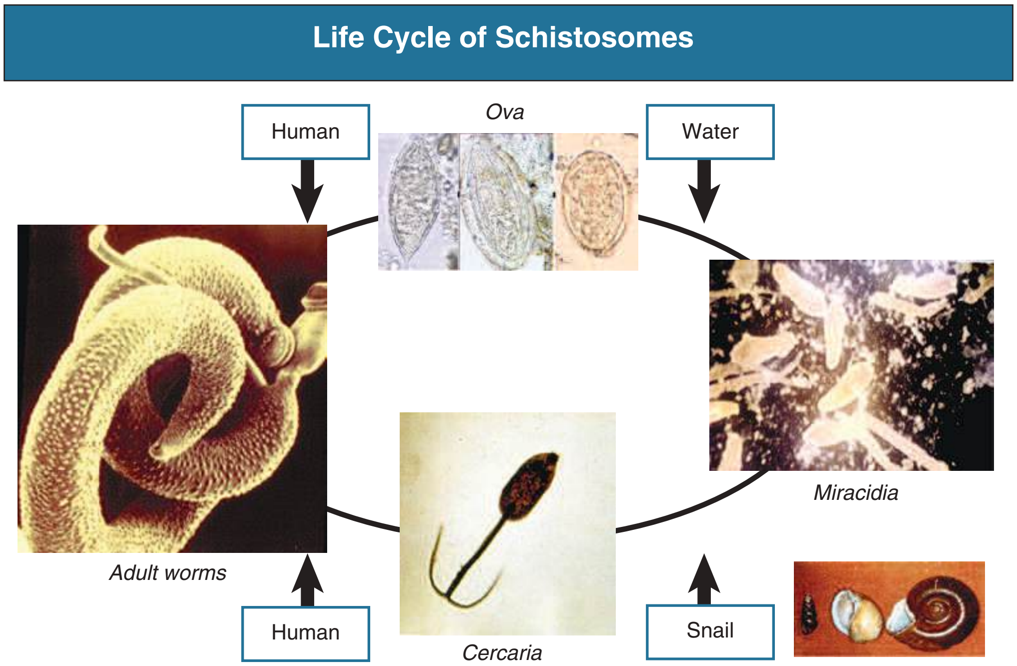

Fig. 54.1 Life cycle of schistosomes.

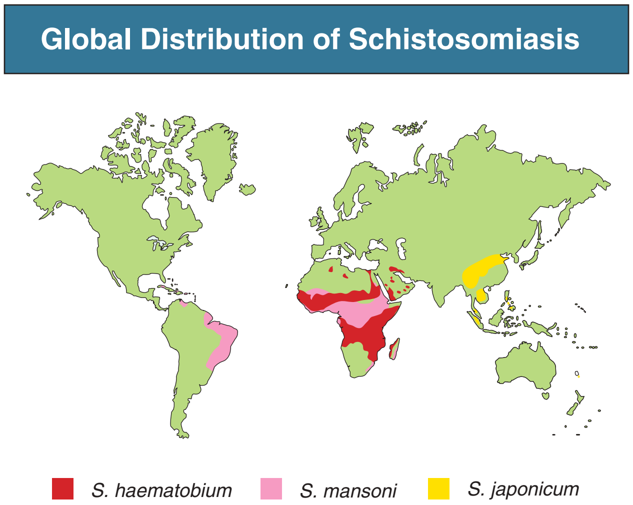

Fig. 54.2 World map showing the geographical distribution of the main pathogenic schistosomes.

worm's digestive enzymes (gut antigens), with a minor contribution from the tegument and ova. The gut antigens consist of a positively charged glycoprotein and a negatively charged proteoglycan (circulating cationic antigens and circulating anionic antigens, respectively). These antigens are present in most of the schistosomal immune complex–mediated lesions, particularly in glomeruli.[8] The antibody response is biphasic, reflecting the successive Th1 and Th2 stages of lymphocyte activation. In the Th1 stage, B cells tend to synthesize immunoglobulin M (IgM), IgG1, and IgG3 under the influence of IL-2. During the Th2 phase, IgG2, IgG4, and IgA predominate; these have a limited ability to fix complement and may even block its deposition, hence their importance in modulating the granulomas.[4,6]

CLINICAL MANIFESTATIONS

Schistosomal lesions in the urinary system mirror the two major pathogenetic mechanisms. On one hand, there are local lesions, mostly affecting the lower urinary tract, caused by the local granulomatous response to *S. haematobium* ova.[9] On the other hand are those lesions caused by immune complex deposition in the glomeruli, usually associated with hepato-intestinal *S. mansoni* and, less commonly, urogenital *S. haematobium* infections.[10] Although glomerular lesions can be readily induced by *S. japonicum* in experimental animals,[11] this species does not seem to cause significant kidney disease in humans.

Lower Urinary Tract Schistosomiasis

The lower urinary tract and adjacent genital structures are the primary sites of *S. haematobium* infection. Clinical disease starts by the coalescence of multiple granulomas that form small pseudotubercles in the bladder mucosa (Fig. 54.5). These may consolidate to form sessile, occasionally pedunculated masses or ulcerate, leading to painful terminal hematuria, the most typical presenting symptom. Hematuria may vary from microscopic (40% to 100% in different reports) to gross (0% to 97%).[12] Ulcers eventually heal by fibrosis, with calcified granulomas under the atrophic and dirty mucosa, leading to the characteristic cystoscopic appearance of sandy patches and also the radiologic appearance of linear bladder calcifications in 2% to 62% of cases.[12] Similar lesions may occur in the lower ureters, bladder neck, seminal vesicles, and other organs in the vicinity (Fig. 54.6).

The bladder lesions predispose to secondary bacterial infection, particularly with *Pseudomonas* or *Proteus* spp., usually after instrumentation. *Proteus* infection is notorious for favoring stone formation, which further complicates the scenario. The subsequent fibrotic process may involve the bladder neck, leading to outflow obstruction, or the vesicoureteral junction, leading to ureteral obstruction or vesicoureteral reflux. Involvement of the detrusor is a late event that may lead to an atonic or a hyperirritable bladder. Eventually, the bladder becomes a

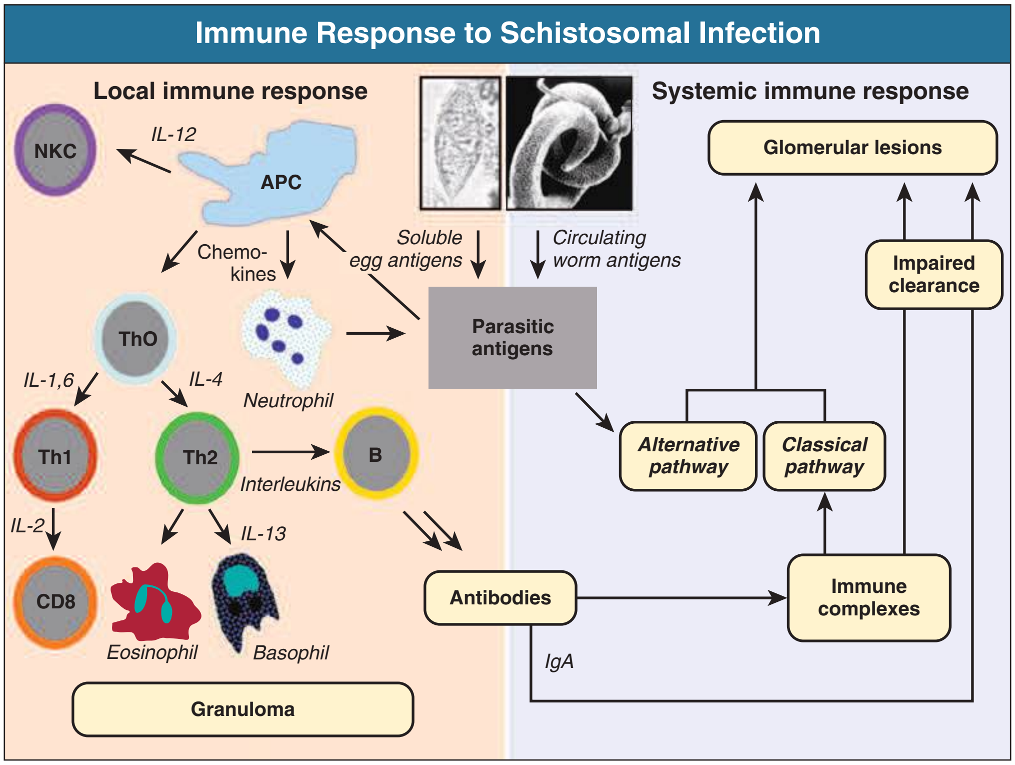

Fig. 54.3 Immune response to schistosomal infection. The local immune response to deposited ova leading to granuloma formation is shown on the *left;* all cells shown in the diagram, in conjunction with antibodies or complement, participate in eventual parasite elimination (see text). The systemic immune response is shown on the *right*; note the important role of impaired clearance of schistosomal antigens and IgA in the development of glomerular lesions. *APC,* Antigen-presenting cell; *IL,* interleukin; *NKC,* natural killer cell.

deformed, contracted, and calcified organ that accommodates a very small amount of urine that it can hardly void.

Bladder Cancer

Chronic bilharzial cystitis is precancerous. In a study of almost 10,000 Egyptian patients with bladder cancer, schistosomal association was confirmed in 55.3%. The predominant lesions were transitional cell carcinoma (65.8%) and squamous cell carcinoma (28.4%).[13] The tumor, particularly when of the squamous cell type, remains localized for a long time before spreading to the surrounding pelvic tissues or a distant site, thanks to the occlusion of lymphatics by the preceding fibrotic process.

Associated infection with high-risk human papillomavirus is encountered in about a third of cases,[14] which suggests an etiologic role in malignant transformation.[15] Specific *p53* gene mutations were detected in one third of cases.[16,17]

Development of malignancy is suspected when the symptoms of chronic cystitis exacerbate, along with recurrence of hematuria many years after the initial presentation and the passage of small pieces of necrotic tissue with urine (necroturia). A characteristic radiologic sign is the irregular "eating up" of the bladder calcification on a plain radiograph. Cystography shows the tumor mass as an irregular filling defect or bladder ulcer. Cystoscopy shows the tumor and provides the means for a histologic diagnosis (Fig. 54.7).

Upstream Consequences

Although ureteral strictures and calcifications are common, the hypertrophied upper ureteral musculature usually overcomes the lower obstruction, thereby limiting the upstream consequences. Nevertheless, hydronephrosis and progressive renal failure may develop when there is extensive ureteral scarring, in the presence of stones or secondary bacterial infection, or when the vesicoureteral junction is incompetent (Fig. 54.8). The frequency of upper urinary tract disease from *S. haematobium* is variably reported from different geographical regions—for example, from less than 10% in Niger to 48% in Cameroon.[10]

Interstitial Nephritis

Progressive renal scarring is the eventual outcome of complicated *S. haematobium* infection, resulting from obstruction, reflux, and bacterial infection. Granulomas have occasionally been seen in the renal interstitium but tend to be discrete and of no functional significance (Fig. 54.9). Immune-mediated tubulointerstitial nephritis has been described with *S. mansoni* in humans,[18] but the role of immune mechanisms remains questionable in *S. haematobium* pyelonephritis.

The typical pathologic picture is that of a deformed kidney with calyceal dilation, distortion, and atrophic parenchyma. Dense interstitial infiltration, fibrosis, and periglomerular scarring are present. The glomeruli may show ischemic collapse or other schistosomal lesions, such as proliferative glomerulonephritis (GN) or amyloidosis.

The clinical picture is that of chronic tubulointerstitial nephritis (see Chapter 62), often associated with residual manifestations of lower urinary tract involvement. Hypertension is a late feature, being checked by concomitant tubular salt wasting. Anemia and osteodystrophy may be disproportionately severe because of the associated secondary distal tubular acidosis and nutritional deficiency in endemic areas.

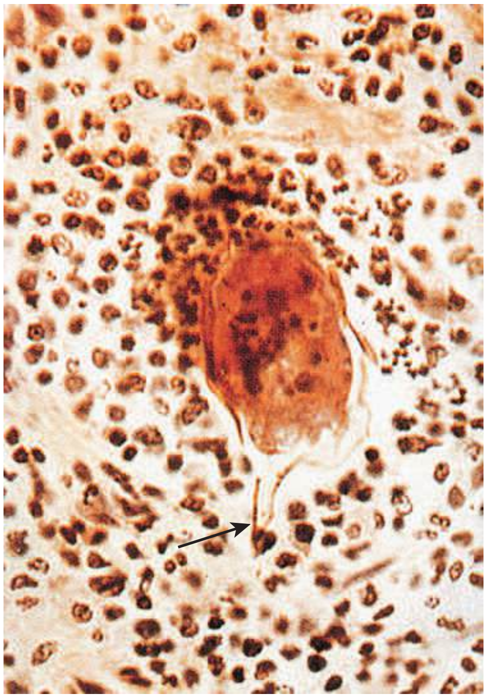

Fig. 54.4 ***Schistosoma haematobium*** **granuloma.** Note the egg's terminal spike *(arrow)*, which identifies *S. haematobium,* and the distortion of shell by proteases and oxidants released by the local neutrophil infiltration. (Hematoxylin-eosin stain, ×500.)

Glomerulonephritis

Immune complex–mediated GN has been described in experimental[11] and human[10] infection, mainly with *S. japonicum* and *S. mansoni*. The latter species accounts for most clinically significant disease in humans. *S. haematobium* GN is rare, transient, and usually subclinical.[19]

Schistosomal gut antigens are present in circulating immune complexes as well as in the immune deposits in mesangial, subendothelial, and intramembranous locations. The presence of liver fibrosis is critical because it results in impaired hepatic clearance of schistosomal antigens and immune complexes. These are mostly generated within the portal venous system, which accommodates the adult worms.

Most patients are 20- to 40-year-old men with evidence of hepatosplenic schistosomiasis. Renal involvement is asymptomatic in up to 40% of those, being identified by accidental or surveillance urinalysis, which may display various grades of proteinuria, or abnormal sediment. Some 15% of those with hepatosplenic schistosomiasis have overt GN, with proteinuria and microhematuria on presentation and with or without the nephrotic syndrome, hypertension, and impaired kidney function. Liver function test results are often normal. A polyclonal gammopathy is seen in most cases, whereas a monoclonal IgM response is seen in those with associated hepatitis C virus (HCV) infection and cryoglobulinemia. Rheumatoid factor activity and anti-DNA antibodies are detected in 5% to 10% of cases, particularly in association with *Salmonella* infection (see later discussion), but they do not correlate with clinical severity. Rheumatoid factor seropositivity is detected in much higher titers when HCV infection is associated.[20]

Six histologic classes of schistosomal GN are recognized (Table 54.1 and Fig. 54.10).[10,20] Class I (mesangial proliferative), class III (membranoproliferative), and class IV (focal segmental proliferative and sclerosing) result from the deposition of immune complexes representing different

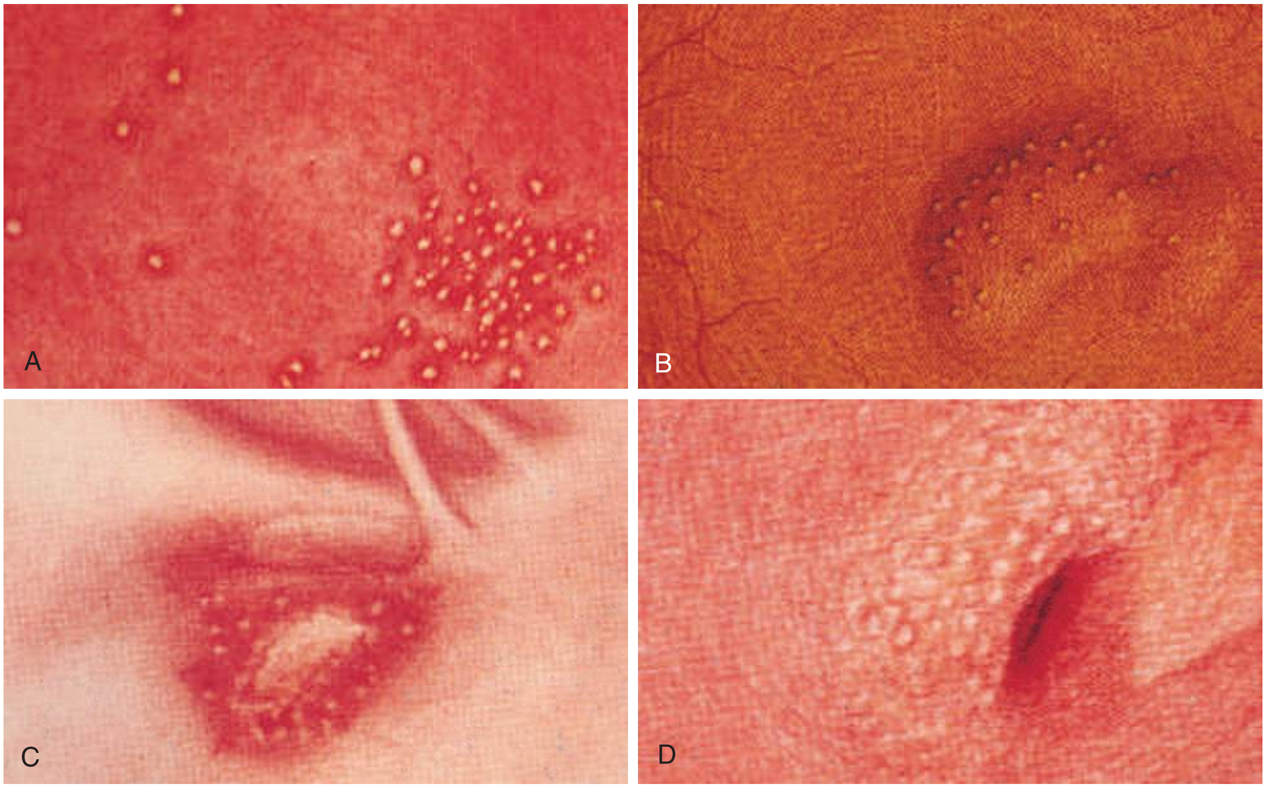

Fig. 54.5 Hand-painted cystoscopic appearances in urinary schistosomiasis. (A) Pseudotubercles. (B) Sessile mass covered by pseudotubercles. (C) Ulcer surrounded by pseudotubercles. (D) Sandy patches. (Courtesy Professor Naguib Makar.)

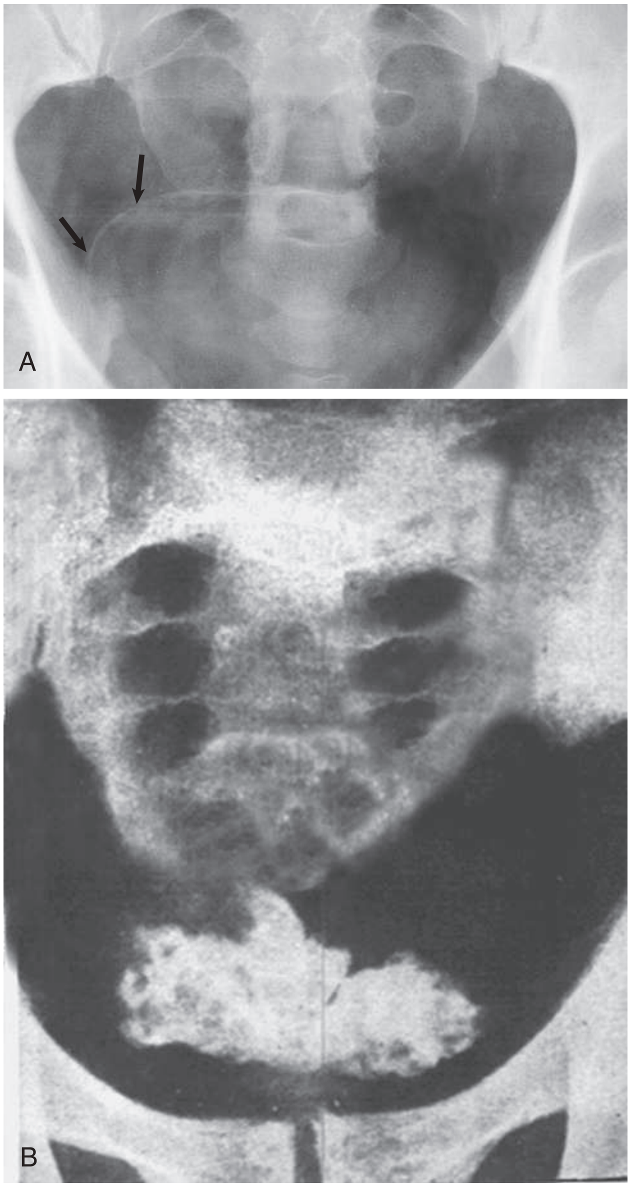

Fig. 54.6 Plain radiographic appearances in *Schistosoma haematobium* infection. (A) Faint linear calcification of the bladder wall *(arrows)*. (B) Dense calcifications of contracted bladder and seminal vesicles.

stages in the evolution of pure schistosomal hepatosplenic disease. The main deposits in class I are schistosomal antigens, IgM, and C3; and in class III and class IV, IgG and IgA, usually without schistosomal antigens. The IgA deposits parallel the severity of proteinuria and mesangial proliferation. Impaired hepatic clearance and increased mucosal synthesis of IgA have been documented in those patients.[21] Whereas class I lesions are seen in most asymptomatic cases, class III and class IV are usually symptomatic and progressive, even with eradication of the parasitic infection.

Class II (diffuse proliferative and exudative) is associated with urinary or biliary coinfection with *Salmonella* strains, usually *Salmonella paratyphi* A in Africa and *Salmonella typhimurium* in Brazil, which are attached to specific receptors in the tissues of adult schistosomes. C3 and *Salmonella* antigens have been detected in the glomerular capillary walls and the mesangium. In these patients the clinical presentation is typical of acute postinfectious GN, associated with manifestations of *Salmonella*-related toxemia (fever, exanthema, and severe anemia).

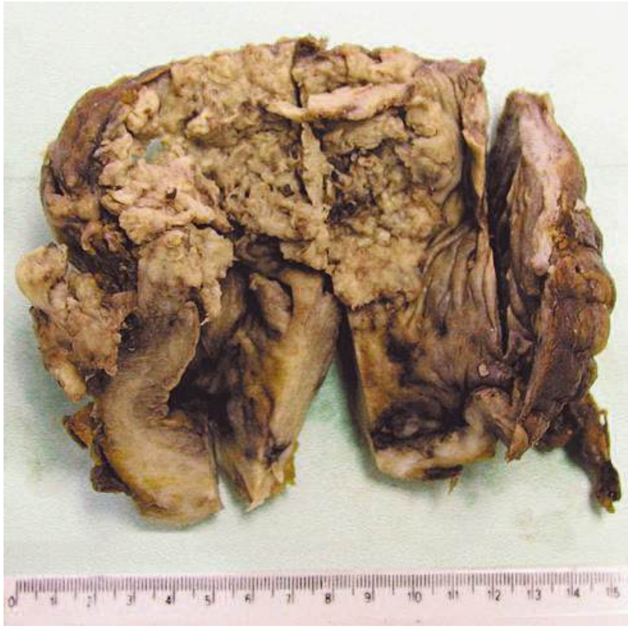

Fig. 54.7 Bilharzial bladder cancer.

Megaureter Resulting From Schistosomal Infection

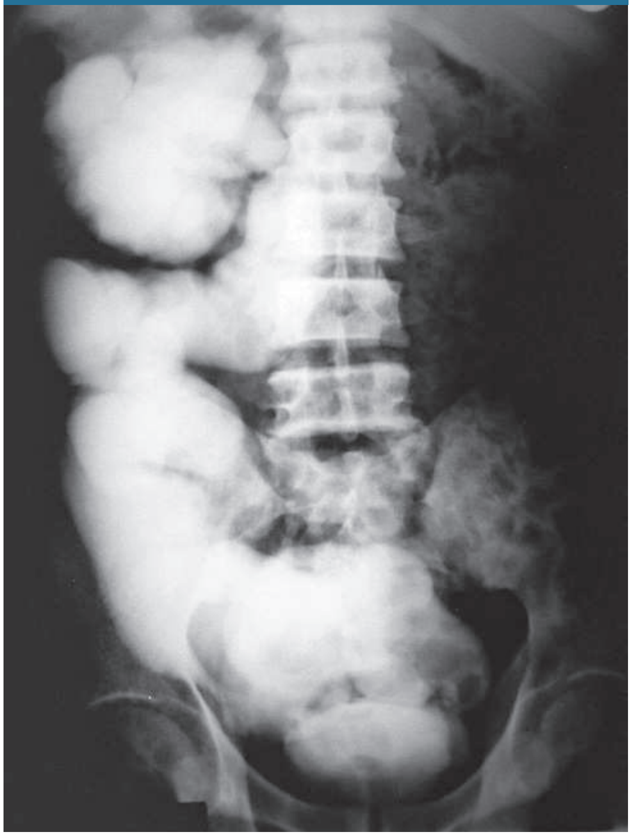

Fig. 54.8 Ascending cystogram showing right megaureter caused by vesicoureteral reflux.

Serum amyloid A protein deposits are detected by special stains or electron microscopy in up to 15% of biopsy samples from patients with class III and class IV, whereas AA-amyloidosis may be the predominant lesion (class V) in less than 5% of patients with clinically overt schistosomal GN. It occurs with heavy, often mixed infection regardless of

TABLE 54.1 Classification of Schistosomal Glomerulonephritis

Class	Histology	Immunofluorescence	Etiologic Agent	Prevalence	Clinical Findings	Treatment of Renal Disease
I	Mesangial proliferative GN	IgM, C3 Schistosomal gut antigens	*S. haematobium* *S. mansoni* *S. japonicum*	27%-60% of asymptomatic patients, 10%-40% of patients with renal disease	Microhematuria Proteinuria	May respond to antiparasitic treatment
II	Diffuse proliferative exudative GN	C3, *Salmonella* antigens	*S. haematobium* *S. mansoni* *plus Salmonella* spp.	*Salmonella* infections Reduced serum C3	Acute nephritic syndrome, toxemia	May respond to treatment of *Salmonella* and schistosomal infections
III	Membranoproliferative GN	IgG, IgA, C3, schistosomal antigens	*S. mansoni* (*S. haematobium*?)	7%-20% of asymptomatic patients and in 80% of patients with overt renal disease	Hepatosplenomegaly, nephrotic syndrome, hypertension, renal failure	No
IV	Focal segmental glomerulosclerosis	IgM, IgG (occasionally IgA)	*S. mansoni*	11%-38%	Hepatosplenomegaly, nephrotic syndrome, hypertension, renal failure	No
V	Amyloid	AA protein	*S. mansoni* *S. haematobium*	16%-39%	Hepatosplenomegaly, nephrotic syndrome, hypertension, renal failure	No
VI	Cryoglobulinemic GN	IgM, C3	*S. mansoni* + hepatitis C virus	Unknown	Hepatosplenomegaly, nephrotic syndrome, purpura, vasculitis, arthritis, hypertension, renal failure	Interferon plus ribavirin, corticosteroids, immunosuppression, plasma exchange

GN, Glomerulonephritis; *Ig,* immunoglobulin.

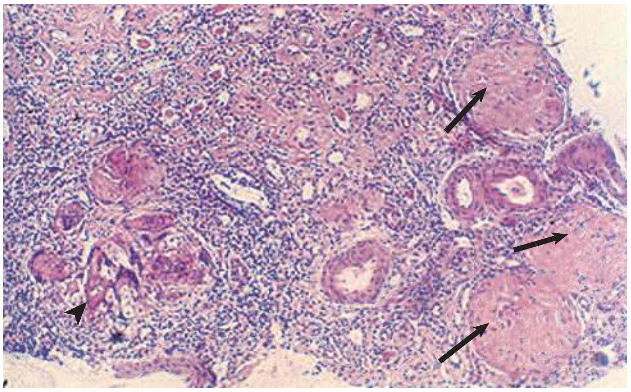

Fig. 54.9 **Schistosomal chronic interstitial nephritis.** Note the dense cellular infiltration and fibrosis, atrophic dilated tubules, and thickened vessels. Three glomeruli heavily infiltrated with amyloid are seen on the right side *(arrows);* a schistosomal granuloma is seen in the *lower left corner (arrowhead).* (Hematoxylin-eosin [HE] stain, original magnification ×75).

the anatomic site. Minimal amyloid deposits do not seem to alter the clinical presentation or prognosis, but typical class V lesions are grossly nephrotic and relentlessly progressive.

Class VI lesion was described in patients with hepatosplenic schistosomiasis and HCV infection.[20] This association is common, particularly in Egypt, where the virus may have been acquired decades earlier from intravenous injections used for mass treatment of schistosomiasis. The lesion consists of a mixture of mesangial proliferation, amyloid deposition, fibrinoid necrosis, and cryoglobulinemic thrombi in the glomerular capillaries with tubular casts. Patients have chronic hepatitis, cirrhosis, nephrotic syndrome, cryoglobulinemic skin vasculitis, polyarthritis, and rapidly progressive renal failure associated with severe protein-calorie malnutrition.

COINFECTION

Patients living in endemic areas may acquire one or more superimposed infections that can perturb schistosomal pathogenicity and modify its presentation. Mutually, schistosomiasis may modify the course of the confounding infection. The first reported coinfection is that of schistosomiasis and salmonellosis,[22] discussed earlier as class II schistosomal glomerulopathy. Likewise, class VI is attributed to coinfection with HCV. As mentioned earlier, superimposed papillomavirus infection is blamed in the pathogenesis of schistosoma-associated bladder cancer.

The list of other infections known to interact with schistosomiasis is expanding (Box 54.1). Some of the documented coinfections, namely those with plasmodium, filaria, mycobacterium tuberculosis, and staphylococci are clinically significant. However, they were not reported to modify the known renal lesions of schistosomiasis alone.

In addition to HCV, two viral infections—HIV and HBV infections—may modify the renal lesions in schistosomiasis.

Human Immunodeficiency Virus

Several recent studies have established an epidemiologic link between schistosomiasis and HIV infection. Women with lower urinary tract schistosomiasis are at significantly increased risk (odds ratio 2.9 in Zimbabwe[23] and 4.0 in Tanzania[24]) of acquiring and subsequently transmitting HIV to their sexual partners. Data on men with *S. hematobium*

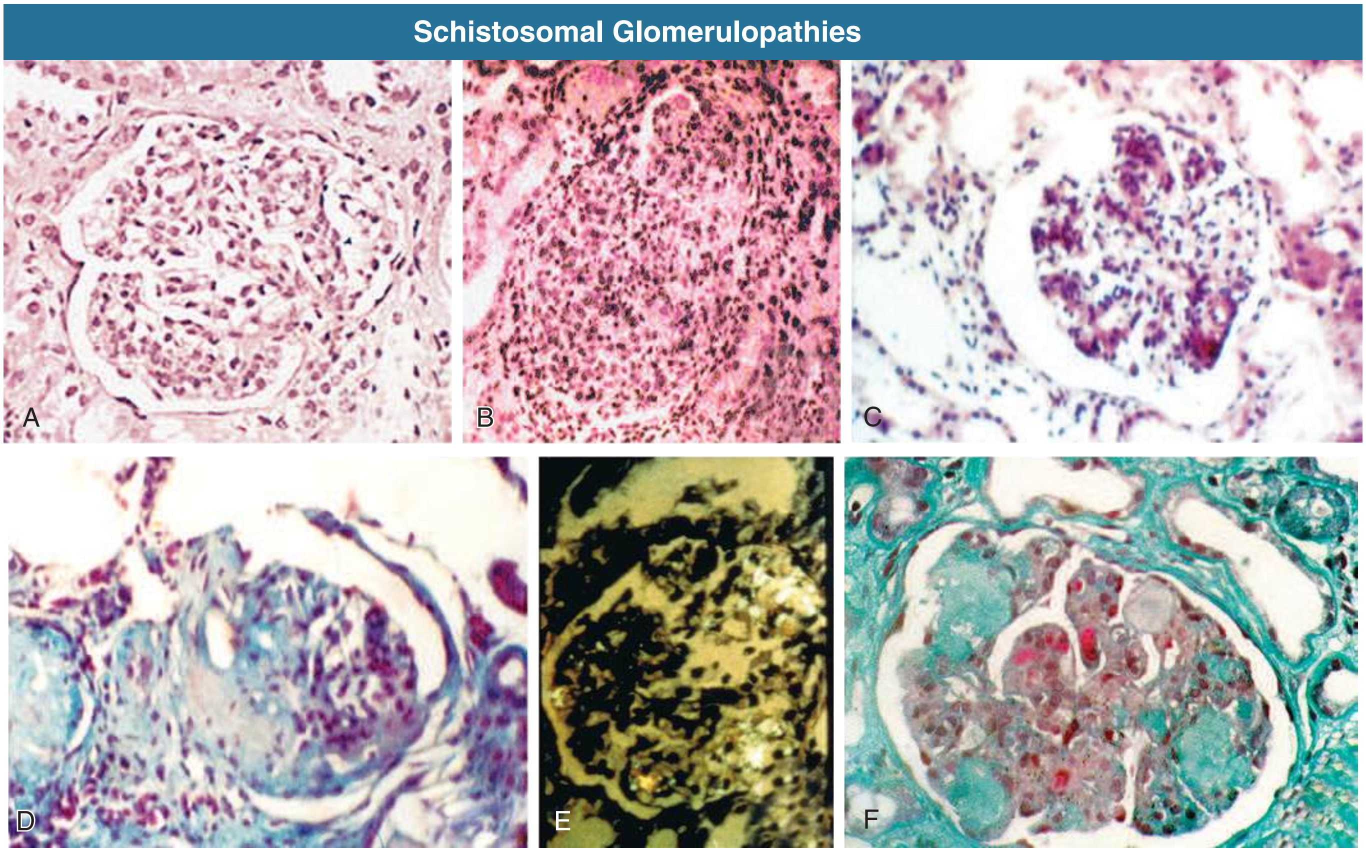

Fig. 54.10 **Schistosomal glomerulopathy.** (A) Mesangial proliferative glomerulonephritis (GN), HE stain (class I). (B) Schistosoma- and *Salmonella*-associated exudative GN, HE stain (class II). (C) Membranoproliferative (mesangiocapillary) GN type I, HE stain (class III). (D) Focal segmental glomerulosclerosis, Masson trichrome stain (class IV). (E) Green birefringence under polarized light in a glomerulus with mesangial proliferation in a patient with mixed *Schistosoma haematobium* and *Schistosoma mansoni* infection, Congo red stain (class V). (F) Amyloid deposits and cryoglobulin capillary thrombi (red stain) in a glomerulus displaying focal mesangial proliferation in a patient with schistosomal hepatic fibrosis and associated hepatitis C virus infection (class VI).

BOX 54.1 Clinically Relevant Coinfection With Schistosomiasis

Viral

- Hepatitis B virus
- Hepatitis C virus
- Human immunodeficiency virus
- Human papillomavirus

Bacterial

- Tuberculosis
- Staphylococci
- Salmonella

Parasitic

- Plasmodium

infection or either gender with *S. mansoni* infection are inconsistent. There are no published data on *S. japonicum* and HIV coinfection

The immunologic perturbation induced by schistosomiasis seems to accelerate the progression and spread of HIV infection.[25] HIV coinfection leads to distortion of schistosomal granulomata, yet without known clinical sequelae. However, HIV-infected patients are more vulnerable to re-infection with schistosomes upon new exposure after successful eradication.[26]

There is some concern about the unexplained 3- to 16-fold increase of HIV viral load after treatment of schistosomiasis by praziquantel.[27] Fortunately, this effect is spontaneously reversible in a few weeks, and the benefit of eradicating the confounding parasitic infection on the clinical course and spread of HIV infection is unquestionable.[27]

Hepatitis B Virus

Vulnerability of patients with hepatosplenic schistosomiasis to coinfection with HBV is well documented in hospital-based,[28] but not in community-based,[29] studies, perhaps owing to the selection of complicated cases in the former. Such coinfection augments the liver injury induced by schistosomiasis,[30] leading to increased incidence of abnormal liver function (46.6%), jaundice (23.3%), hepatocellular carcinoma (17.8%), and liver-related mortality (23.3%).[31] It is unknown whether schistosoma and HBV coinfection influences the nature or severity of the renal lesions associated with either.

DIAGNOSIS

Schistosoma haematobium Urinary Tract Disease

The clinical diagnosis of lower urinary tract schistosomiasis is easily made, particularly in patients with the typical pattern of painful terminal hematuria after exposure to fresh river waters in an endemic area. Diagnosis is more difficult when the history of exposure is less convincing (e.g., swimming pools) or when the clinical presentation is atypical (e.g., bacterial pyelonephritis, typhoid, or amyloidosis).

The diagnosis is made by finding ova in a fresh urine sample, which is easy because of their abundance, large size, and typical appearance (see Fig. 54.4). Live ova, containing mobile miracidia, indicate active infection, whereas dead, calcified ova may continue to be shed from fibrotic lesions for many months or even years.

Serologic diagnosis is based on finding circulating schistosomal antigens or antibodies.[32] The circumoval precipitin test is most frequently used in clinical laboratories. Serologic diagnosis is useful for diagnosis in the absence of ova, which occurs with old infections when the worms are sterile but continue to release their antigens. Serologic tests are also useful in assessing the response to treatment because titers usually become negative within 3 to 6 months of complete eradication of infection.

A polymer chain reaction real-time assay is available for detection of the dra-1 *S. hematobium* antigen in the serum.[33] Owing to its high cost, its clinical use is limited to early detection of infection in expatriates visiting endemic areas.

The radiologic appearances of bladder and seminal vesicle calcification are so typical that no further confirmatory tests are needed in an endemic area. Cystoscopic findings are equally pathognomonic although seldom required. Early pseudotubercles are easily distinguished from mycobacterial infection by their size and the surrounding mucosal pathologic changes. The presence of sandy patches with associated masses, polyps, and even neoplasms makes the diagnosis. Tissue biopsy confirms the parasitic nature of the lesions. Different imaging techniques (e.g., ultrasound, intravenous urography, voiding cystography) are useful in the diagnosis of upstream complications, including obstruction and reflux (see Chapters 58 and 61).

The main differential diagnosis for urinary schistosomiasis is tuberculosis, which also causes hematuria, strictures, back pressure, and chronic kidney disease. This differential can be resolved with appropriate parasitologic and bacteriologic techniques (see Chapter 52).

SCHISTOSOMA MANSONI GLOMERULONEPHRITIS

Overt glomerular disease in patients with hepatosplenic schistosomiasis is suspected in those who develop hypertension, nephrotic or nephritic syndrome, or chronic kidney disease. Occult glomerular disease is indicated by the presence of abnormal urinary sediment or kidney function. Although renal biopsy is essential for diagnosis and classification, none of the lesions is pathognomonic unless schistosomal antigens are detected, which is unusual in clinically overt cases when sought with conventional immunofluorescence. Identification of *S. mansoni* eggs in the stools (Fig. 54.11) or submucosal rectal biopsy samples supports the diagnosis. Serologic tests for schistosomal gut antigens[34] and molecular tests for Sm1-7 antigens[35] are usually positive. However, it is important to remember that these tests only indicate schistosomal infection and do not necessarily implicate schistosomes as causing the kidney disease.

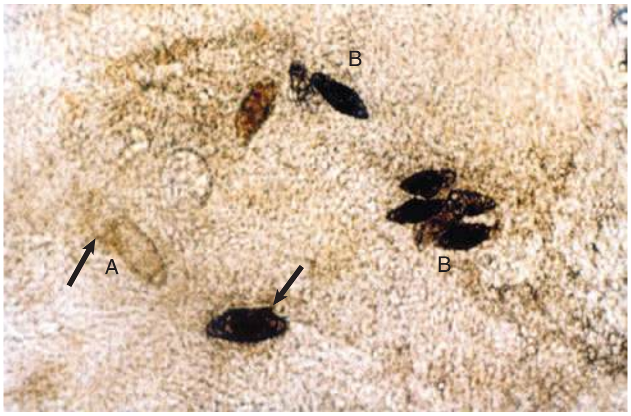

Fig. 54.11 Stool smears showing living *(A)* and dead *(B) Schistosoma mansoni* ova. Species are identified by the lateral spike *(arrows)*.

Concomitant *Salmonella* or HCV infection can be detected by appropriate microbiologic tests. The various serologic abnormalities described are of limited diagnostic value, except the high rheumatoid factor, monoclonal IgM expansion, and low C4 that are typical of class VI.

Other glomerular disorders associated with hepatic fibrosis, such as secondary IgA nephropathy and hepatic glomerulosclerosis, should be considered in the differential diagnosis. However, in both these conditions the renal disease is rather mild, mainly with microhematuria at presentation but rarely with nephrotic-range proteinuria or impaired renal function. The glomerular deposits are mostly mesangial, in contrast to those seen in schistosomiasis, in which subendothelial and intramembranous deposits may also be present.

TREATMENT

Schistosoma haematobium Urinary Tract Disease

S. haematobium is susceptible to antimony compounds, organophosphates (metrifonate), and niridazole. The drug of choice is praziquantel, with a cure rate greater than 85% and the least toxicity. It is administered as a single oral dose of 40 mg/kg body weight, which may be repeated 2 weeks later if there is evidence of active disease. In infections resistant to praziquantel, the antimalarial *Artemisia annua* may be used as an alternative with equal effectiveness.[36] Antiparasitic treatment cures the early bladder disease, yet has no effect on sandy patches or other fibrotic lesions. Ureteral distension with radiologic evidence of hydronephrosis may be reversed in a few weeks after successful treatment.

Antibacterial therapy usually controls acute episodes of cystitis and pyelonephritis. However, it must be combined with simultaneous eradication of parasitic infection if still active, especially when the urinary bacterial infection is due to typhoid *(Salmonella typhi)*.

Chronic fibrotic lesions are difficult to treat. Surgery or the placement of stents may be necessary for the relief of an obstructive lesion. However, particular caution is required in dealing with the vesicoureteral junction to avoid induction of reflux. Several plastic procedures are available to restore the distorted ureteral, bladder, or urethral anatomy. Associated bacterial infections may require long-term low-dose antibiotics.

Chronic dialysis in such patients can be difficult owing to the negative effects of the associated schistosomal lesions in the liver, lungs, and other organs and the comorbid impact of undernutrition, viral infection, or malignant disease. The same factors can compromise outcomes of renal transplantation, with the additional risk for urinary leakage, which is many-fold higher than usual owing to the presence of fibrotic granulomas and anatomic distortion in the bladder wall. Reinfection with *S. haematobium* also has been described.[37]

Schistosoma mansoni Glomerulonephritis

S. mansoni is more resistant to treatment and may require higher doses of praziquantel (40 to 60 mg/kg body weight) or the use of oxamniquine (single dose of 15 mg/kg body weight in South America or 2 doses of 15 mg/kg body weight given 12 hours apart in Africa). Research is under way to overcome oxamniquine resistance, which is limiting its use in many geographical regions.[38] Nevertheless, eradication of the parasite can be curative only in classes I and II. In the latter, it must be combined with antibiotics for the control of *Salmonella* infection (usually quinolones, macrolides, or third-generation cephalosporins). Antischistosomal and immunosuppressive therapy are ineffective in all other classes of schistosomal GN.[10] No data are available on the course of class VI schistosomal glomerulopathy after treatment with anti-HCV direct-acting antiviral drugs.

Chronic dialysis may be complicated by the risk for bleeding from esophageal or gastric varices after anticoagulation. Endoscopy is essential before the start of regular hemodialysis, with prophylactic sclerotherapy if necessary. Although peritoneal dialysis is viable for some, it is relatively contraindicated in those with significant ascites.

Renal transplantation is a viable option in those who develop end-stage renal disease, in the absence of major risk factors such as viral infection, undernutrition, or hepatic insufficiency. Uncomplicated residual hepatic fibrosis in the recipient does not seem to significantly modify the pharmacokinetics of immunosuppressive agents, but variations in cyclosporine blood levels can occur, perhaps secondary to altered gastrointestinal absorption.[37] Associated viral hepatitis may have a considerable impact on donor selection, choice of immunosuppression, and the eventual outcome (see Chapters 21, 55 and 102).

Recurrence of schistosomal GN after transplantation has been described in a few patients,[39] suggesting the persistent release of antigens from living worms. Although it is not an evidence-based practice, many authorities recommend the administration of a single dose of praziquantel to recipients known to have been previously infected with the parasite.

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SELF-ASSESSMENT QUESTIONS

1. A 45-year-old male recent Egyptian immigrant to Canada presents with a 4-week history of pyrexia, abdominal discomfort, asthenia, and increasing generalized edema. His medical history includes two treatment courses for intestinal schistosomiasis. Examination shows significant pallor, facial puffiness, a faint macular itchy eruption on the forearms and abdominal wall, and bilateral soft pedal edema. Temperature is 38.7° C (101.7° F), and blood pressure is 100/70 mm Hg. The liver edge is felt 2 cm below the right costal margin, firm and moderately tender. The spleen is felt 5 cm below the left costal margin and acutely tender. Urinary protein is 14 g/g creatinine, and the sediment shows 20 to 25 white cells, 8 to 10 red cells, and a few blood casts per high-power field. Peripheral blood hemoglobin is 8.6 g/dl; leukocyte count is 14,300/µl, of which 85% are neutrophils with left shift. Rheumatoid factor is positive at 48 IU/l, C-reactive protein is 128 units, and C3 is 54 mg/dl. Aspartate aminotransferase (AST) is 75 IU/ml, alanine aminotransferase (ALT) is 62 IU/ml, and γ-glytamyl transferase (GGT) is 123 IU/ml. Serum albumin is 1.8 g/dl, serum creatinine is 2.1 mg/dl, and blood urea nitrogen (BUN) is 73 mg/dl. Which of the following is the *most* likely explanation for the patient's recent illness?
   A. Ascending pyelonephritis complicating neglected urinary schistosomiasis
   B. Schistosoma-associated *Salmonella* bacteremia
   C. Active hepatitis viral infection on top of hepato-intestinal schistosomiasis
   D. Schistosoma-associated secondary immunoglobulin A nephropathy
   E. Cryoglobulinemic vasculitis
2. A 50-year-old male Nigerian patient presents with severe burning during micturition, with passage of blood and necrotic tissue with urine for 2 weeks. He received treatment for urinary schistosomiasis 30 years previously and for recurrent urinary bacterial infection many times after that. Examination shows an ill man, with bilateral edema of the left lower limb. The left kidney is palpable and slightly tender. Rectal examination reveals a mass indenting the anterior rectal wall. Midstream urine examination shows a protein-to-creatinine ratio of 4 g/g, and uncountable red and pus cells. Serum creatinine is 4.3 mg/dl, and BUN is 103 mg/dl. The *most* likely cause of his edema is:
   A. Schistosomal glomerulonephritis
   B. Schistosoma-associated chronic pyelonephritis
   C. End-stage post-obstructive kidney disease
   D. Infiltrative bladder cancer
   E. Advanced prostatic cancer
3. A 38-year-old female Brazilian patient presents with painful swelling of the small joints of her hands, right knee, and left shoulder; bilateral soft lower limb swelling; and a raised brownish-purple macular skin eruption over the tibial shins. She has been under medical follow-up for compensated chronic hepatosplenic schistosomiasis. Urine examination shows a protein-to-creatinine ratio of 5.2 g/g, and the sediment shows many red cells, few leukocytes, and red cell and granular casts. Serum creatinine is 2.1 mg/dl; BUN is 26 mg/dl; serum albumin is 2.7 g/dl; serum C3 is 86 mg/dl, and C4 is 3.2 mg/dl. Rheumatoid factor is 256 IU/ml. ALT is 128 IU/l, AST is 9 IU/l, and GGT is 396 IU/l. Which of the following is the *most* likely diagnosis?
   A. Acute schistosomiasis
   B. Autoimmune hepatitis
   C. Schistosomal glomerulonephritis
   D. Concomitant virus-induced cryoglobulinemia
   E. Superimposed rheumatoid arthritis

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Glomerular Diseases Associated With Infection

Cynthia C. Nast, Bernardo Rodríguez-Iturbe

More than 250 years ago, dark scanty urine was observed in the convalescent period of scarlatina. In the nineteenth century, Bright and others identified symptoms of nephritis in patients with scarlet fever. In the early 1900s, clinical observations by von Pirquet led him to propose that nephritis occurring after scarlet fever resulted from antibodies that were pathogenic, an insight that opened the field of immune-mediated renal disease. We now recognize that a wide variety of infectious organisms can induce a spectrum of glomerular lesions via differing pathogenetic mechanisms, including immune complex deposition, direct renal cell infection and injury, and sequelae of ongoing chronic inflammation (Table 55.1). Glomerular injury may occur as a consequence of resolved or ongoing infection; therefore the term *infection-related glomerulonephritis* (GN) is more accurate.[1] As demographics, access to health care, and public health conditions change, there are alterations in the epidemiology, clinical presentation, morphology, and therapeutic approaches to glomerular lesions associated with infectious organisms.[2] Table 55.2 shows microorganisms and their associated glomerular lesions.

BACTERIAL INFECTIONS

Poststreptococcal Glomerulonephritis

Etiology and Pathogenesis

Poststreptococcal GN (PSGN) is an immune complex–mediated lesion occurring after infection with a nephritogenic bacterial strain. There are three immunologic mechanisms likely involved in the glomerular injury associated with this infection; passive entrapment and deposition of circulating immune complexes, in situ immune complex formation associated with nephritogenic planted bacterial antigens or intrinsic antigens resulting from molecular mimicry, and deposition of nephritogenic bacterial antigens that activate plasmin resulting in local complement activation.[3-5] There are two known nephritogenic streptococcal antigens thought to be involved in PSGN immune complex formation. These include nephritis-associated plasmin receptor (NAPlr), characterized as glyceraldehyde-3-phosphate dehydrogenase, and streptococcal pyrogenic exotoxin B (SPEB) and its more immunogenic zymogen precursor (zSPEB).

Evidence for these mechanisms includes demonstration of NAPlr and SPEB in renal biopsy specimens of acute PSGN, and elevation of antibody titers to both antigens in most convalescent sera.[6] In a Japanese study, 92% of PSGN convalescent sera and 60% of sera from patients with uncomplicated streptococcal infections contained anti-NAPlr antibodies.[7] NAPLr has been localized to glomerular areas with plasmin-like activity but not with complement or immunoglobulin, suggesting the ability to bind plasmin locally producing glomerular inflammation and enhancing immune complex deposition.[4,7] SPEB also can bind plasmin, a possible common mechanism of action. However, unlike NAPlr, SPEB co-localizes with glomerular complement and IgG, suggesting participation in the immune-mediated glomerular damage.[5] SPEB is the only streptococcal nephritogenic antigen demonstrated in subepithelial "hump" electron-dense deposits characteristic of PSGN, possibly as a result of its cationic charge. Studies from Latin America and Central Europe demonstrated SPEB, but not NAPlr, in PSGN renal biopsy samples. In contrast, the group C *Streptococcus zooepidemicus* strain responsible for a Brazilian epidemic showed absence of the SPEB-related gene, suggesting that different streptococcal antigens induce PSGN in different ethnic groups.[8] Thus there likely are multiple nephritogenic antigens depending on the streptococcal species and genetic and other host factors.

PSGN is thought to occur when glomerular immune complexes or deposition of plasmin-activating nephritogenic bacterial antigens initiate an inflammatory cascade with local complement activation and recruitment of neutrophils and monocyte-macrophages. Subepithelial immune deposits (humps) develop associated with cationic antigens (e.g., SPEB) and result from dissociation of subendothelial immune complexes with transit and re-formation on the outer aspect of the glomerular basement membrane or in situ immune complex formation. Several issues remain unresolved. Immune complex disease generally results in classical complement pathway activation, yet C4 levels typically are normal and deposits have dominant C3. This may result from antigens, such as NAPlr, that activate the alternative pathway. C3Nef immunoglobulin G (IgG) antibodies, which activate the alternative complement pathway, have been demonstrated in sera of patients with PSGN. Bacterial antigen activation of the mannose-binding lectin complement pathway also has been postulated (see Chapter 16); however, individuals genetically unable to activate this pathway may still develop PSGN.

Autoimmune mechanisms may play a role in PSGN. Rheumatoid factors (especially IgG) and cryoglobulins have been found in 35% of patient sera in the first week of the disease. Rheumatoid factors similarly were demonstrated in PSGN renal tissue and kidney eluates from a fatal case. Loss of sialic acid from autologous IgG due to streptococcal neuraminidase or from binding of the IgG Fc fragment to type II Fc receptors in the streptococcal wall may induce anti-IgG reactivity.[6] This anti-IgG antibody may play a role in deposition of IgG-containing complexes. Additional manifestations of autoimmune reactivity include anti-C1q antibodies, particularly in severe cases, and rarely anti-DNA reactivity, antineutrophil cytoplasmic autoantibody (ANCA), and autoimmune hemolytic anemia.[6]

Epidemiology

PSGN is decreasing in incidence worldwide; however, it remains a problem in developing countries, with an incidence of 9.3 to as high as 28.5 in 100,000.[2,9] This likely is an underestimate, with the

TABLE 55.1 Pathogenetic Mechanisms of Infection-Related Glomerular Injury

Mechanism	Representative Microorganism	Supportive Evidence
Circulating immune complexes	*Streptococcus*	Circulating antibodies against SPEB and NAPlr antigens
In situ immune complex formation	*Streptococcus*	Identification of SPEB in subepithelial deposits in PSGN
Nephritogenic antigen deposition with complement activation	*Streptococcus*	Glomerular deposition of NAPlr with plasmin activity
Superantigen binding to APCs activates T cells and polyclonal B cells, inducing immunoglobulin production	*Staphylococcus*	Selective peripheral blood activation of TCR V_β repertoire
Direct renal cell infection	HIV, parvovirus	Virus identification in glomerular epithelial cells
Direct renal cell injury	Hepatitis B virus	HBV induces mesangial cell proliferation and type IV collagen production in vitro.
Cryoglobulin production	Hepatitis C virus (HCV)	IgM rheumatoid factor against the HCV E2 envelope protein

APCs, Antigen-presenting cells; *HIV,* human immunodeficiency virus; *NAPlr,* nephritis-associated plasmin receptor; *PSGN,* poststreptococcal glomerulonephritis; *SPEB,* streptococcal pyrogenic exotoxin B.

TABLE 55.2 Infectious Organisms Causing Glomerular Injury

Microorganism	Associated Glomerular Lesions*
Bacteria	
Gram Positive	
Streptococci	PIGN, MPGN, DDD, IgA-dominant IRGN
Staphylococci	IgA-dominant IRGN, ICMGN
Pneumococcus	DPGN, MPGN
Propionibacterium	MPGN, ICMGN (shunt nephritis)
Gram Negative	
Brucella	ICMGN
Campylobacter	DPGN, MesPGN
Escherichia coli	IgA-dominant IRGN
Hemophilus	IgAN
Klebsiella	DPGN, IgA-dominant IRGN
Legionella	Crescentic GN, PIGN, MesPGN
Meningococci	MesPGN, DPGN
Pseudomonas	MPGN, ICMGN (shunt nephritis)
Salmonella	MesPGN, IgAN
Serratia	MPGN, ICMGN (shunt nephritis)
Yersinia	IgAN, PIGN
Other	
Bartonella	Crescentic GN (endocarditis)
Coxiella	Crescentic GN (endocarditis)
Leptospira	Segmental glomerular necrosis
Mycobacteria	MPGN, ICMGN, DPGN, amyloidosis
Mycoplasma	ICMGN
Treponema	MN, MPGN, DPGN, MesPGN

Microorganism	Associated Glomerular Lesions*
Viruses	
Hepatitis A	MPGN, IgAN, MesPGN
Hepatitis B	MN, MPGN, MesPGN, IgAN, PIGN, FSGS, Amyloidosis
Hepatitis C	MPGN ± cryoglobulins, MN, fibrillary GN, immunotactoid GN, MesPGN, collapsing GP
HIV	Collapsing GP, FSGS, IgAN, ICMGN (including lupus-like), MCD
Parvovirus B19	Collapsing GP, ICMGN, IgAN, FSGS
Adenovirus	PIGN, MesPGN
Coxsackie B virus	Proliferative GN
Cytomegalovirus	MPGN, MesPGN, collapsing GP, MN, crescentic GN
Dengue	MesPGN
Epstein-Barr	Collapsing GP, MN, crescentic GN, MPGN, MesPGN
Hantavirus	MCD, MesPGN
Influenza	MesPGN, DPGN
Measles	DPGN
Mumps	MesPGN, DPGN
Rotavirus	MesPGN
Varicella	MesPGN, DPGN
Parasites and Protozoa (see Table 55.3 for more detail)	
Echinococcus	MN, MPGN
Filaria	MesPGN, MPGN, DPGN, MN, MCD, FSGS, amyloidosis
Malaria	MPGN, MesPGN, MN, IgAN, MCD
Leishmania	MesPGN, MPGN, amyloidosis
Schistosoma	MPGN, FSGS, MesPGN, MN, amyloidosis
With Salmonella	PIGN
Toxoplasma	MPGN, FSGS, MesPGN
Trichinella	MesPGN, MPGN
Trypanosoma	MesPGN, MPGN

*These are glomerular lesions described in humans. More infection-associated glomerulopathies have been identified in animal models.
Collapsing GP, Collapsing glomerulopathy; *DDD,* dense deposit disease; *DPGN,* diffuse proliferative glomerulonephritis (may be exudative); *FSGS,* focal and segmental glomerulosclerosis; *ICMGN,* immune complex–mediated glomerulonephritis; *IgAN,* immunoglobulin A nephropathy; *IRGN,* infection-related glomerulonephritis; *MCD,* minimal change disease; *MN,* membranous nephropathy; *MesPGN,* mesangial proliferative glomerulonephritis; *MPGN,* membranoproliferative glomerulonephritis; *PIGN,* immune complex–mediated postinfectious glomerulonephritis.

actual incidence fourfold to fivefold higher because of subclinical cases. Over the past several decades, likely because of early antibiotic administration, the incidence of PSGN in children has decreased dramatically in developed countries, where it now is very infrequent; however, the incidence is increasing in older adults with comorbid conditions such as diabetes, alcoholism, and malignancy.[2,10] The higher incidence in developing countries and in alcoholics likely is associated with poor socioeconomic conditions, limited access to health care, delayed antibiotic administration, and a tropical climate.

PSGN is the most common finding in children with acute nephritis in developing countries and occurs sporadically or in epidemics. It typically affects those 2 to 14 years old, with a 2 : 1 male predominance, and represents a major problem in indigenous populations as in Australia, where more than 95% of the cases occur in aboriginal people residing in remote locations.[11] The risk for PSGN varies depending on the infection site and bacterial strain. The risk for developing PSGN ranges from 1% to 35%, averaging 15% after infection with a nephritogenic strain. Preceding skin infection confers a fivefold increased risk compared with that for throat infections, and risk reduction occurs with early antibiotic therapy. Epidemics have been associated with both sites of infection, as well as consumption of unpasteurized milk from cows infected with *S. zooepidemicus.* More cases of PSGN occur after impetigo caused by streptococci of M types 47, 49, 55, and 57 and with upper respiratory tract infections caused by types 1, 2, 4, and 12.[6] There also appears to be a genetic predisposition to developing PSGN, because of association with human leukocyte antigen (HLA)-DR4 and HLA-DR1, and siblings of sporadically affected patients have a 38% risk for developing clinical or subclinical glomerular disease.[10]

Clinical Manifestations

The presentation of PSGN differs in children and older debilitated adults. Children with symptomatic disease typically present with acute nephritis, including hematuria in virtually all patients, macroscopic hematuria in 30%, hypertension in 80%, edema in 80% to 90% (the chief complaint in 60%), and oliguria in 25% to 40%. Nephrotic syndrome occurs in only 2% and ascites is uncommon. In contrast, 20% of adults with PSGN have nephrotic syndrome, 83% have renal impairment, and 43% have congestive heart failure. Rapidly progressive renal failure with glomerular crescents occurs in less than 1% of children and adults. Asymptomatic subclinical cases have microscopic hematuria and transiently reduced complement levels. Serum CH50 is low and C3 levels are depressed in more than 90% of patients in the first week of disease; these normalize within 2 months of disease resolution. Levels of C1 and C4, indicating classical and lectin complement pathway activation, often are normal. Eighty percent have elevated IgG and IgM with normal IgA in contrast to rheumatic fever. Cryoglobulins, rheumatoid factor, and anti-C1q antibodies occur in up to one third of patients in the acute phase. Families may have various manifestations of PSGN; therefore inquiring about a family history of streptococcal infections and signs of glomerular disease is recommended.

Most patients give a history of a previous streptococcal infection, although it often has resolved at presentation. *Streptococcus* cultures are positive in 10% to 70% of cases during epidemics and in 20% to 25% of sporadic cases. Impetigo was more commonly associated with PSGN with a latent period of 2 to 4 weeks preceding glomerular symptoms. Pharyngitis now is the more frequently associated infection with a latent period of 7 to 10 days; however, skin infections predominate in group A streptococcal epidemics. Because cultures are often negative, antistreptococcal antibody levels are used to ascertain prior infection. The most widely used are antistreptolysin O (ASO) titers, which are increased in more than 65% of patients with PSGN after throat infections, and anti-DNAse B titers, which are elevated in 73% of post-impetigo cases. The more sensitive streptozyme panel measures anti-DNAse B, antihyaluronidase, antistreptolysin O, and antistreptokinase antibodies and is positive in more than 80% of patients. Antibody titers to NAPlr and SPEB/zymogen are more sensitive and specific, but currently are not clinically available.[6,9]

Pathology

Renal biopsy is not routinely indicated in PSGN but may be required to confirm the diagnosis when there are atypical clinical features such as nephrotic proteinuria, decreased C3 levels for more than a month (suggesting transformation to C3 GN or rarely to dense deposit disease), increasing renal dysfunction, or adult age. By light microscopy, renal biopsy typically shows diffuse proliferative GN characterized by endocapillary hypercellularity, including monocytes and often many neutrophils (exudative GN) with variable mesangial hypercellularity (Fig. 55.1). Less often or in the resolving phase, there may be a focal exudative pattern or mesangial proliferation; membranoproliferative GN (MPGN) is infrequent. Recent reports have identified NAPLr antigen in biopsy samples with MPGN features, raising the possibility of a more varied histologic presentation of PSGN than previously recognized. Small numbers of necrotizing and crescentic lesions are found in up to 50% of cases, whereas extensive involvement with crescents is unusual.[12]

Immunofluorescence is characterized by dominant C3 staining, and the pattern varies depending on the phase of the disease.[13] In acute and subacute disease the immune deposits are found in glomerular capillary walls and mesangial regions in a “starry sky” pattern, contain strong C3 with less frequent and intense IgG, and may have IgM in up to 50% of cases; IgA and C1q are not features of PSGN. The “garland” pattern is associated with numerous subepithelial hump deposits and heavy proteinuria, corresponding to active disease, although it has been described in later disease as well. As deposits are cleared in subacute to chronic injury, those in the mesangial regions remain the longest, resulting in a mesangial pattern with predominant C3 staining, loss of immunoglobulins and fewer infiltrating leukocytes (see Fig. 55.1). Although not part of routine renal biopsy assessment, properdin and the terminal membrane attack complex C5b-C9 have been identified in capillary wall and mesangial deposits.[14]

Electron microscopy (EM) demonstrates subepithelial individual hump deposits, which are typical, although not pathognomonic, of PSGN. These deposits may be infrequent or abundant and are preferentially sited where the capillary basement membrane reflects over the mesangium. GN resolves by clearing of the deposits and cell apoptosis. However, deposit fragments may remain for years with remote biopsy samples showing weak irregular granular glomerular staining for C3 with electron-lucent areas indicative of remote immune complex deposition.[15]

Differential Diagnosis

In a patient with typical symptoms and serologic findings, the diagnosis is straightforward. However, when there is oliguria lasting more than a week, azotemia lasting 2 weeks, hypocomplementemia lasting more than 1 month, or no clear history of preceding infection, renal biopsy is indicated to clarify the diagnosis. The renal biopsy differential diagnosis encompasses the spectrum of C3 dominant glomerulopathies and crescentic GN (see Chapter 22). C3 GN may appear morphologically indistinct from PSGN, including subepithelial humps, exudative GN, and weak immunoglobulin deposition. The rare case of dense deposit disease will demonstrate diagnostic electron-dense transformation of glomerular and tubular basement membranes. Correlating clinical findings and patient course with alternative complement factor and activity assessment may be required for a correct diagnosis. When there are glomerular crescents and a positive ANCA titer, the differential diagnosis

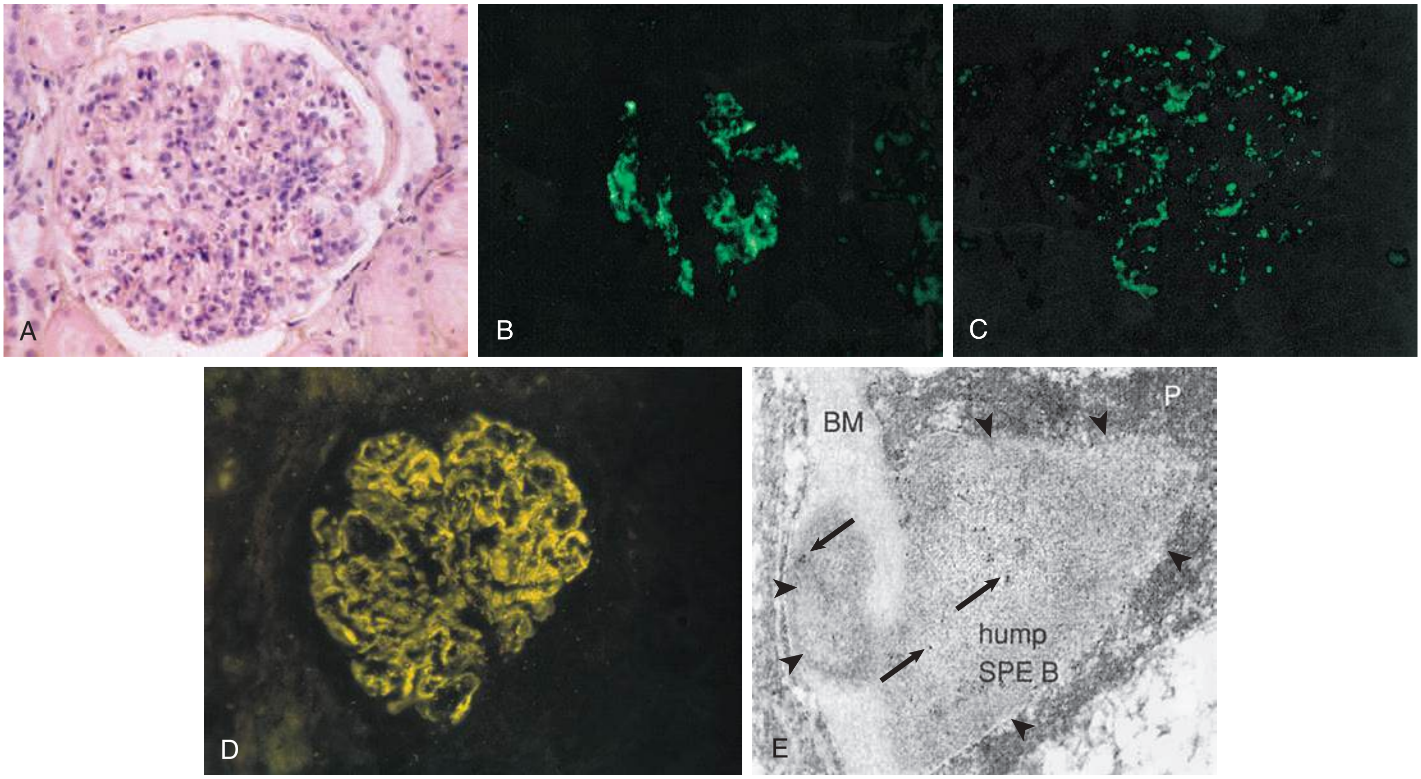

Fig. 55.1 **Poststreptococcal glomerulonephritis (PSGN).** (A) A diffuse proliferative and exudative GN can be seen with light microscopy. (B to D) Immunofluorescence showing the mesangial (B), starry sky (C), and garland (D) patterns. (E) Immune electron microscopy showing the characteristic subepithelial electron dense deposit (hump) with intramembranous extension (arrowheads), inside which streptococcal pyrogenic exotoxin B *(SPE B)* is demonstrated *(arrows)* (immunogold staining). *BM,* Basement membrane; *P,* podocyte. (Reprinted with permission from reference 5.)

is pauci-immune (ANCA-associated) crescentic GN; the diagnosis depends on identifying C3-containing electron-dense deposits in a pattern consistent with PSGN.

Natural History

Most children with PSGN recover with increased urine output by 1 week and resolution of clinical symptoms and serologic tests within 1 month. End-stage renal disease (ESRD) occurs in less than 1% of children observed for one to two decades after the acute attack.[9] After recovery, mild proteinuria (<500 mg/day) and microscopic hematuria may persist for up to 1 year without worsening the long-term prognosis. However, older patients with comorbidities have higher acute complication rates, including renal impairment, in 30% to 77%, with initially nephrotic patients at higher risk, congestive heart failure in 40%, nephrotic proteinuria in 20%, and mortality up to 30%.[9,16] Underlying alternative complement pathway dysregulation may represent a risk factor for progressive renal disease, leading to C3 GN, which is now thought to encompass most cases of atypical postinfectious GN. Certain epidemics also have reported a high incidence of chronicity, perhaps related to a predominance of affected adults, who tend to have worse outcomes.[17] A nephrotic presentation and persisting proteinuria also are associated with worse long-term prognosis. Studies in Australian aboriginal communities have shown that PSGN in infancy increases risk for subsequent albuminuria, hematuria, and chronic kidney disease (CKD).[16] The latter is attributed to a two-hit injury resulting from imposition of diabetes, metabolic syndrome, or low birth weight on early PSGN.

Treatment

Management includes culture and treatment of any persistent streptococcal infection. Early antibiotic treatment is likely to prevent PSGN, and prophylactic treatment of family members in high-risk communities or epidemic circumstances may be indicated. Treatment is with oral penicillin, intramuscular penicillin (a single intramuscular injection of 1.2 million units of benzathine penicillin in adults or half this dose in small children) erythromycin (in patients allergic to penicillin), or cephalosporins. Oral treatments should be given in doses every 6 hours for 7 to 10 days.[18] Treatment of acute nephritic syndrome includes fluid and sodium intake restriction and administration of loop diuretics for circulatory congestion. An oral long-acting calcium antagonist is usually sufficient to control hypertension. Intravenous medications may be indicated in exceptional cases with hypertensive emergency. Dialysis (hemodialysis or peritoneal dialysis) is required in 25% to 30% of adults but seldom in children. In those with acute tubular necrosis, supportive therapy should be provided; whereas those with PSGN complicated with crescents may benefit from pulse methylprednisolone. The prognosis of crescentic PSGN is significantly better than that for crescentic GN from other causes, but residual renal impairment occurs in more than half the cases.

IgA–Dominant Infection-Related Glomerulonephritis

Etiology and Pathogenesis

IgA-dominant infection-related GN (IRGN) is an immune complex–mediated lesion typically associated with *S. aureus* infections in adult patients with underlying comorbidities.[19] Koyama and colleagues[20] suggested the pathogenesis involves staphylococcal enterotoxins functioning as superantigens that bind directly to the major histocompatibility complex (MHC) class II molecules on antigen-presenting cells. This enterotoxin–MHC class II complex engages the V_β T cell–receptor region, resulting in T cell activation and a cytokine burst, initiating a B cell polyclonal IgG and IgA response putatively against a *S. aureus* cell envelope antigen.[20] This antigen co-localizes with glomerular IgA deposits and induces mesangial deposits in an experimental model.

Epidemiology

IgA-dominant IRGN usually occurs in the setting of an ongoing (rather than a sequela of) infection in adults, with an average age of 58 and up to 41% over 65 years of age.[21,22] There is a male predominance, and most patients have comorbidities, including diabetes in up to 65% of patients, malignancy, heart disease, or alcohol or substance abuse.[10] The incidence is unknown, but IgA-dominant IRGN occurred in 1.6% of kidney biopsies in adults in one institution.[23] In developed countries, it has a 300% increased prevalence compared with that of PSGN, and many cases of IgA-dominant IRGN likely are asymptomatic and undiagnosed. Approximately 65% of patients are infected with methicillin-resistant *Staphylococcus aureus* (MRSA), and 25% have methicillin-sensitive *Staphylococcus aureus* (MSSA).[21] The most frequent sites of infection are the skin and viscera, including pneumonia, endocarditis, and osteomyelitis. Although less common, other pathogens such as *S. epidermidis, Streptococcus, Klebsiella,* and *Escherichia coli* have been associated with IgA-dominant IRGN.[10,19,22]

Clinical Manifestations and Pathology

Active disease often presents with acute or rapidly progressive renal failure, nephrotic range proteinuria in 50%, and universal hematuria with gross hematuria in 25%.[19] However, a mild clinical course is not uncommon, with subacute or chronic disease and delayed diagnosis due to underlying chronic disease in an elderly patient. Low C3 levels are found in 55% to 70% of patients, and serum IgA levels may be mildly increased.

Renal biopsy reveals endocapillary proliferative and exudative GN in 40% to 80% of cases, mesangial proliferative GN (MesPGN) in 20% to 60%, and crescentic GN in less than 5%.[20,24] Crescents are present in up to 35% and positive ANCA in 22%.[25,26] The deposits contain mild or intense IgA with co-dominant C3 staining in the same pattern and kappa light chain similar to or greater than lambda.[19,26] EM shows mesangial dense deposits in most cases, with up to 83% having variable numbers of subepithelial hump deposits and half with small and less frequent subendothelial deposits[2,25] (Fig. 55.2).

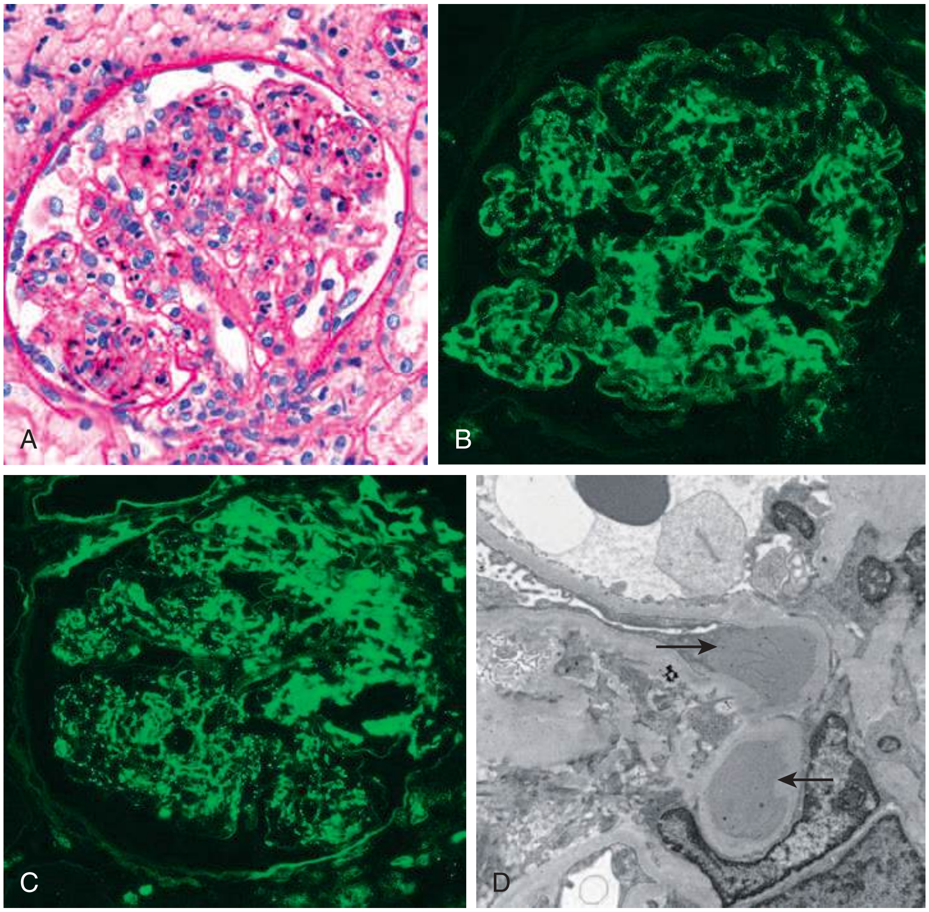

Fig. 55.2 IgA-dominant glomerulonephritis (GN) in a diabetic patient with methicillin-sensitive *Staphylococcus aureus* infection. (A) A diffuse exudative GN is present with neutrophil infiltration. (B) Immunofluorescence shows IgA irregular granular mesangial and capillary wall deposits. (C) Immunofluorescence shows C3 in a pattern similar to that of IgA. (D) Electron microscopy shows dome-shaped subepithelial deposit *(black arrow)* and mesangial deposit *(yellow arrow).*

Differential Diagnosis, Natural History, and Treatment

Differentiation from IgA nephropathy is important for treatment and outcome. IgA-dominant IRGN is favored in the presence of associated staphylococcal infection, hypocomplementemia, severe proteinuria, and renal biopsy demonstrating deposits with strong C3 and IgA staining in the same pattern with kappa staining the same as or greater than lambda staining and subepithelial hump-shaped deposits. There is a worse outcome compared with IgA nephropathy, likely because of underlying comorbid conditions. There may be persistence of mesangial IgA deposits despite recovery from infection, possibly related to an underlying risk for IgA immune complex disease.

Active infection should be treated with appropriate antibiotics, and this may lead to renal functional recovery when there is ongoing infection. Corticosteroid treatment is contraindicated, at least during active infection, highlighting the importance of differentiation from IgA nephropathy, in which corticosteroids may be indicated in severe cases (see Chapter 23).

Endocarditis-Associated Glomerulonephritis

Etiology and Pathogenesis

Endocarditis may be an acute or subacute infection. The pathogenesis of endocarditis-associated GN involves the deposition of immune complexes containing bacterial antigens similar to that proposed for PSGN. It has been suggested that less virulent organisms with longer undiagnosed endocarditis predispose to immune complex formation and development of GN.[27] Polyclonal type III cryoglobulins are present in 50% of patients but rarely found in glomeruli. Some bacteria, classically MRSA, express superantigens that can activate T cells directly and lead to a polyclonal gammopathy and immune complex GN.

Epidemiology

The epidemiology of infective endocarditis (IE) has been changing over the last four decades. Historically, this disease affected young adults with rheumatic heart disease; however, it now occurs in older and at-risk patients, including drug users, prosthetic valve and implantable device recipients, and those with human immunodeficiency virus (HIV) and hepatitis C infection, diabetes, and health care–associated bacteremia.[27,28] *S. aureus* and *Staphylococcus epidermidis* are the most common pathogens in hospital-acquired IE, whereas *Streptococcus* infections are more frequent in community-acquired and native valve endocarditis, although the incidence of MRSA-associated community-acquired IE is increasing.[29] Gram-negative bacteria (*Enterococcus faecalis, E. coli, Brucella,* and *Proteus*) and HACEK microorganisms (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella*) less frequently cause IE. Culture-negative IE is usually caused by *Coxiella burnetii, Bartonella* spp., and *Tropheryma whipplei* in untreated patients and by streptococcal spp. in those with prior antibiotic administration.[30] HACEK organisms require special laboratory procedures for isolation; if these are not used, infected patients will be culture negative. *Bartonella henselae* endocarditis is frequently associated with congenital valvular disease and exposure to cats. Polymicrobacterial infections are usually associated with drug abuse.

Clinical Manifestations

Patients often have fever, arthralgias, anemia, and purpura. Rarely, IE may manifest as primary renal disease without systemic symptoms. Classic findings such as Osler nodes, Janeway lesions, and splinter hemorrhages are seldom seen, and the diagnosis may be missed until autopsy in 38% of the patients.[27] Renal manifestations include reduction in kidney function, microhematuria, and mild proteinuria, with infrequent nephrotic syndrome or rapidly progressive GN. In recent studies, cardiac valvular disease occurred in only 30% of patients, involving the tricuspid valve in 43%.[28] Decreased C3 and C4 levels, elevated rheumatoid factor, circulating immune complexes, and type III cryoglobulins are identified in 50% of patients with IE. In patients who develop GN, there is more frequent hypocomplementemia, particularly C3, suggesting alternative complement pathway activation. However, complement levels may be normal in superantigen-mediated GN.[28]

Pathology

Studies examining autopsied kidneys from patients with IE demonstrated variable glomerular lesions in 7% to 17%, including crescentic GN, MPGN, and focal and diffuse PIGN patterns, although morphologic details are not uniformly provided.[27,31] Renal biopsy findings also are variable, with up to 45% of biopsies demonstrating GN, including 55% crescentic GN, approximately 35% diffuse or focal endocapillary proliferative GN or infrequently MPGN, and 10% MesPGN.[28,31] Immunofluorescence discloses C3 in all proliferative GN cases with IgG or IgA in mesangial regions in more than half and less frequently in capillary walls. Electron-dense deposits occur in 90% of all GNs, including mesangial in 85%, subepithelial hump-like in 49%, and subendothelial in 45%.[28,31]

Differential Diagnosis, Natural History, and Treatment

In crescentic GN with or without positive ANCA titers, hypocomplementemia should raise suspicion for underlying IE. Antibiotic treatment usually results in eradication of endocarditis and correction of serologic abnormalities. However, microhematuria, proteinuria, and renal functional impairment may persist for months after successful therapy. The overall mortality of IE is 20% and increases to 36% in patients who develop renal failure. Early diagnosis, risk stratification, and prompt antibiotic therapy are critical for an improved prognosis, with diminution of circulating immune complex levels correlating with better outcomes.[32] In patients with crescentic GN, pulse corticosteroid therapy and plasma exchange have been used in addition to effective antibiotic therapy, but the value of these treatments remains unconfirmed.

Shunt Nephritis

Etiology, Pathogenesis, and Epidemiology

Shunt nephritis is an immune complex GN. Ventriculoatrial shunts used to relieve increased intracranial pressure become infected in approximately 6% of adult patients. Ventriculoatrial shunts are used infrequently in children but have a similar rate of infection. GN develops in 0.7% to 2% of those with infected ventriculoatrial shunts 2 months to many years after insertion. The microorganisms are usually *S. epidermidis* and *S. aureus* and less frequently *Propionibacterium acnes,* diphtheroids, *Pseudomonas,* or *Serratia.* In contrast to atrioventricular shunts, ventriculoperitoneal shunts are rarely associated with GN.

Clinical Manifestations and Pathology

Children are most frequently affected, typically within 6 months of surgery, and have recurrent low-grade fever, arthralgias, weight loss, anemia, rash, hepatosplenomegaly, hypertension, and signs of increased intracranial pressure.[10] There also may be no signs of systemic infection. Microscopic hematuria is present in 90% of patients, often with nephrotic range proteinuria. Serologic findings include elevated rheumatoid factor, cryoglobulinemia, and decreased serum C3, less often with reduced C4, and occasionally positive PR3-ANCA titers. Cerebrospinal fluid may demonstrate eosinophils. Renal histology shows MPGN type I in nearly 60% of the cases and MesPGN in the remainder. IgM, IgG, and C3 with electron-dense deposits are present in subendothelial and mesangial regions.

Natural History and Treatment

Treatment requires antibiotic therapy and prompt removal of the infected ventriculoatrial shunt, which is usually replaced by a ventriculoperitoneal shunt. Delay in diagnosis and shunt removal worsens the renal prognosis. If dialysis is required, hemodialysis is preferred because peritonitis carries the risk for meningitis in patients with a ventriculoperitoneal shunt. Complete recovery occurs in more than half of the patients, 22% have persistent urinary abnormalities, and 6% develop ESRD.

Glomerulonephritis Associated With Other Bacterial Infections

Osteomyelitis and intra-abdominal, pelvic, pleural, and dental abscesses can be associated with GN, typically when infection has been present for several months. Renal disease varies from mild urinary abnormalities to rapidly progressive GN, with nephrotic syndrome the most frequent presentation. Unlike in other infection-associated GNs, complement levels are often normal. Renal histologic examination reveals MPGN, diffuse proliferative GN, MesPGN, or IgA-dominant IRGN, as discussed previously. Crescents may be present. Antibiotic treatment may result in recovery of renal function if it is started early.

Congenital, secondary, or early latent syphilis may be associated with GN. In congenital syphilis, nephrotic syndrome may be the primary clinical manifestation, with anasarca occurring 4 to 12 weeks after birth. Renal involvement is rare in acquired syphilis; when it ensues, the presentation is nephrotic syndrome or occasionally acute nephritis with positive serologic test results for syphilis. Membranous nephropathy (MN) is the most common glomerular finding, but diffuse proliferative GN with or without crescents, MPGN, and MesPGN have been observed. Treponemal antigens have been identified in the immune deposits. Syphilitic GN responds to antibiotic treatment, although remission may not occur for 4 to 18 months.

Acute typhoid fever from *Salmonella typhi* is characterized by fever, splenomegaly, and gastrointestinal symptoms. In severe cases, patients rarely may develop disseminated intravascular coagulation or thrombotic microangiopathy. Microhematuria and mild proteinuria are found in 25% of patients with MesPGN.[33]

Leprosy (*Mycobacterium leprae* infection) is calculated to affect 10 to 15 million patients worldwide, with up to 45% having glomerular diseases. GN is immune complex–mediated with frequent hypocomplementemia. Non-nephrotic to nephrotic range proteinuria occurs in 2% to 68% and renal dysfunction in 4% of patients.[34,35] Nephrotic syndrome is rare and usually associated with amyloidosis, often with erythema nodosum.[35] Prospective studies indicate that on follow-up, serum creatinine is elevated in 35% of patients at some time during their course and patients frequently have hypertension and nonsteroidal antiinflammatory drug use before beginning multidrug therapy. Renal biopsy samples show proliferative GN and MN with similar frequencies, whereas in autopsy studies, 4% to 31% have amyloidosis and 5% to 14% demonstrate MPGN or diffuse proliferative GN with IgG, C3, and less frequently IgM, IgA, and fibrin deposition.[33] The incidence of renal impairment decreases to 9% after 8 months of multidrug therapy

Pneumococcal pneumonia is rarely associated with microhematuria and proteinuria, seen with delayed treatment. Diffuse proliferative GN and MPGN have been reported, and pneumococcal antigen is present in the immune deposits. *Streptococcus pneumoniae* is rarely associated with hemolytic uremic syndrome because of unmasking of the glomerular and erythrocyte Thomsen-Friedenreich antigen by pneumococcal neuraminidase A, which allows preformed antibodies to bind and elicit an immune response.

Gastroenteritis caused by *Campylobacter jejuni* may be associated with MesPGN or diffuse proliferative GN. Other bacteria, including *E. coli, Yersinia,* meningococcus, and *Mycoplasma* pneumonia may induce GN in this setting (see Table 55.2).

VIRAL INFECTIONS

Glomerular injury can occur in a number of viral infections, primarily hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV. These may occur with acute or chronic infection, depending on the virus and host response, including genetic risk factors such as *APOL1*. The advent of better antiviral therapeutic agents has modified associated glomerulopathies and improved prognoses for patients with virus-associated GN.

Hepatitis A–Associated Glomerulonephritis

Renal involvement is uncommon in patients infected with hepatitis A virus (HAV). IgA nephropathy has occurred temporally associated with HAV, with simultaneous resolution of the viral infection and GN suggesting a causal relationship. There are case reports of MesPGN and MPGN, including with dominant IgA. There is experimental evidence for HAV-associated mesangial proliferation and immune complex GN, further supporting causation in humans. Patients present with microscopic hematuria and non-nephrotic proteinuria or may be nephrotic, particularly in association with MPGN. Recovery from GN usually coincides with recovery from the viral infection.

Hepatitis B–Associated Glomerular Lesions

Etiology and Pathogenesis

HBV is a DNA virus of the Hepadnaviridae family and contains the hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg), which is a splice variant of the core antigen. HBV causes immune complex–mediated glomerular injury predominantly through deposition of circulating immune complexes that have been identified in the serum of infected patients with GN. These immune complexes contain all three major hepatitis B antigens. Different antigens are associated with specific immune complex locations, likely related to their size and charge. HBeAg occurs in smaller cationic subepithelial immune complexes in MN. The larger HBcAg and HBsAg typically deposit in subendothelial and mesangial regions.[36] In situ immune complex formation may occur associated with locally expressed HBcAg, evidenced by identification of glomerular HBcAg and its corresponding RNA. There also is evidence of direct viral injury to glomerular cells, because HBV induces mesangial cell proliferation and increased expression of type IV collagen production in vitro. There likely are contributing host factors, including MHC class II risk alleles.

Epidemiology

Chronic HBV infection is defined as persistence of HBsAg-positive serology without IgM antibodies to HBcAg.[37,38] Persistent infection occurs in 0.1% to 15% of those with HBV infection and afflicts approximately 350 million people worldwide, who often are symptomatic. HBV infection becomes chronic in more than 90% of infants, 25% to 50% of children infected between 1 and 5 years of age, and 6% to 10% of older children and adults. Vertical transmission (maternal-infant) often occurs in endemic areas, such as China and Southeast Asia. Horizontal transmission follows blood contamination or direct mucous membrane contact. The prevalence of HBV infection is lower in Europe and the United States, with most carriers becoming infected as adolescents or adults by horizontal transmission because of drug abuse, blood transfusions, or sexual relations.

Clinical Manifestations and Pathology

Acute HBV infection may cause nausea, vomiting, fever, hepatomegaly, and a short-lived serum sickness–like syndrome with urticaria,

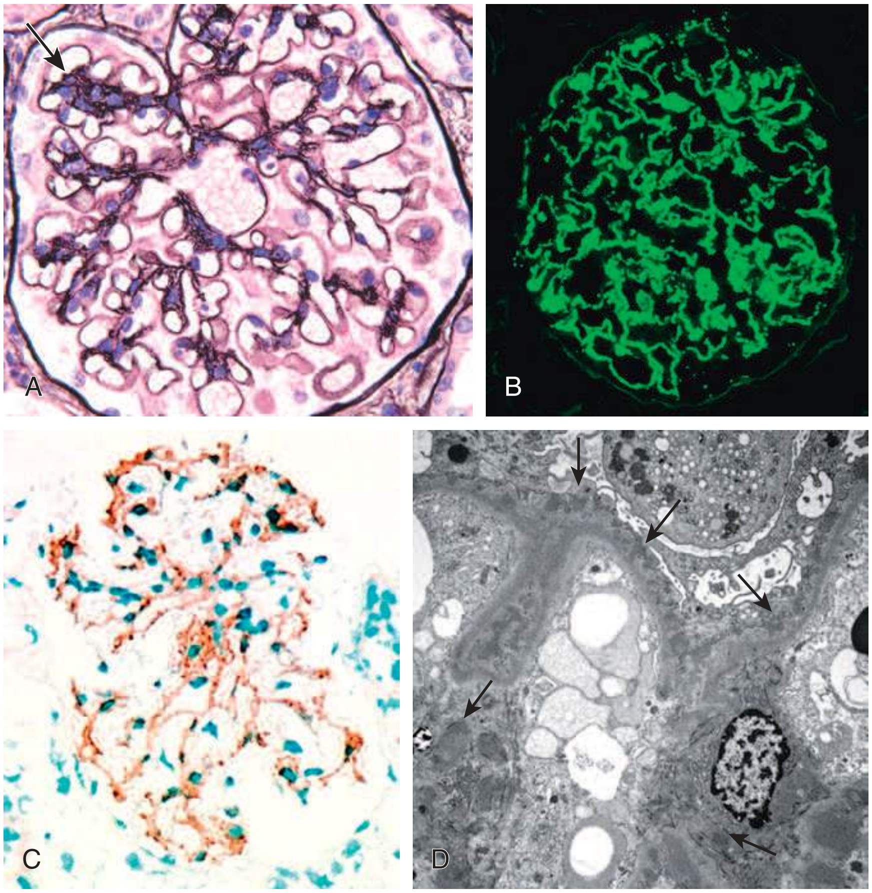

Fig. 55.3 Hepatitis B–associated membranous nephropathy (MN). (A) Capillary walls are irregular with small subepithelial spikes, and there is segmental mesangial hypercellularity *(yellow arrow)*. (B) Immunofluorescence shows granular IgG along capillary walls and segmentally in mesangial regions. (C) Immunohistochemistry is positive for HBsAg within glomerular deposits. (D) Electron microscopy shows subepithelial *(black arrows)* and mesangial (*yellow arrows)* deposits

maculopapular rash, neuropathy, arthralgias, arthritis, microscopic hematuria, and non-nephrotic proteinuria.[37] There are no published renal biopsy studies in acute infection, and renal symptoms resolve in 1 to 2 months in concert with recovery from the viral illness.

In chronic HBV infection, 3% to 5% of patients develop renal disease; additionally, 10% to 30% of patients with chronic HBV are coinfected with HCV and 5% to 10% with HIV.[36]

Hepatitis B Virus–Associated Membranous Nephropathy

MN is the most common glomerular disease in chronic HBV carriers. Children usually present between 6 and 12 years of age, show a strong male predominance, and often have asymptomatic proteinuria or nephrotic syndrome, microhematuria, normal renal function, and minimal liver disease.[37] The prognosis is usually good, and spontaneous remission is common associated with the appearance of circulating anti-HBeAg antibodies. Adults develop proteinuria or nephrotic syndrome, often with impaired kidney function and clinically apparent liver disease; approximately 30% will progress to CKD and 10% to ESRD. Hypocomplementemia occurs in less than half the patients.

Renal histologic examination shows MN, including subepithelial deposits in any stage of progression (Ehrenreich and Churg stage I to IV) depending on chronicity of the lesion. In contrast to primary MN, there often are mesangial hypercellularity and mesangial and/or subendothelial deposits indicative of secondary MN but not unique to HBV (Fig. 55.3). Endocapillary hypercellularity and endothelial cell tubuloreticular inclusions may be found. Circulating antiphospholipase A2 receptor (PLA2R) antibodies and PLA2R in subepithelial deposits typically are associated with primary MN and are not usual features of HBV-associated MN, although there are reports of PLA2R in HBV-associated MN, including co-localization with HBV antigens in glomerular deposits.[1] This appears to occur in HBV endemic areas in Asia, and the significance of this observation remains to be determined. Determination of IgG subclasses in glomerular deposits may be helpful because IgG1 usually predominates in secondary MN whereas IgG4 is dominant in primary MN. HBeAg and HBsAg may be identified in glomerular deposits and HBeAg in eluted proteins, but these are not standard procedures (see Fig. 55.3).

Hepatitis B Virus–Associated Membranoproliferative Glomerulonephritis

MPGN is the second most frequent HBV-associated glomerular lesion, more commonly found in adults. Patients present with nephrotic or less frequently non-nephrotic proteinuria and microhematuria; half are hypertensive and 20% have reduced renal function.[36] This pattern is associated with serum HBsAg and HBcAg and reduced serum C3 and C4 levels. Cryoglobulinemia, predominantly type III, occasionally occurs in HBV-infected patients but is more prevalent with concurrent HCV infection and found in 10% of the population worldwide.[1] Renal biopsy shows MPGN type I, or type III if there is concomitant MN.

HBsAg has been identified in eluted immune deposits from HBV-associated MPGN.

Other Hepatitis B Virus–Associated Glomerular Lesions

There are several reports of IgA nephropathy (IgAN) associated with HBV infection, including one in which a sustained remission of the clinical symptoms followed successful HBV treatment with pegylated interferon. However, other studies have shown no difference in outcome for patients with IgAN with and without HBV infection. This may be coincidental, because IgAN has a high prevalence in HBV endemic areas in Asia and mesangial IgA deposits occur in chronic liver disease secondary to impaired clearance of IgA circulating immune complexes (see Chapter 23). There is a recent report of PIGN in 10 patients with chronic HBV infection and all three HBV antigens in the serum.[39] Glomeruli demonstrated typical PIGN, although with fewer subepithelial humps compared with PSGN; HBsAg and HBV DNA were detected in glomeruli. AA amyloidosis is associated with chronic inflammatory diseases and has been identified in patients with chronic HBV infection, including children. The presentation is proteinuria or nephrotic syndrome, with amyloid infiltration of glomeruli, vessels, and less often the tubulointerstitium. There is one case report of collapsing focal segmental glomerulosclerosis (FSGS) associated with HBV infection and HBV DNA in shed urinary podocytes, suggesting direct infection with HBV. After entecavir therapy, HBV infection improved and the collapsing FSGS resolved.

Polyarteritis Nodosa

This vasculitis has been associated with HBV infection and is discussed in Chapter 25.

Treatment

Treatment should be considered when the HBV DNA level is greater than 2000 IU/ml, serum alanine aminotransferase (ALT) levels are elevated, and liver biopsy or other diagnostic tests show moderate to severe hepatitis and/or moderate fibrosis.[40,41] Newly diagnosed HBeAg-positive patients with normal liver function should be watched for 3 to 6 months to allow for spontaneous seroconversion. Treatment options include pegylated interferon, nucleotide analogues (lamivudine, entecavir, tenofovir, adefovir, telbivudine), or a combination of these agents. Dose adjustment is required with reduced renal function. Interferon should not be used in decompensated disease because of severe adverse effects. Standard interferon doses are 5 MU daily or 10 MU 3 times per week and pegylated interferon is given for 12 to 24 weeks in HBeAg-negative patients and 16 to 32 weeks in HBeAg-positive patients. Interferon treatment has resulted in improvement of HBV-associated MN; however, pegylated interferon-α2a may induce MN after several months of treatment.

Lamivudine 100 mg orally once daily for 52 weeks is frequently used as initial therapy and results in 75% to 80% resolution of MN in association with reduction of serum HBV DNA. However, there is a 20% annual rate of resistance, which may worsen renal disease. Dosing should be adjusted for renal function: creatinine clearance (CrCl) 30 to 49 ml/min: 100 mg first dose, then 50 mg/day; CrCl 15 to 29 ml/min: 100 mg first dose, then 25 mg/day; CrCl 5 to 14 ml/min: 35 mg first dose, then 15 mg/day; CrCl less than 5 ml/min or hemodialysis: 35 mg first dose, then 10 mg/day (after dialysis).[42]

Entecavir monotherapy is used in treatment-naïve patients and those refractory to lamivudine who cannot tolerate tenofovir. Entecavir confers less resistance, better seroconversion, and normalization of liver function and histology compared with lamuvidine or adefovir. Entecavir dosing is 0.5 mg/day and requires adjustment for reduced renal function: CrCl 30 to 50 ml/min: normal dose every 48 hours; CrCl 10 to 29 ml/min: normal dose every 72 hours; and CrCl less than 10 ml/min: normal dose every 7 days or after hemodialysis for patients on chronic dialysis.[42] Treatment should be maintained for 12 months after seroconversion and demonstration of undetectable HBV DNA, except in patients with cirrhosis in whom discontinuation carries the risk for fatal hepatitis. Tenofovir is used as initial therapy or in patients with resistance to other drugs. The main tenofovir adverse effects are reduced bone density and nephrotoxicity. Tenofovir 300 mg should be given once daily, or every 48 hours or every 72 to 96 hours if the CrCl is less than 50 ml/min or less than 30 ml/min, respectively. In patients on chronic dialysis, 300 mg should be given after dialysis once weekly.[42] Adefovir has been used in HBV resistant to lamivudine, but it has been replaced by tenofovir, which is more potent and effective.[42]

Drug combinations have been used with variable success. Lamivudine and interferon improved seroconversion and liver histology findings. Interferon and telbivudine should not be used together because of the risk for peripheral neuropathy. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment with the previously mentioned agents for patients with HBV infection regardless of glomerular involvement. It has been argued that corticosteroid and immunosuppressive agents should not be used because they are ineffective and may delay or prevent seroconversion and accelerate the progression of liver disease. However, a meta-analysis of 12 clinical trials with 317 patients found that combined antiviral and immunosuppressive therapy can improve proteinuria in HBV-associated GN without altering HBV replication or damaging liver or renal function.[43]

Children with HBV-associated MN often have a benign course, with up to two thirds achieving spontaneous remission 4 years after disease onset. In contrast, approximately 30% of adults develop CKD. Therefore treatment generally is not required for children with HBV-associated MN. However, in controlled studies, clearance of HBV DNA and HBeAg was achieved in about half of the children, with more proteinuria resolution in the treated group. Because HBV-associated MN rarely progresses to ESRD in children, it is reasonable to treat when proteinuria is severe or kidney disease progresses. Treatment consists of a short course of corticosteroids (prednisone 1 mg/kg/day for 2 weeks) and plasma exchange (9 to 12 exchanges during 3 weeks) followed by interferon-α therapy or oral antiviral agents as indicated earlier.

Hepatitis C–Associated Glomerular Lesions

Etiology, Pathogenesis, and Epidemiology

HCV is an RNA virus of the Flaviviridae family and a common cause of chronic hepatitis, cirrhosis, and hepatoma. Up to 90% of infected patients have chronic infection, with HCV proteins inducing a polyclonal antibody response and development of immune complexes. HCV RNA has been detected in glomerular mesangial and endothelial cells and immune complexes, and Toll-like receptor 3 may play a pathogenic role in the development of GN.[44] In association with immune complex production, the HCV E2 envelope protein can induce an IgM rheumatoid factor response, with resulting cryoglobulins.[36] HCV thus induces a variety of glomerular lesions, most often MPGN with or without cryoglobulins (see Chapter 21). An estimated 170 million people in the world have chronic HCV infections, and renal disease is not common in this population, although the true incidence is unknown.

Clinical Manifestations and Pathology

Most patients with HCV-associated renal disease are asymptomatic. When symptoms occur, they include nephrotic syndrome in 20%, non-nephrotic proteinuria, nephritic syndrome in 25%, microscopic hematuria, and refractory hypertension in more than half. Low complement levels are common.[36] HCV infection may be associated with MPGN, MN, mixed cryoglobulinemia syndrome, and other lesions.

Hepatitis C Virus–Associated Membranoproliferative Glomerulonephritis

MPGN is the most frequent renal lesion associated with HCV infection, and most patients have cryoglobulins, although these may not be identified on renal biopsy. The presence of GN also may relate to host factors such as age and HLA polymorphisms. Renal biopsy discloses MPGN type I or type III if there is a MN component. When cryoglobulins are present, there are large protein thrombi occluding glomerular capillaries associated with marked endocapillary hypercellularity because of infiltrating monocytes (Fig. 55.4). Cryoglobulin deposits are in the subendothelium or form protein thrombi with a substructure consisting of 20- to 30-nm curvilinear microtubular, annular, fibrillar, or cylindrical forms, which also may be found in monocyte secondary lysosomes.

A limited number of patients with HCV infection develop mixed cryoglobulinemia, which is a systemic vasculitis associated with purpura, arthralgias, fever, neuropathy, and renal disease. Cryoglobulins are usually type II and occasionally type III, with HCV RNA and HCV antigen-antibody complexes present in the cryoprecipitate. C3, C1q, and particularly C4 are reduced. This is also discussed in Chapter 21.

Hepatitis C Virus–Associated Membranous Nephropathy

There is an association between MN and hepatitis G virus (HCV) infection and these likely are linked, although conflicting data exist regarding pathogenesis. Patients with MN are more commonly HCV RNA–positive compared with other GNs, except for MPGN, and MN appears more prevalent in HCV-positive transplant recipients, supporting this association.[44] MN has been found to have a similar incidence in HCV-infected and diabetic patients; however, MN also may be increased in the setting of diabetes. The clinical and renal morphologic findings are similar to those observed in idiopathic MN. Cryoglobulins, rheumatoid factor, and hypocomplementemia are absent.

Polyarteritis Nodosa

Polyarteritis nodosa may occur in patients with HCV infection with or without cryoglobulinemia (see Chapter 25).

Other Hepatitis C Virus–Associated Glomerular Lesions

Other reported associated glomerular lesions include fibrillary GN, immunotactoid GN, FSGS including the collapsing variant (especially in African Americans), and MesPGN.

Natural History and Treatment

In a large Italian study, 80% of patients had mild urinary or renal functional changes and 15% developed ESRD. Guidelines for HCV infection treatment have been published by the World Health Organization, the American Association for the Study of Liver Diseases, and the Infectious Diseases Society of America (www.hcvguidelines.org).[45] Interferon-free regimens are preferred because they have a 95% or higher virologic response (absent HBV RNA 3 months after treatment suspension) and minor side effects. Ledipasvir 90 mg and sofosbuvir 400 mg

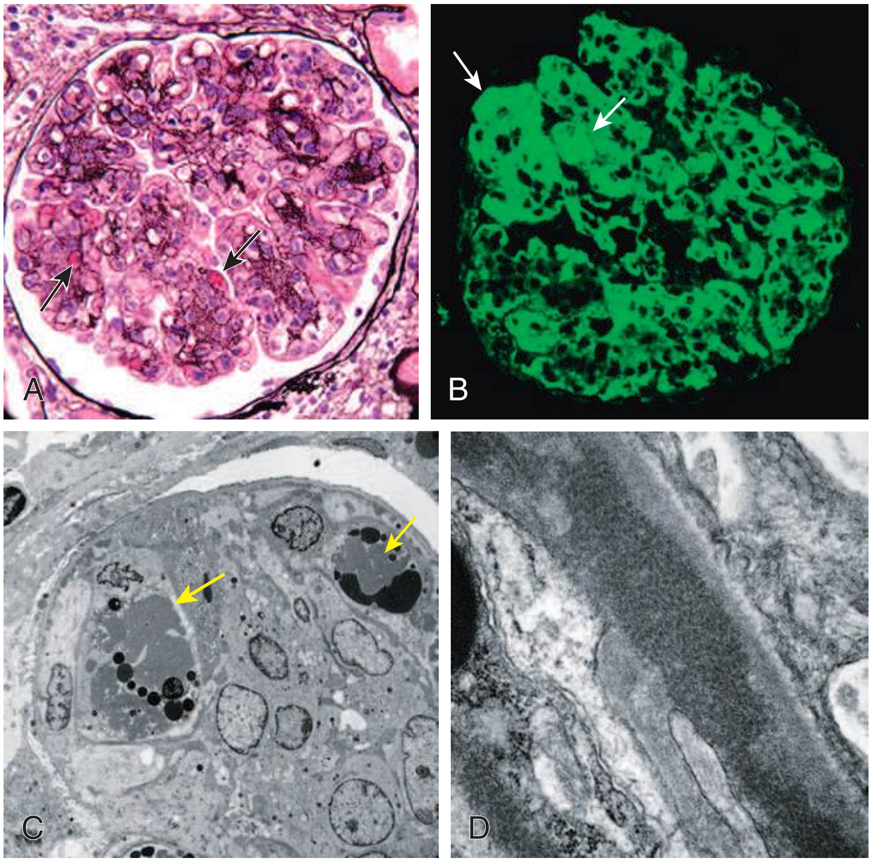

Fig. 55.4 Hepatitis C–associated membranoproliferative glomerulonephritis (MPGN) with cryoglobulins. (A) Lobular hypercellular glomerulus with capillary wall double contours and cryoglobulin thrombi *(yellow arrows)*. (B) Immunofluorescence for IgM demonstrates large intracapillary thrombi *(yellow arrows)* and segmental capillary wall deposition. (C) Electron microscopy of a glomerular lobule showing capillary luminal occlusion by a cryoglobulin thrombi *(yellow arrows)*. (D) High magnification electron micrograph showing the annular microtubular substructure of cryoglobulin.

or sofosbuvir and velpatasvir 100 mg given daily in a combination tablet, with or without ribavirin 1000 mg/day if less than 75 kg or 1200 mg/day if 75 kg or greater are preferred treatments, given for 12 weeks in treatment-naïve and for 24 weeks in cirrhotic treatment-experienced patients. Ribavirin is teratogenic; therefore contraception is recommended during and for 6 months after ribavirin treatment.[45] When there is eradication of the HCV, diminished proteinuria, less progression to ESRD, and loss of cryoglobulins has been reported in up to half of treated patients.

Human Immunodeficiency Virus–Associated Renal Disease

HIV infection has been associated with a number of glomerular lesions, the most common of which used to be collapsing glomerulopathy in HIV-associated nephropathy (HIVAN). HIV-associated renal disorders are discussed in Chapter 56.

Other Virus-Associated Renal Disease

Cytomegalovirus (CMV) infection rarely has been reported to cause diffuse proliferative GN with immune deposits containing CMV antigens in native kidneys. CMV also has been linked to collapsing glomerulopathy and ESRD in patients without HIV infection. In renal allograft patients with CMV infection, antimetabolite immunosuppression is stopped. Depending on infection severity, oral valganciclovir 900 mg twice daily or ganciclovir 5 mg/kg intravenously every 12 hours is administered until clinical recovery and two blood samples negative for CMV by polymerase chain reaction are obtained, followed by oral valganciclovir 900 mg daily for 3 months.

Parvovirus B19 is a single-stranded DNA virus with marked tropism for erythroid precursor cells. In patients with sickle cell disease, parvovirus-induced aplastic crises are occasionally followed by nephritic or nephrotic syndrome, assumed to be the result of immune complex deposition. Diffuse proliferative GN and MPGN have been reported with C3 and IgG deposits in capillary walls and subendothelial regions. Collapsing FSGS similar to HIVAN has been attributed to parvovirus B19 infection, and some, but not all, studies have detected viral DNA in kidney biopsy samples. There is no specific treatment for parvovirus infection.

Dengue hemorrhagic fever, currently the most prevalent mosquito-borne urban viral infection worldwide, may be caused by four serotypes of the Flaviviridae virus family. The most common renal complication is acute kidney injury (AKI) (see Chapter 67). Acute endocapillary GN with IgG, IgM, and C3 deposits presenting with hematuria, proteinuria, and renal failure has been reported in infected patients.

Mild renal abnormalities occur in acute Epstein-Barr virus (EBV) infection, with microhematuria and proteinuria in 10% to 15% of cases. Diffuse proliferative GN and MPGN may occur, and there is an association with collapsing FSGS. Many viral infections, including varicella, mumps, adenovirus, coxsackievirus, and influenza, can be associated with transient microscopic hematuria, non-nephrotic proteinuria, and a mesangial or diffuse proliferative GN in which viral antigens can be identified in the mesangium. Measles may cause diffuse proliferative GN, but is better known for its unique ability to induce remission in patients with minimal change disease (MCD) and nephrotic syndrome, likely because of its ability to increase Treg cells as infection abates.

PARASITIC INFECTIONS

Kidney involvement is common in various parasitic infections and includes a range of renal lesions (Table 55.3). With the exception of malaria, leishmaniasis, filariasis, and schistosomiasis, glomerular involvement is usually mild and transient.[46]

Malaria

Etiology and Pathogenesis

There are four major species of *Plasmodium,* only two of which typically are associated with GNs in humans—*Plasmodium falciparum* and *Plasmodium malariae.*[47] Malarial antigens activate the immune system by interaction with monocytes, secretion of chemokines and cytokines, polyclonal B cell activation, and circulating immune complex formation. Malarial antigens have been identified in 25% of glomerular immune complexes and in the absence of immune complexes, suggesting in situ immune complex formation also may occur. Infected erythrocytes may participate in immune activation through preferential expression of surface antigens. Additionally, the alternative complement pathway may be directly activated.[33,47,48] Concomitant infection with other parasites (schistosomiasis) or viruses (EBV), or genetic factors such as *APOL1* risk alleles may participate in the pathogenesis of kidney injury and influence geographical disease variations.

Epidemiology, Clinical Manifestations, and Pathology

Malaria is a major world health problem, with 200 million cases predominantly occurring in Africa, India, Southeast Asia, and Latin America causing 600,000 deaths each year (Fig. 55.5). It can be acquired by the bite of infected *Anopheles* mosquitoes or infected vectors from aircraft, blood transfusion, or infected organs. *P. falciparum* invades erythrocytes of any age, and may cause AKI and multiple organ failure (see Chapter 67). Transient mild proteinuria and microhematuria are encountered in 25% to 50% of patients, and nephritic syndrome and impaired renal function are uncommon. Patients develop MesPGN with deposits of IgG, IgM, and C3; there are rare reports of IgAN (Fig. 55.6). In contrast, GN in patients infected with *P. malariae* (quartan malaria) infects aging erythrocytes and is less severe. Patients present with steroid-resistant nephrotic syndrome (tropical nephritis or nephrotic syndrome) primarily in children 4 to 8 years old. When adults develop GN, it often manifests with hypertension and renal impairment. Renal biopsy shows MPGN with granular IgG, IgM, and C3 deposition and subendothelial and mesangial electron-dense deposits[47,49] (Fig. 55.7). Infrequently, *P. malariae* induces MN or MCD. Despite treatment of the infection with or without corticosteroids, there is progression to ESRD, which is attributed to continuing autoimmune mechanisms. *Plasmodium vivax* causes AKI and rarely thrombotic microangiopathy (see Chapter 67), but GN has not been reported. Control of malaria and improvement of health care in general has resulted in a decline in renal disease in developing countries.

Filariasis

Filariae are nematodes, of which only eight of the hundreds of species affect humans and only three are associated with kidney disease. *Wuchereria bancrofti* is responsible for several clinical syndromes, including tropical eosinophilic pneumonia, elephantiasis, and chyluria, which induces proteinuria, hypoproteinemia, and hematuria in infected patients. The dominant glomerular lesion is MesPGN with less frequent MPGN and rare amyloidosis. Immune complex deposits containing worm antigens have been demonstrated in glomeruli.[47,50] Less often there is acute proliferative and exudative GN with eosinophilic predominance. Bancroftiasis is often associated with bacterial infection, usually staphylococci and certain streptococci; it is uncertain if this contributes to the development of GN. Even less understood is a potential role of the rickettsia-like bacteria *Wolbachia,* discovered within filarial nematodes and blamed for activation of innate immune pathways.

Onchocerca volvulus is less widely spread and causes scrotal lymph node obstruction ("hanging scrotum"). Onchocercosis is associated with several immune-mediated manifestations, including keratitis, anterior

TABLE 55.3 Renal Lesions in Parasitic Infections

Parasite	Glomerular Lesions	Tubulointerstitial Lesions	Amyloidosis	Tissue Reaction, Symptoms	Acute Kidney Injury	Post-Transplant Disease
Schistosomiasis						
_S. haematobium_*	MesPGN DPGN with _Salmonella_	+++	++	Granulomas		+
_S. mansoni_*	MesPGN, MPGN FSGS MN DPGN with _Salmonella_	+	++	Granulomas		+
S. japonicum	MesPGN MPGN (primates, rabbits)	+				
S. mekongi		+++				
Malaria						
_Plasmodium malariae_*	MPGN MesPGN MCD (rare) FSGS (rare) MN (rare)					
_Plasmodium falciparum_*	MesPGN DPGN MPGN (rare) IgAN (rare)	+			++	+
Filariasis						
Onchocerciasis*	MesPGN, MPGN MCD			River blindness		+
Loiasis	MN, MesPGN MPGN FSGS (rare)					
Bancroftiasis	MesPGN, MPGN, DPGN			Chyluria Pneumonia Elephantiasis		
Dirofilariasis	MPGN (dogs) MN (dogs, cats)					
Other						
Brugia malayi	MesPGN, MPGN DPGN	+ (rare)	+ (rare)			
Visceral leishmania	DPGN MesPGN MPGN	++	++		+	+
Kala-azar*						
Trichinosis	MesPGN MPGN				+	
Strongyloidiasis	MesPGN					
Echinococcosis	MPGN MN (rare)			Hydatid cysts		
Opisthorchiasis*	MesPGN	++	+		++	
Chagas disease*	MesPGN (mice)					
Babesiosis	MesPGN (rat)				++	+
Trypanosomiasis	MesPGN MPGN (monkey, rat)					
Toxoplasmosis*	MesPGN MPGN FSGS (rare)	+				

All conditions documented in humans unless otherwise indicated.

*Parasitic antigens or specific antibodies detected in the glomeruli.

DPGN, Diffuse proliferative glomerulonephritis; _FSGS,_ focal segmental glomerulosclerosis; _IgAN,_ immunoglobulin A nephropathy; _MCD,_ minimal change disease; _MesPGN,_ mesangial proliferative glomerulonephritis; _MN,_ membranous nephropathy; _MPGN,_ membranoproliferative glomerulonephritis. Ondetorum, nocto ellatus.

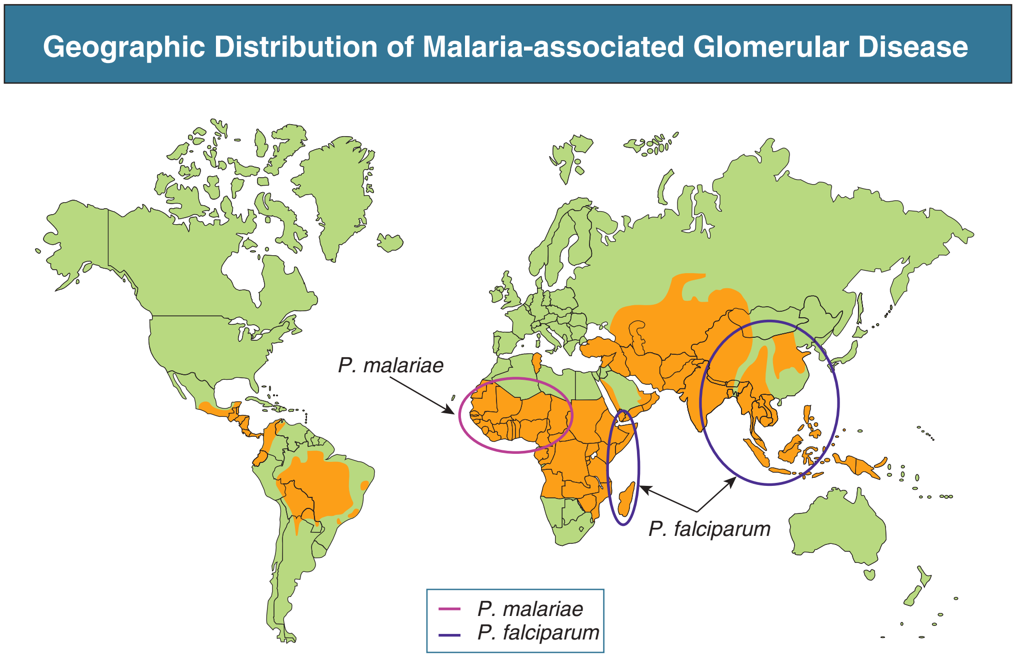
Geographic Distribution of Malaria-associated Glomerular Disease

Fig. 55.5 Geographical distribution of malaria-associated glomerular disease. Although malaria is endogenous to many areas of the world *(shaded orange),* the major areas where malaria-associated glomerular disease has been reported *(ringed)* and their respective species are shown.

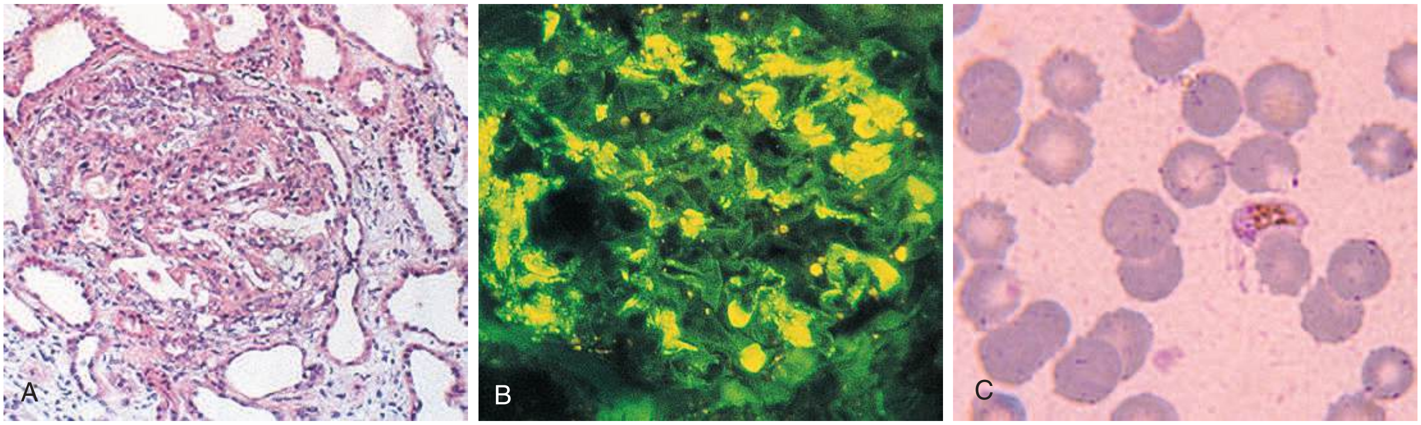

Fig. 55.6 Glomerulonephritis (GN) associated with *Plasmodium falciparum* malaria. (A) Light microscopy shows mesangial proliferative GN. (B) Immunofluorescence may reveal *P. falciparum* antigens in a mesangial pattern. (C) Peripheral blood smear confirms acute *P. falciparum* infection, with banana-shaped gametocytes and multiple ring forms in erythrocytes. (**A,** reprinted with permission from reference 49; **B** and **C,** courtesy V. Boonpucknavig.)

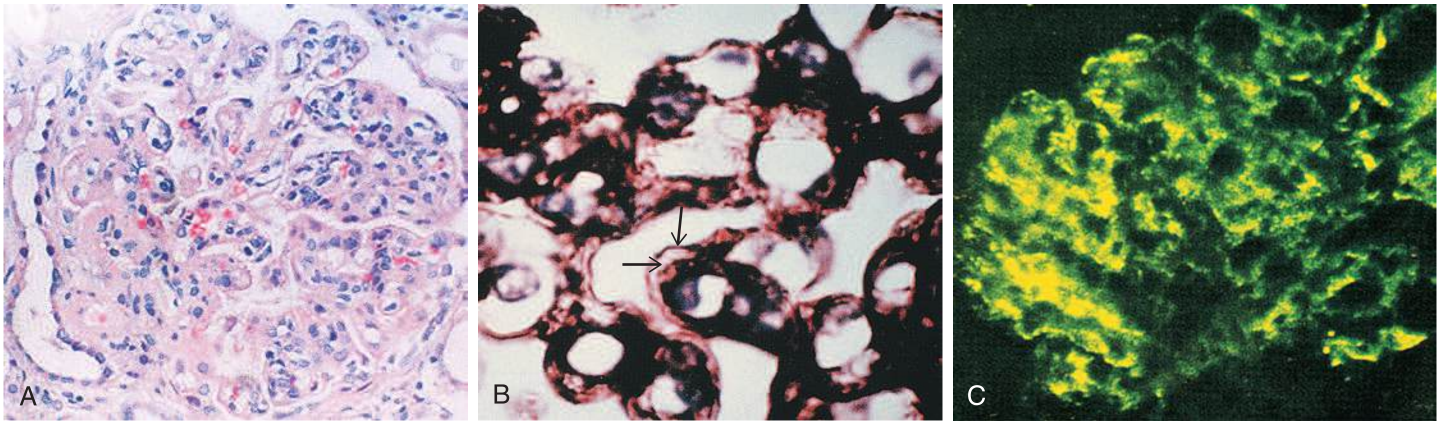

Fig. 55.7 Quartan malarial nephropathy. (A) Light microscopy shows sclerosing membranoproliferative glomerulonephritis. (B) Silver stain shows a double contour *(arrows)* of the basement membrane. (C) Malarial antigens are present on immunofluorescence. (From reference 49.)

uveitis, and optic atrophy leading to "river blindness." Infected patients with GN have proteinuria, including steroid-resistant nephrotic syndrome with progressive renal impairment.[47,50] Most common is MPGN with IgM, IgG, and C3 in subendothelial and mesangial deposits, with less frequent MCD and sclerosing glomerular lesions. Onchocercal antigens have been detected in the glomeruli, and onchocercal GN recurs in transplanted kidneys. When *W. bancrofti* or *O. volvulus* are treated, there may be worsening of the proteinuria and hematuria as a result of parasitic disintegration and increase in circulating immune complex formation. After successful eradication of the parasites, there is usually resolution of the renal symptoms.

Loa is the least prevalent of the nephritogenic filariae. Kidney disease associated with this infection includes MN and less commonly MPGN and FSGS.[47,51] Unlike the other forms of filariasis, treatment for *L. loa* generally is not effective in resolution of the GN. Infections with all three Filarioidea parasites often occur with hepatitis B and/or malaria coinfection, which independently can cause immune complex–mediated GN. It is unknown whether this affects the incidence or types of GN seen in patients with filariasis.

Leishmaniasis

Leishmaniae are obligatory intracellular protozoa that infect 12 million humans and many animals. Of 30 known leishmanial spp., only visceral leishmaniasis (kala-azar) induced by *Leishmania donovani* and by *Leishmania infantum* (*Leishmania chagasi*), which is closely related, involve the kidney. Sixty percent of those infected with *L. donovani* have mild proteinuria and microscopic hematuria. Reported glomerular lesions related to immune complex deposition include MesPGN and MPGN; the latter may occur with cryoglobulinemia.[52] Amyloidosis has been described, most frequently associated with coincident HIV infection.

Schistosomiasis

Schistosomiasis is a common cause worldwide of glomerular disease. This is discussed in Chapter 54.

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SELF-ASSESSMENT QUESTIONS

1. At the present time, infection-related glomerulonephritis (GN) in developed countries is associated with debilitating conditions (neoplasia, diabetes, AIDS, alcoholism) and immunoglobulin A (IgA) deposits.
   A. True
   B. False
2. Patients with acute poststreptococcal GN usually have:
   A. Low serum CH50 and C3 levels
   B. Low serum C4 levels
   C. High serum C3 levels
   D. High serum CH50 and high serum C4 levels
3. Patients with infective endocarditis may have crescentic GN without immune deposits.
   A. True
   B. False
4. Combined antiviral therapy and immunosuppression (cyclophosphamide and steroids) is:
   A. Contraindicated in patients with HBV-associated GN
   B. Potentially useful in patients with HBV-associated GN

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Human Immunodeficiency Virus Infection and the Kidney

Jeffrey B. Kopp, Saraladevi Naicker

The 2017 Joint United Nations Programme on HIV/AIDS (UNAIDS) report estimated that there are 36.7 million people worldwide with HIV virus infection (nearly 21 million on antiretroviral therapy [ART]). Since 2005, there has been a 48% decline in AIDS-related deaths each year, 1.5 million in 2010 to 1 million in 2016.[1]

HIV-1 infection is associated with glomerular and tubulointerstitial disease, and patients with HIV infection are at risk for nephrotoxicity from ART as well as from other medications such as blockers of the renin-angiotensin-aldosterone axis and prostaglandin inhibitors. The presence of kidney dysfunction in the setting of HIV infection acts as an independent predictor of poor outcome.

Acute kidney injury (AKI), interstitial nephritis from medication and opportunistic infection, and co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) are all relatively common. With advances in treatment, patients with HIV are more likely to experience complications such as atherosclerosis, metabolic syndrome, type 2 diabetes, and end-stage renal disease (ESRD). In addition to HIV-1, HIV-2 can cause immunodeficiency but rarely causes kidney disease. In this chapter, we use HIV to refer to HIV-1.

EPIDEMIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS CHRONIC KIDNEY DISEASE

Developed World

In the European EUROSIDA observational study, only 3% of HIV-infected subjects had an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 and only 0.3% had an eGFR less than 30 ml/min/1.73 m^2.[2] In the United States, the incidence of ESRD attributed to HIV continues to decline.[3] The U.S. Renal Data System (USRDS) reported that for the period 2006 to 2010, there were 3834 cases of AIDS nephropathy, representing 0.7% of total ESRD. The USRDS 2017 data report states that for the period 2011 to 2015, there were 2356 cases of AIDS nephropathy (0.4% of total ESRD). Among these cases, 79% were Black, 13% European American and 8% Hispanic, who can be of any race.

The Developing World

Globally, an estimated 37 million individuals are infected with HIV, including an estimated 0.8% of those aged 15 to 49 years. Sub-Saharan Africa is home to 71% of the world HIV infections, with an overall HIV prevalence of 4.4%. Of HIV-positive individuals in sub-Saharan Africa, 48% have access to ART, but access to renal replacement therapy is frequently limited. The prevalence of chronic kidney disease (CKD) has been assessed by the presence of proteinuria or eGFR (based on serum creatinine measurements) and ranges widely from 6% to 48.5% in Africa. This wide variation may be partly ascribed to differences in study design, populations studied, and the definitions used for CKD. CKD prevalence in HIV-positive persons has been estimated at 1% to 6% in Brazil, 17% in India, 23% to 38% in Nigeria, and 35% among children in Zimbabwe.

In South Africa, HIVAN is the dominant HIV kidney disease and is present in up to 80% of kidney biopsy specimens of HIV-positive individuals, which is consistent with findings in the United States in the pre-ART era. As in developed countries, other renal causes are also observed, including HIV-immune complex kidney disease (HIVICK) from postinfectious and other causes, membranous nephropathy, and interstitial nephritis. Some renal biopsy samples show nonspecific changes (e.g., mesangial hyperplasia and chronic interstitial nephritis) that show regression on combination ART, which suggests that the diagnostic criteria for HIV-associated CKD may need to be revised.

GLOMERULAR DISORDERS

Human Immunodeficiency Virus–Associated Nephropathy

HIV infection is associated with various glomerular disorders (Table 56.1). The classic glomerulopathy of HIV infection is collapsing focal segmental glomerulosclerosis (FSGS) or HIVAN.

Etiology and Pathogenesis

HIVAN occurs with both acute infection and chronic infection; in the latter case, it is associated with higher viral RNA levels and lower CD4 T lymphocyte counts. Studies of human kidney biopsy samples have shown that HIV can infect glomerular and tubular cells, setting up a chronic and possibly latent infection.[4] HIV accessory proteins such as Vpr and Nef can damage renal cells independent of direct infection. In transgenic mice, the expression of HIV accessory proteins Vpr or Nef in podocytes is associated with progressive CKD, leading to ESRD, loss of podocyte differentiation markers, and collapsing FSGS.[5,6] Transgenic mouse experiments also suggest that HIV gene products are toxic to tubular epithelial cells, resulting in apoptosis and blocking cell proliferation.

Host factors also determine susceptibility to HIVAN, especially in individuals of African descent compared with those of European or Asian descent. Apolipoprotein L1, encoded by *APOL1* on chromosome 22, is a component of particular high-density lipoprotein particles termed *trypanosome lytic factors*.[7] *APOL1* variants have been identified as a major cause of the predilection for chronic glomerular disease that characterizes populations of sub-Saharan African descent.[8,9] The presence of two *APOL1* codon-changing variants confer an odds ratio of

TABLE 56.1 **Kidney Diseases Associated With Human Immunodeficiency Virus Infection or Its Treatment**

	Entity	Frequency	Associations
Glomerular	HIV-associated nephropathy (HIVAN)	Common	African descent; often advanced HIV disease
	HIV-associated immune complex kidney disease (HIVICK)	Common	All ethnic backgrounds
	Thrombotic microangiopathy	Uncommon	
	Membranoproliferative glomerulonephritis, with or without cryoglobulin-associated vasculitis	Rare	Hepatitis C; enfuvirtide
	Membranous nephropathy	Rare	Hepatitis B
	Fibrillary and immunotactoid glomerulopathies	Rare	
	Amyloid nephropathy (AA type)	Rare	
	Minimal change nephropathy	Rare	Nonsteroidal antiinflammatory medication
Tubular	Acute kidney injury	Moderately common	Aminoglycosides, cidofovir, foscarnet
	Proximal tubule injury (Fanconi syndrome)	Moderately common	Tenofovir disoproxil fumarate, adefovir, cidofovir, didanosine
	Diabetes insipidus	Uncommon	Amphotericin, tenofovir disoproxil fumarate, didanosine, abacavir
	Chronic tubular injury	Moderately common	Amphotericin, cidofovir, adefovir, tenofovir disoproxil fumarate
	Crystal nephropathy	Uncommon	Indinavir, atazanavir; sulfadiazine, ciprofloxacin, intravenous acyclovir
Interstitial	Interstitial nephritis	Uncommon	Allergy to β-lactam, sulfa, ciprofloxacin, rifampin, proton pump inhibitor, allopurinol, phenytoin; also causes of crystal nephropathy listed earlier, BK virus; generally advanced disease Immune reconstitution inflammatory syndrome; generally advanced disease; after initiation of antiretroviral therapy

29 in the United States and 89 in South Africa, a strikingly large effect for a complex disease.[10,11] Homozygosity or dual heterozygosity for two risk alleles (termed G1 and G2; G1 is actually a haplotype, but the term *allele* is used here for simplicity) are observed in 72% of African Americans and South Africans with HIVAN, compared with only 12% of African American controls and 3% of South African controls.[10,11] Among South Africans, a single copy of the *APOL1-G1* variant confers an odds ratio of 21 for HIVAN, an important finding with regard to mechanism because it demonstrates a dominant effect. These variants appear to protect individuals from African sleeping sickness caused by *Trypanosoma brucei rhodesiense,* and this may explain the rapid rise in allele frequency in Africa, particularly West African populations, that has occurred during the past 40,000 years. HIV-positive women with CKD with two *APOL1* risk alleles were shown to have greater proteinuria, more rapid decline in eGFR and 1.7- to 3.4-fold greater risk for incident CKD than those with low-risk genotypes.[12] Studies in cell culture suggest that *APOL1* variants may act by diverse mechanisms, including endolysosomal dysfunction, mitochondrial dysfunction, and altered transcellular cation flux leading to potassium depletion and activation of stress kinases. Transgenic mouse models have shown altered endolysomal trafficking, FSGS,[13] and preeclampsia.[4]

Clinical Manifestations

Patients with HIVAN typically present with proteinuria and renal impairment. Some patients present with edema, although edema is less common than with other conditions associated with nephrotic range proteinuria, suggesting a defect in tubular sodium handing. Imaging studies may reveal increased kidney size despite reduced GFR and, in some cases, increased echogenicity; this unusual feature is shared with diabetic nephropathy and amyloid nephropathy. However, no radiologic features predict the renal histologic findings and renal biopsy is required for diagnosis.

Pathology

HIVAN is largely indistinguishable from idiopathic collapsing FSGS, with pathologic changes in glomeruli (proliferation and dysregulation of podocytes or podocyte stem cells, together with glomerular collapse), tubules (acute and chronic injury, sometimes with microcystic tubular changes), and interstitium (chronic inflammation, fibrosis) (Fig. 56.1). On electron microscopy, both HIVAN and idiopathic collapsing FSGS may manifest tubuloreticular inclusions within dilated endosomal compartments within glomerular endothelial cells, which are believed to be markers for interferon-mediated injury and may also indicate *APOL1*-mediated injury. Some patients with progressive loss of kidney function (e.g., from HIVICK or interstitial nephritis) may develop adaptive FSGS from the consequences of glomerular hyperperfusion and hyperfiltration.

Diagnosis and Differential Diagnosis

The evaluation of AKI or CKD in a patient with HIV infection resembles that performed in other settings: history, focused particularly on medication use and other infections; physical examination; examination of the urine sediment; serum and urine chemistries; and in many cases renal imaging studies, and in some cases kidney biopsy. Urine chemistries may include 24-hour timed or spot urine measurement of protein and albumin (for suspected glomerular disease), glucose, phosphate, and uric acid (for suspected proximal tubular disease). Indications for kidney biopsy include AKI without clear associated cause, especially with a nephritic sediment, nephrotic proteinuria, clinical evidence of thrombotic microangiopathy (TMA), and unexplained CKD. In the past, some clinicians argued that nephrotic proteinuria in an individual of African descent is likely to be HIVAN or idiopathic collapsing FSGS and that a biopsy is not necessary. The widespread use of ART in the current era makes this decision less tenable, and renal biopsy appears to be indicated to guide prognosis and therapy, particularly when substantial proteinuria is present.

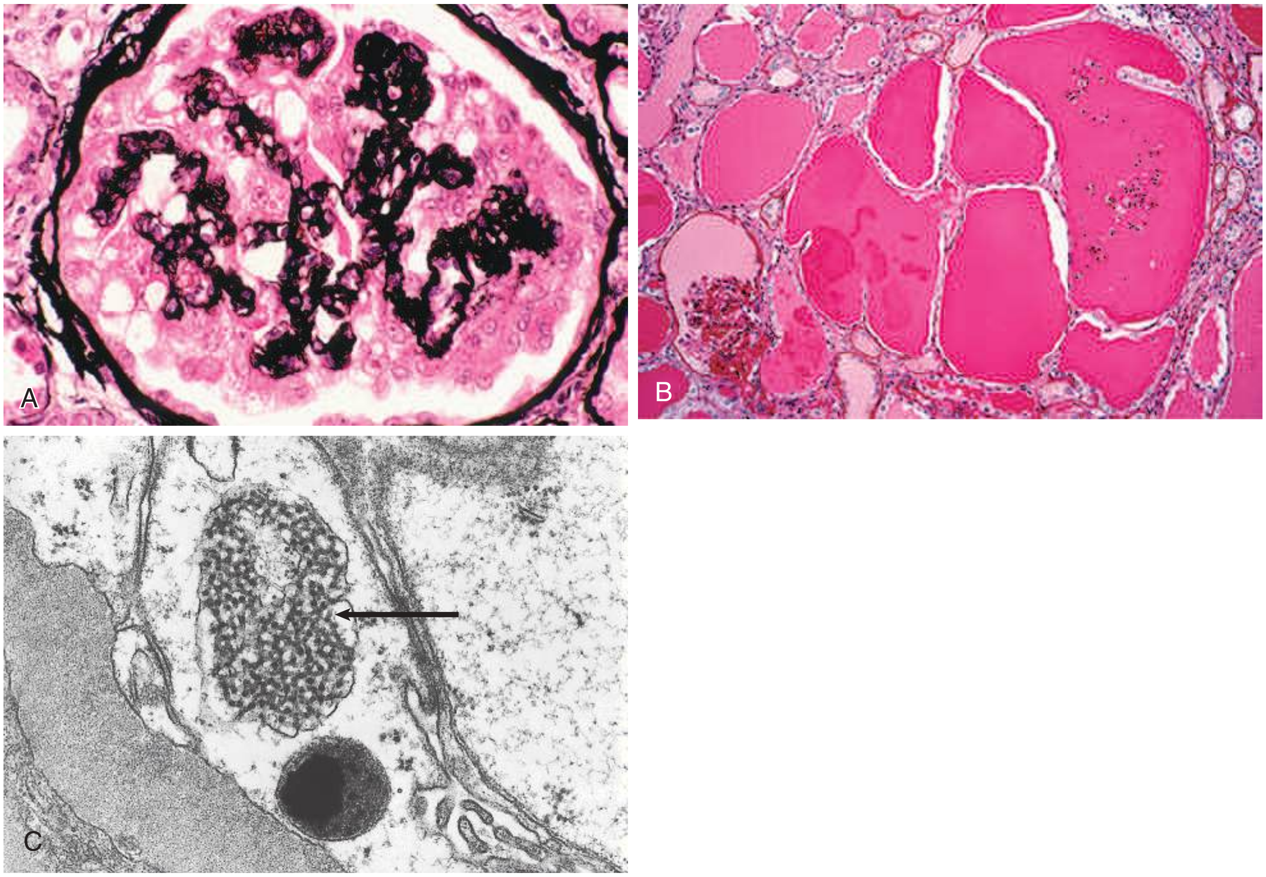

Fig. 56.1 **HIV-associated nephropathy.** (A) A globally collapsed glomerulus shows marked podocyte hypertrophy and hyperplasia. (Jones methenamine silver.) (B) At low power, the renal parenchyma contains abundant tubular microcysts with proteinaceous casts. The glomerulus is collapsed with dilated urinary space. (Periodic acid–Schiff.) (C) The glomerular endothelial cell pictured here contains a large intracytoplasmic tubuloreticular inclusion ("interferon footprint"; *arrow*) composed of inter-anastomosing tubular structures within a dilated cisterna of endoplasmic reticulum. (Electron micrograph.)

With the advent of ART, the range of common renal diagnoses has expanded from HIVAN in individuals of African descent and HIVICK among all ethnic backgrounds, to include diseases such as FSGS, diabetic nephropathy, and arterionephrosclerosis. In patients with HIV and hepatitis, membranoproliferative glomerulonephritis (MPGN) associated with HCV should be considered. Other diagnoses include membranous nephropathy (associated with HBV infection, or presumably idiopathic, but possibly related to the polyclonal B cell expansion typical of HIV disease) and amyloidosis. Chronic tubular injury, especially associated with tenofovir disoproxil fumarate (TDF) therapy but possibly associated with other ART, is not uncommon; but when early diagnosis leads to cessation of the offending medication, CKD is usually averted. Despite the plethora of diagnoses, HIVAN remains the leading cause of ESRD in patients with HIV disease in the United States.

The diagnosis of HIVAN is made by renal biopsy, although nephrotic proteinuria and low CD4 count in individuals of African descent is highly suggestive of HIVAN. Among individuals of African descent, other possible diagnoses include primary or adaptive FSGS (although a pathogenic role for HIV cannot be excluded in conferring susceptibility) and arterionephrosclerosis (see later discussion). In all individuals, diabetic nephropathy and HIVICK should be considered (see later discussion and Table 56.1).

Treatment

The HIV Medicine Association of the Infectious Diseases Society of America provides clinical practice guidelines for the management of adults and children with HIV.[2] All HIV-positive individuals should receive combination ART, beginning at the time of diagnosis. ART appears to prevent CKD. The presence of kidney disease does not affect this recommendation. In the era before ART was available, HIVAN progressed rapidly, with patients reaching ESRD in months to a few years. The marked decline in HIV-associated ESRD in the United States after the introduction of ART in 1995 suggests that effective control of viral replication with ART may prevent HIVAN. Retrospective studies also suggest that ART treatment of HIVAN may prolong renal survival. Rapid resolution or decrement in proteinuria within 6 months of commencing ART has been reported.[14]

The Development of Anti-Retroviral Therapy in Africa (DART) study, conducted in Uganda and Zimbabwe, demonstrated improvement of kidney function of 2 to 6 ml/min/1.73 m^2 after 4 to 5 years of ART.[2,15] Other studies suggest that ART is most effective when initiated before the onset of severe renal disease.[16] In a few cases, regression of histologic lesions with combined anti-retroviral therapy (cART) has been demonstrated.[17,18] A recent study of 221 HIV-positive patients in South Africa with renal histologic findings reported that both HIVAN and HIVICK respond to ART.[19]

There is some evidence that the pattern of renal disease has changed since the introduction of ART, with a relative decrease in HIVAN and emergence of classic FSGS as the most common cause of glomerular disease. In this study, HIVAN occurred more frequently in Black patients with severe immunodeficiency and severe renal failure; patients with FSGS were older, more likely to have received ART, more frequently had cardiovascular risk, and had more severe interstitial fibrosis on kidney biopsy.[20]

Treatment of HIV-associated renal disease also includes standard therapies for CKD, including control of blood pressure (BP) and the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), as well as ART if this has not been started. A prospective and controlled, but nonrandomized trial of HIVAN demonstrated improved renal survival with ACE inhibitor therapy. Glucocorticoids have shown benefit for HIVAN in a prospective study and several retrospective studies, as reviewed recently.[21] Nevertheless, although there is no consensus, these medications should be considered in HIVAN and HIVICK only when viral replication is suppressed with ART and proteinuria or progressive renal function decline continues.

BP targets should be similar to those for other patients with CKD. The Systolic blood PRessure INTervention (SPRINT) study suggests that BP targets should be lower than previously thought: less than 130 mm Hg in the general population over 50 years of age (excluding those with diabetes or prior stroke, who may not tolerate this lower target). Although HIV-positive subjects were not included in the SPRINT study, it would seem reasonable to treat them to this target if they lack the exclusions noted earlier.[22]

Natural History

Progression of CKD is more rapid in HIV-positive individuals of African descent, probably reflecting the effect of the *APOL1* variants. Patients with HIVAN may progress to ESRD despite ART. Predictors of progression are a high degree of chronic damage on histology, presence of large numbers of sclerotic glomeruli, severe renal dysfunction at baseline, and high-grade proteinuria.[23,24]

Human Immunodeficiency Virus Immune Complex Kidney Disease

In populations of European and Asian ancestry, the most common glomerular diseases associated with HIV disease are immune complex diseases.[25] HIVICK has been reported from both developed countries such as the United States,[26,27] the United Kingdom,[28] and France[20] and from developing countries (e.g., Thailand and India[29]). HIVICK is observed in populations of African descent, although much less frequently than HIVAN, and most lack two *APOL1* risk alleles. Compared with those with HIVAN, individuals with HIVICK tend to have lower HIV viral copy number and are more likely to have diabetes and hypertension.[30]

HIVICK can take various forms, including postinfectious glomerulonephritis, membranous nephropathy, and a lupus-like pattern. Patients with HCV coinfection may manifest MPGN (see Chapter 21). Some patients may have only mesangial immunoglobulin A (IgA) deposits (especially those with microhematuria and non-nephrotic proteinuria), resembling idiopathic IgA nephropathy. Hence, the diagnosis of HIVICK may be fraught with difficulties for the pathologist, who must exclude other immune complex disease.

HIVICK may be clinically indistinguishable from HIVAN, although hematuria may be more marked, and some patients present with lower levels of proteinuria. Renal biopsy findings may vary from mesangial proliferative glomerulonephritis (GN) to focal or diffuse proliferative GN with endocapillary proliferation (Fig. 56.2). In some cases, changes consistent with HIVAN also may be present, including tubuloreticular inclusions within glomerular capillary endothelial cells. Immune deposits may be in mesangial, subendothelial, or subepithelial locations and may include IgG and IgM or IgG, IgM, and IgA (so-called "full house deposits"), often with C3. These forms resemble lupus nephritis, although lupus serologic test results are typically negative.

The pathogenesis of HIVICK is not well understood and may involve heterogeneous mechanisms. It is not known whether complexes form locally within the glomeruli or are passively trapped as from the glomerular microcirculation. In some cases, immune complexes include HIV antigens. Other cases may represent generalized polyclonal B cell expansion that accompanies HIV disease.

HIVICK is often associated with progressive loss of kidney function. Foy and colleagues[30] in the United States found that at 2 years after diagnosis, 70% of HIVAN cases and 32% of HIVICK cases had reached ESRD. Further, the use of combination ART or the attainment of viral suppression was not associated with lower risk for ESRD in HIVICK (N = 83), whereas use of combination ART was associated with reduced likelihood of progression with HIVAN (N = 56.[30] In contrast, a U.K. study reported a slower rate of progression of HIVICK to ESRD, but these authors considered HIV-associated IgA nephropathy to be a

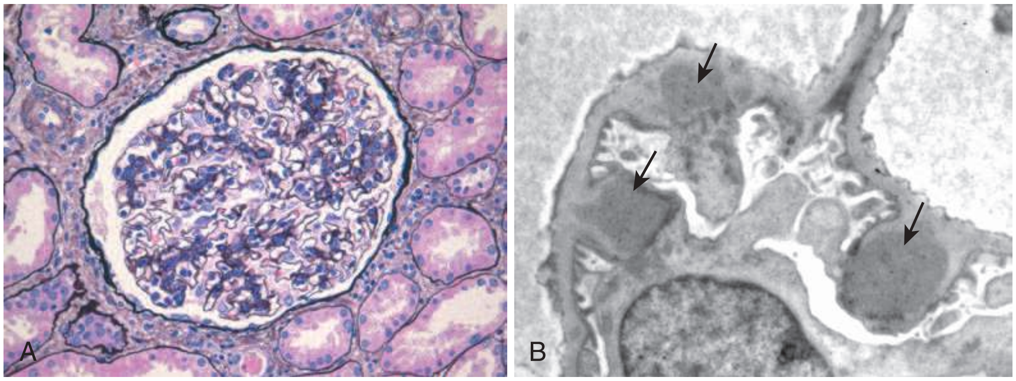

Fig. 56.2 **HIV-associated glomerulonephritis.** This HIV-positive patient presented with microhematuria and non-nephrotic proteinuria with normal renal function. Renal biopsy shows mild mesangial expansion (A), with mesangial and paramesangial deposits, together with varying numbers of subepithelial-based deposits *(arrows),* resulting in the "ball-and-cup" appearance (B). (Courtesy Professor Stewart Goetsch, University of the Witwatersrand, Johannesburg, South Africa.)

distinct entity and with likelihood of progression intermediate between HIVAN and HIVICK.[28]

OTHER GLOMERULAR DISORDERS

TMA may occur with HIV infection and is associated with lower CD4 cell counts, higher viral burden, and AIDS.[31] Fibrillary GN, immunotactoid GN, and amyloidosis also have been reported in HIV infection, but a causal role for HIV infection has not been firmly established.

SYSTEMIC INFLAMMATION AND ARTERIONEPHROSCLEROSIS

A paradigm shift has emerged over the past decade, with the recognition that long-term suppression of HIV replication dramatically improves survival but at the cost of chronic inflammation and premature aging.[32] Peripheral inflammatory markers correlate with Framingham risk scores and Veteran Aging Cohort Scores,[33] and hypertension is common.[34]

The causes of chronic inflammation in HIV disease are complex. Chronic immune activation is associated with lymphocyte depletion, manifesting as reduced numbers of $CD4^+$ and $CD8^+$ naïve T cells. Alterations in the intestinal microbiome and microbial translocation may contribute.[35] Inflammation leads to disease processes that resemble premature aging (including atherosclerosis) and manifests in the kidney as arterionephrosclerosis, comprised of arterial intimal thickening, medial hypertrophy, duplication of the internal elastic lamina, and global glomerulosclerosis. Arterionephrosclerosis is traditionally ascribed to hypertension, but increasing evidence suggests that afferent arteriolar lesions predispose to glomerulosclerosis and hypertension by altering renal autoregulation. Arterionephrosclerosis is associated with genetic mutations (e.g., *APOL1*), metabolic disorders (e.g., diabetes, obesity, hyperlipidemia, metabolic syndrome, and HIV infection), and chronic inflammation (smoking, oxidative stress, hemodynamic shear stress, and renin-angiotensin system activation).[36] A recent U.S. study of patients with HIV reported that isolated arteriosclerosis with glomerulosclerosis was the most common single pathologic condition,[37] and this is a trend that is likely to grow stronger.

TUBULAR DISORDERS

HIV infection is associated with tubular disorders, often resulting from medications (see Table 56.1), most commonly from TDF. AKI most commonly occurs in outpatient settings, with prerenal causes (extracellular volume contraction or reduced renal blood flow as a result of nonsteroidal antiinflammatory drugs [NSAIDS]) and postrenal causes (including obstruction as a result of prostate disease, kidney stone, or crystalluria). Renal causes of AKI, including tubular injury from medication, particularly TDF; interstitial nephritis resulting from NSAIDS or antibiotics; and, less commonly, acute presentations of glomerular disease. Risk factors for HIV-associated AKI include male sex, black race, low CD4 count, high viral load, diabetes, CKD, and hepatic disease.[38] Chronic proximal tubular injury manifests as various components of Fanconi syndrome: glycosuria, phosphaturia (sometimes associated with clinically significant hypophosphatemia), uricosuria, tubular proteinuria (predominantly low molecular weight proteins), and aminoaciduria. Nephrogenic diabetes insipidus also may be present, indicating that the distal nephron is also involved.

Current Antiretroviral Drug Regimens and Renal Toxicity

Current recommendations for first-line therapy for HIV in adults include a combination of three medications. These are TDF, a nucleotide reverse transcriptase inhibitor (NRTI); either lamivudine or emtricitabine (the latter a nucleoside reverse transcriptase inhibitor, also abbreviated NRTI); and efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI). The difference between a nucleotide and a nucleoside is that the latter must be phosphorylated to become active. To underscore its ubiquity, TDF is a component of four of the six regimens currently recommended for treatment of naïve patients and hence is widely used globally. TDF nephrotoxicity is discussed later. By contrast, NNRTIs have an excellent renal safety profile.

In addition to these two drug classes, there are four other classes of antiretroviral medications currently in clinical use (Table 56.2). These include protease inhibitors, fusion inhibitors (GP41 antagonist), entry inhibitors (CCR5 antagonist), integrase inhibitors, and pharmacokinetic enhancers. Of these, only protease inhibitors exhibit renal toxicity by forming crystals or stones. Indinavir was a formerly common cause of tubular injury but is rarely used at present. Currently, atazanavir is widely used. Case series show that in individuals taking ritonavir-boosted atazanavir, urinary crystals affect 10% of subjects[39] and renal stones occur at a rate of 2.4 cases per 100 patient-years.[40] Risk factors for nephrolithiasis include alkaline urine and renal impairment but not elevated serum atazanavir levels.[41] Atazanavir also has been associated with interstitial nephritis.[42]

TABLE 56.2 **Renal Toxicity of Antiretroviral Therapy**

Antiretroviral Class	Antiretroviral Therapy	Renal Effect	Clinical Recommendations
Protease inhibitors	Indinavir	Nephrolithiasis, crystalluria, dysuria, papillary necrosis, acute kidney injury, interstitial nephritis Ritonavir may increase toxicity of indinavir	Daily fluid intake of >2 l/day
	Atazanavir	Crystalluria, stones, interstitial nephritis	
	Ritonavir	Increases levels of TDF	
Reverse transcriptase inhibitors	Tenofovir disoproxil fumarate (TDF)	Renal tubular damage: Proximal tubular dysfunction, Fanconi syndrome, nephrogenic diabetes insipidus, acute tubular necrosis, acute kidney injury	Patients taking TDF should be monitored for signs of tubular dysfunction (elevated serum creatinine, hypophosphatemia, low serum uric acid, acidosis, glycosuria, proteinuria)

TABLE 56.3 Adjustments in Drug Dosing for Antiretroviral Medications in Current Use

Medication Class	Medication	Adjustment for GFR	Dosing in Dialysis
NRTI (8)	Abacavir	No change	No change
	Didanosine (ddi)	Reduce for eGFR <60	No dose after dialysis
	Emtricitabine (FTC)	Reduce for eGFR <50	Dose after dialysis
	Lamivudine (3TC)	Reduce for eGFR <50	No dose after dialysis
	Stavudine (d4T)	Reduce for eGFR <50	Reduce dose
	Tenofovir disoproxil fumarate (TDF)	Reduce for eGFR <50	Dose after dialysis
	Tenofovir alafenamide	Not needed	Use not recommended
	Zidovudine (AZT)	Reduce for eGFR <15	Reduce dose
NNRTI (4)	Efavirenz	No change	No change
	Etravirine	No change	No change
	Nevirapine	No change >eGFR 20, not recommended eGFR <20	Dose after dialysis
	Rilpivirine	Not recommended for severe chronic kidney disease	Dose after dialysis probably not needed
Protease inhibitor (8)	Atazanavir	No change	Depends on status
	Darunavir	No change	No data
	Fosamprenavir	No data	No data
	Indinavir	No change	No change
	Nelfinavir	No data	No data
	Ritonavir	No change	No data
	Saquinavir	Not recommended for severe chronic kidney disease	No data
	Tipranavir	Probably no change	No data
Fusion inhibitor (CCR5)	Enfuvirtide	No change	No data
Entry inhibitor (gp41)	Maraviroc	Avoid for eGFR <30	Avoid
Integrase inhibitor (3)	Dolutegravir	Complex, suggest reviewing primary data	Avoid
	Elvitegravir	No change	No data
	Raltegravir	No change	Avoid administering before dialysis
Pharmacokinetic enhancer	Cobicistat	No change. For eGFR, avoid combination with TDF	No data

Shown are 26 antiretroviral drugs approved by the U.S. food and drug administration (FDA) as of 2018. Combination drugs, of which 14 are currently approved by the FDA, are not listed here.

eGFR, Estimated glomerular filtration rate; *TDF,* tenofovir disoproxil fumarate.

Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide

TDF is the most common cause of tubular injury in HIV-positive individuals and manifests primarily as proximal tubular dysfunction with Fanconi syndrome. TDF is taken up by proximal tubular cells by one or more organic anion transporters, converted to the active drug, which inhibits DNA repair and replication in host cells as well as in HIV. TDF also causes mitochondrial enlargement, dysmorphic changes, and depletion of mitochondrial cristae.[43] A mild decrease in GFR also has been associated with TDF use, but usually it is not severe enough to require discontinuation of treatment. Nonetheless, recovery of renal dysfunction may take months to years after stopping TDF,[44] and in some cases recovery is partial and CKD ensues.[45] Risk factors for TDF-induced renal toxicity include low CD4 count, prior renal impairment, duration of therapy, and combined therapy with didanosine and protease inhibitors (lopinavir and ritonavir); the latter elevates TDF plasma levels, which in turn is associated with higher risk for nephrotoxicity.[46]

TDF is taken up into the renal tubular epithelial cell from basolateral space by the organic anion transporter (OAT) 1, and OAT3 and is secreted into the tubular lumen by the multidrug resistance protein (MRP) 4. Mutations in *ABCC4,* encoding MRP4, are associated with increased plasma TDF concentrations and nephrotoxicity risk,[47] and mutations in *ABCC10,* encoding MRP10, are associated with increased risk for phosphate wasting.[46,48] On the other hand, the use of MRP inhibitors such as NSAIDs, salicylates, and dipyridamole does not increase toxicity.[49]

TAF represents a potentially important advance.[50] Like TDF, TAF is a pro-drug, but unlike TDF, it is not a substrate for the OAT1 and OAT2 organic ion transporters, which transport solutes from plasma into the tubular epithelial cell. Current data suggest lower levels of renal toxicity than that with TDF.

ANTIRETROVIRAL THERAPY DOSING IN CHRONIC KIDNEY DISEASE

Many antiretroviral medications are partially or completely eliminated by the kidney and require dosage adjustment in CKD. Certain drug classes, such as the protease inhibitors and the NNRTIs, are extensively metabolized by the liver and do not require dosage adjustment. Most NRTIs are excreted unchanged in the urine and require dosage adjustment, except for abacavir, which has substantial extrarenal biotransformation that requires little if any dosage adjustment. In uremia, drug dosages may be affected by altered gastric pH and variable volumes of distribution. Factors that influence dialyzability of antiretroviral medications relate to the properties of the dialysis membrane and molecular weight, degree of protein binding, molecular charge, and water solubility of the drug. Drugs that are substantially removed by hemodialysis (HD) should be taken after dialysis sessions. If the drug is removed in peritoneal dialysis (PD) effluent, the dose may have to be supplemented. Dosage recommendations (Table 56.3) in both HD and PD are limited; there is a recommendation for NRTI dosing in patients undergoing veno-venous hemofiltration.[51]

END-STAGE RENAL DISEASE

With the increasing survival of HIV-positive individuals with treatment and the declining cost of combination ART, the incidence of HIV-associated ESRD will likely increase worldwide, as it has in developed countries. Currently, survival among dialysis-dependent HIV-positive patients who are stable on combination ART is comparable to that among patients on dialysis without HIV infection, and choice of dialysis modality does not have an impact on survival.

Immunization schedules are the same as for non–HIV-negative patients on dialysis.[2] In both CKD and HIV infection, anemia is independently associated with shorter survival. The response to recombinant erythropoietin in HIV-positive patients with ESRD is similar to that seen in HIV-negative patients.[52] Measurements of iron indices are complicated in HIV-positive patients, because levels of ferritin (an acute phase reactant) are often elevated in patients with HIV infection. Elevated soluble transferrin receptor concentrations are more reliable than serum ferritin to distinguish iron deficiency in inflammatory disease states.[53,54]

Hemodialysis

Strict adherence to universal precautions is the best form of prevention of HIV transmission in dialysis units, and there is no reason for these patients to be isolated. Reprocessing of dialyzers from HIV-positive patients does not place staff members at increased risk for infection if necessary sterile precautions are undertaken. The risk for viral seroconversion after a needle-stick injury has been estimated as 6 in 1000 for HCV, 4 in 1000 for HBV, and 2 in 1000 for HIV.[55] ART may reduce the risk for transmission after a needle-stick injury, and postexposure prophylaxis for 28 days with a combination of two reverse transcriptase inhibitors and one protease inhibitor is recommended. Native arteriovenous fistulas are the preferred types of access for all patients with ESRD because of better patency rates once established and lower complication rates than other access options. A recent study from South Africa showed similar survival outcomes for HIV-positive and HIV-negative patients on HD, except for increased incidence of tuberculosis in the HIV-positive cohort.[14]

Peritoneal Dialysis

HIV has been shown to remain infectious at room temperature in PD exchange tubing for up to 48 hours and for up to 7 days in peritoneal effluent.[56] Dialysate should therefore be handled as a contaminated body fluid. Sodium hypochlorite (50% solution) and household bleach (10% solution), each further diluted 1 : 512, are effective at inactivating HIV in dialysate. Patients on PD should be instructed to pour dialysate into the home toilet, together with a cup of household bleach. Used dialysis bags and lines should be placed in plastic bags, exposed to household bleach, and disposed of in conventional home garbage or returned to the dialysis unit, according to instructions from the dialysis unit.

Kidney Transplantation

The past few years have seen a surge of interest in kidney transplantation for HIV-positive patients with ESRD. In a report of 150 kidney transplants from HIV-negative donors (both living and deceased) to HIV-positive recipients, acute rejection rates were higher than in other subjects but HIV replication remained controlled.[57] Similar outcomes were reported subsequently from other centers, including 27 HIV-positive recipients who received kidneys from HIV-positive deceased donors in South Africa[58] and 92 patients in the United States.[59] With longer term follow-up, compared with HIV-negative recipients, HIV-positive recipients had a marginally increased risk for graft loss and no increased risk for death.[60] Interestingly, Canaud and associates[61] reported that kidneys from HIV-negative donor kidney cells became infected after transplantation into HIV-positive recipients, with HIV RNA detected in podocytes and tubular. In 2013 the HIV Organ Policy Equity Act (HOPE Act) was passed by the U.S. Congress; this act legalized research involving HIV-positive living donors providing kidneys to HIV-positive recipients, and studies with this population are being developed.

EVALUATION FOR KIDNEY DISEASE

HIV-positive individuals should undergo regular evaluation for kidney disease: probably at least every 6 months and more frequently if renal disease is suspected (Fig. 56.3). Early identification of kidney injury disease offers the prospect of discovering kidney injury when it first appears, defining the nature of the process, removing provocative factors when possible (particularly medications), and initiating therapy to slow, halt, or possibly reverse the disease process.

Periodic testing should include a history of nephrotoxic medications and measurement of BP, serum creatinine, and blood urea nitrogen. Three studies in HIV-positive patients compared the CKD–Epidemiology Collaboration (CKD-EPI) equations against the gold standard iothalamate GFR; all three concluded that the CKD-EPI equation correlated well with measured GFR. When actual doses prescribed were compared with those recommended by the CKD-EPI eGFR, 6% to 19% of patients received an inappropriate dose; these subjects tended to be older and were more likely to have diabetes.

If serum creatinine is elevated or dipstick proteinuria is noted, a spot ratio of urine protein to creatinine (uPCR) should be measured. Most proteinuria in HIV-positive patients is tubular proteinuria. In a study from London, 10% of subjects had proteinuria (defined as uPCR >200 mg/g), most of which was not albumin; 17% had microalbuminuria, and 67% had increased excretion of the low molecular protein neutrophil gelatinase–associated lipocalin (NGAL).[62]

Moderately severe albuminuria (previously known as *microalbuminuria*) may indicate early glomerular disease (including in diabetic nephropathy, arterionephrosclerosis, HIV-associated glomerular disease), tubular disease, metabolic syndrome, or systemic inflammation. In six of seven South African patients with persistent modestly elevated albuminuria HIVAN was found on kidney biopsy, documenting that this disease may have an insidious presentation. Modestly elevated albuminuria may be persistent or intermittent and may reflect other processes, such as diabetes and hypertension. Indeed, in HIV-positive individuals, modestly elevated albuminuria is associated with Framingham risk score,[63] endothelial dysfunction,[64] and intimal medial thickness and with all-cause mortality.[65]

ACKNOWLEDGMENT

The authors appreciate the assistance of Alice Pau, Pharm D, NIH, with reviewing the information on medications. This work was supported by the Intramural Research Program, NIDDK, NIH, Bethesda, MD.

Management algorithm for screening HIV-positive individuals for acute and chronic kidney disease

All HIV-positive individuals should be offered anti-retroviral therapy at the time of HIV diagnosis and if they decline, should be offered at each clinic visit

Assessment for kidney disease in all HIV-infected individuals
Risk factors for CKD: Sub-Saharan African descent, family history of CKD, use of nephrotoxic therapies includingtraditional medicines, hepatitis C, HIV viral load >400 copies/ml, CD4 cell count <200 cell^3/mm^3
Assessment: Urine dipstick and serum creatinine, then calculate eGFR (see Chapter 3)

1. Urine dipstick for leukocytes
If negative, repeat annually
If positive, perform urine microscopy and culture for bacteria
UTI symptoms: Culture or treat empirically, adjust therapy when sensitivities are known
Sterile pyuria: Test for sexually transmitted infections, including syphilis, and tuberculosis
Repeat urine dipstick at follow-up visit

2. Urine dipstick for proteinuria
If negative, measure urine albumin-to-creatinine ratio and repeat in 1 year
If positive, measure urine albumin/creatinine and urine protein/creatinine ratio

Microalbuminuria (albumin/creatinine ratio 20-200 mg/g). See Chapter 30
- Acute causes: Fever, pregnancy, uncontrolled hypertension, uncontrolled diabetes, congestive heart failure
- Chronic causes: Metabolic syndrome, diabetes

Macroalbuminuria (albumin/creatinine ratio >200 mg/g)
Acute causes: Fever, systemic infection, hypertensive emergency

Chronic causes:
Nephrotic or subnephrotic proteinuria: HIVAN, FSGS, arterionephrosclerosis, diabetes, hepatitis B, syphilis,
Nephritic syndrome: HIVICK, lupus, hepatitis C, postinfectious glomerulonephritis
Consider kidney biopsy

Tubular proteinuria (albumin/total protein <40%)
- Tenofovir toxicity
- Interstitial nephritis (NSAIDS, antibiotics, tenofovir)

3. Serum creatinine and eGFR
Acute kidney injury: If eGFR has recently fallen by >25% (risk) or >50% (injury)
- Pre-renal conditions: Look for signs of extracellular volume contraction
- Renal conditions
  Review nephrotoxic medications including non-prescription medications (particularly NSAIDs), prescription medications (particular tenofovir disoproxil fumarate, atazanavir) and intravenous contrast
  Consider rhabdomyolysis if heme pigment is present without erythrocytes
- Post-renal conditions: Bladder retention (including prostatism), stone, cancer. Consider renal ultrasound

Chronic kidney disease: If eGFR is stable or slowly declining and <60 ml/min/1.73 m^2
- Renal ultrasound for kidney size and echogenicity
- Review nephrotoxic medications
- Serologic testing for hepatitis B and C
- Evaluation for *Plasmodium malariae* in endemic areas
- Serum K <5 mmol/L: Start RAAS antagonist
- Manage blood pressure and CKD stage appropriately (Chapter 80)

Fig. 56.3 Management algorithm for screening of HIV-positive antiretroviral therapy–naïve patients for chronic kidney disease. Tuberculosis may be pulmonary or extrapulmonary. Antiproteinuric agents may be used in normotensive individuals with gradual up-titration of dose, depending on tolerance and severity of proteinuria. *CKD,* Chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *FSGS,* focal segmental glomerulosclerosis; *HIVAN,* HIV-associated nephropathy; *HIVICK,* HIV-associated immune complex kidney disease; *NSAIDs,* nonsteroidal antiinflammatory drugs; *RAAS,* renin-angiotensin-aldosterone system; *UTI,* urinary tract infection.

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SELF-ASSESSMENT QUESTIONS

1. In individuals of African descent with HIV infection, genetic variants in the *APOL1* gene are associated with which of the following renal biopsy diagnoses?
   A. HIV-associated nephropathy (collapsing glomerulopathy) or focal segmental glomerulosclerosis (FSGS)
   B. Membranous nephropathy
   C. Immune complex glomerulonephritis
   D. Immunoglobulin A (IgA) nephropathy
2. An HIV-positive individual is receiving antiviral therapy and has suppressed viral replication. At a routine clinic visit, reduced serum phosphate and uric acid along with glycosuria are noted. Which of the following is the *most* likely explanation for these abnormalities?
   A. Efavirenz
   B. Allopurinol
   C. Tenofovir disoproxil fumarate
   D. Ritonavir
3. The clinician of the patient in question 2 was not provided with the laboratory results, and no changes were made in the clinical management of the patient. On the next visit, 6 months later, the serum creatinine value has risen and a renal biopsy is performed. Which of the following findings would be *most* specific in clarifying the cause of the injury?
   A. Arterionephrosclerosis
   B. Focal global glomerulosclerosis
   C. Tubular atrophy and interstitial nephritis
   D. Giant mitochondria within the tubular cells

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Nephrolithiasis and Nephrocalcinosis

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NEPHROLITHIASIS

Epidemiology

Kidney stones are common in industrialized nations, with an annual incidence of over 1 in 1000 persons and a lifetime risk for forming stones of approximately 5% in women and 13% in men.[1-4] In the United States the prevalence of nephrolithiasis increased from 3.2% in the late 1970s to 5.2% in the 1990s and further to 8.8% in the first decade of the 2000s, in parallel with the rising incidence of obesity, insulin resistance, and type 2 diabetes mellitus.[5,6] Factors that determine renal stone prevalence include age, sex, race, and geographical distribution. Incidence peaks in the third and fourth decades, and prevalence increases with age until approximately 70 years in men and 60 years in women. Men are more prone to stone formation than women.[6] In the United States, Whites are more likely to develop renal stones than African Americans, Hispanics, or Asian Americans, but the prevalence is rising in non-Whites as well.[6] The tendency in the United States for the development of stones also depends on geographical location, with an increasing prevalence from north to south and, to a lesser degree, from west to east. The increase in nephrolithiasis rates from north to south may be due to increased environmental temperatures, and greater sunlight exposure leading to an increase in insensible losses through sweating and more concentrated urine.[4,7] The higher urine calcium excretion in a smaller urine volume will increase the risk for supersaturation for calcium-containing crystals, thereby promoting stone formation.

Stone type varies with worldwide geography and genetic predisposition. In the Mediterranean and Middle East, 75% of stones are composed of uric acid. In the United States, the majority of stones are calcium oxalate or calcium phosphate (>70%), with less than 10% being pure uric acid stones. Magnesium ammonium phosphate (struvite) stones account for 10% to 25% of stones formed (with a higher incidence in the United Kingdom), and cystine stones constitute 2% of all stones formed (Fig. 57.1).[8]

Outbreaks of kidney stones also can occur as a result of dietary supplements or medications. A large number of Chinese infants and toddlers developed kidney stones, and some children developed renal failure because of obstruction caused by stones. This outbreak was associated with melamine contamination in infant formulas and powdered milk as a means of raising the apparent concentration of protein in the products.[9]

Kidney stones are associated with systemic conditions including chronic kidney disease (CKD), cardiovascular disease, and bone disease. In a Canadian registry cohort of close to 2 million participants without end-stage renal disease (ESRD) at baseline,[10] having one or more episodes of kidney stones during follow-up was associated with increased risk for ESRD (adjusted hazard ratio [HR] 2.16, 95% confidence interval [CI] 1.79-2.62) and new CKD stage 3b-5 (HR 1.74, 95% CI 1.79-2.62) compared with those without kidney stones during follow-up. The risk for CKD development was greater in women than in men and in people younger than 50 years of age. However, the absolute increase in the rate of adverse renal outcomes associated with kidney stones was small; the unadjusted rate of ESRD was 2.48 and 0.52 per million person-days in people who developed kidney stones and in people without stones, respectively. In a prospective study of participants without a history of coronary heart disease, development of kidney stones was associated with increased risk for coronary heart disease in women but not in men.[11] In a retrospective, matched case-control study, calcium kidney stone formers had significantly higher degrees of aortic calcification and lower bone mineral density than age- and sex-matched non–stone formers.[12]

Pathogenesis

Stones occur in urine that is supersaturated with respect to the ionic constituents of the specific type of stone. Supersaturation depends on the product of the free ion activities of stone components rather than on their molar concentrations. The free ion activities of stone components can be affected by crystal component concentration, presence of inhibitors, and urine pH. An increasing concentration of crystal components increases their free ion activity. When calcium and oxalate are dissolved in pure water, the solution becomes saturated when the addition of any more calcium or oxalate does not result in further dissolution. However, urine, unlike pure water, contains numerous calcification inhibitors that can form soluble complexes with the ionic components of the stone. The interactions with these inhibitors (e.g., citrate) may result in a decrease in free ion activity that allows the stone constituents to increase in total concentration to levels that would normally cause stone formation in water. Urinary pH also influences free ion activity. The level of chemical free ion activity in which stones will neither grow nor dissolve is referred to as the *equilibrium solubility product,* or the upper limit of metastability. Above this level, the urine will be supersaturated and any stone present will grow in size.

When the solution becomes supersaturated with respect to a solid phase, ions can join together to form the more stable, solid phase, a process termed *nucleation.* Homogeneous nucleation refers to the joining of similar ions into crystals. The more common and thermodynamically favored heterogeneous nucleation results when crystals grow adjacent

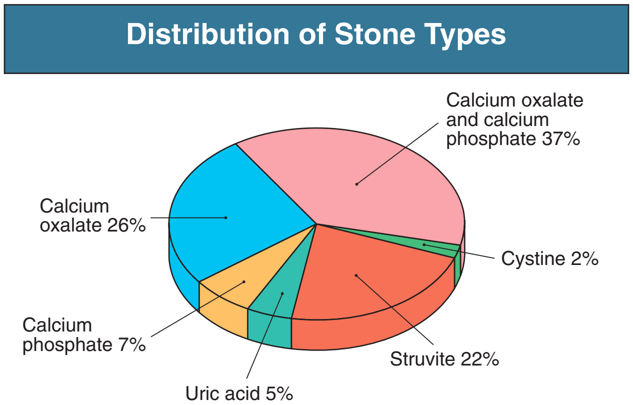

Fig. 57.1 Proportion of stone types in a typical U.S. population.

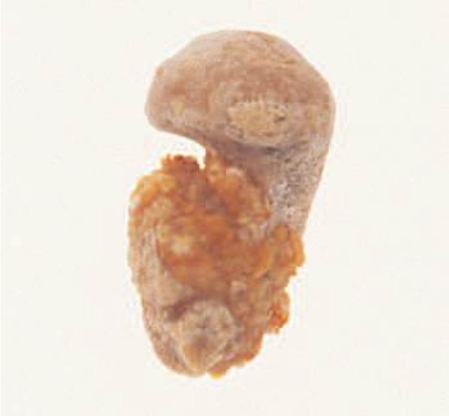

Fig. 57.2 **Ureteral calculus.** A 1-cm-wide calcium oxalate stone that provoked ureteral colic and required surgical removal.

to crystals or other substances in the urine, such as sloughed epithelial cells. Calcium oxalate crystals, for example, can nucleate with uric acid crystals. These small crystals may then aggregate to form larger stones, which would pass into the urine, causing crystalluria, if they did not anchor to the urothelium.

Calcium oxalate crystals anchor on areas of calcium phosphate deposits termed *Randall plaques* that are located in the renal papillae. Randall plaques appear to originate around the thin loop of Henle. In the outer medulla, the vascular bundles are surrounded by the thick ascending limb, which absorbs calcium independently of water. As the delivery of calcium to the thick ascending limb increases, the calcium concentration in the vascular bundles increases. This promotes supersaturation of crystals in the thin limb, which fosters plaque formation. This theoretical mechanism is referred to as *vas washdown* and has yet to be proven experimentally.[13] Calcium oxalate crystals attach to Randall plaques, allowing significant stone growth.[14] Clinically apparent stone disease occurs when the calcium oxalate crystals break off from the Randall plaques and cause injury or obstruction.

Several genetic polymorphisms have been implicated in the pathogenesis of calcium stones in genome-wide association studies. They include genes coding for proteins regulating tubular calcium and phosphate reabsorption (e.g., calcium-sensing receptor, vitamin D receptor, and claudins), genes coding for proteins preventing calcium salt precipitation (e.g., matrix gla protein), and genes coding for aquaporin in the proximal tubule.[2,15]

Clinical Manifestations

The two most characteristic symptoms of nephrolithiasis are pain and hematuria. Other presentations include urinary tract infections (UTIs) and acute kidney injury caused by obstructive uropathy if stones cause bilateral renal tract obstruction or unilateral obstruction in a single functioning kidney (Table 57.1).

TABLE 57.1 Clinical Presentations of Nephrolithiasis

Presentation	Characteristics
Pain	Ureteral colic, loin pain, dysuria
Hematuria	—
Urinary tract infection	Recurrent, chronic infection, pyelonephritis
Asymptomatic urine abnormality	Microhematuria, proteinuria, sterile pyuria
Interruption of urinary stream	—
Calculus anuria	—

Pain

The classic manifestation of pain in patients with nephrolithiasis is ureteral colic. Pain is of abrupt onset and intensifies over time into an excruciating, severe flank pain that resolves only with stone passage or removal. The pain may migrate anteriorly along the abdomen and inferiorly to the groin, testicles, or labia majora as the stone moves toward the ureterovesical junction. Gross hematuria, urinary urgency, frequency, nausea, and vomiting may occur. Stones smaller than 5 mm usually pass spontaneously with hydration, whereas larger stones often require urologic intervention (Fig. 57.2).[14] Ureteral colic may occur with the passage of clots from hematuria of any cause ("clot colic") or with papillary necrosis. Nephrolithiasis also may provoke less-specific loin pain that poorly localizes to the kidney and therefore has a wide differential diagnosis, particularly if not associated with other urinary symptoms. The finding of a stone on radiologic examination does not preclude a coincidental cause of pain from another source.

Hematuria

Stone disease is a common cause of hematuria. Macrohematuria occurs more commonly with large calculi and during UTI and colic. Although typically associated with loin pain or ureteral colic, the hematuria of nephrolithiasis also may be painless. The clinical differential diagnosis of hematuria is wide (Box 57.1). Painless microhematuria in children may occur with hypercalciuria in the absence of demonstrable stones.

Loin Pain–Hematuria Syndrome

Loin pain–hematuria syndrome is a poorly understood condition that must be considered in the differential diagnosis of nephrolithiasis. It is diagnosed by exclusion when patients (most typically young and middle-aged women) present with loin pain and persistent microhematuria or intermittent macrohematuria.[16] Careful evaluation is required to exclude small stones, tumor, UTI, and glomerular disease. Angiographic abnormalities implying intrarenal vasospasm or occlusion have been reported, as have renal biopsy abnormalities typified by deposition of complement C3 in arteriolar walls. However, these findings are not consistent, nor do they provide a coherent framework to explain the pathogenesis of this condition.

In one study, 43 consecutive patients with clinical manifestations of loin pain–hematuria syndrome were evaluated by renal biopsy after other causes of their symptoms had been excluded with at least two

BOX 57.1 Causes of Hematuria

- Nephrolithiasis
- Infection: Cystitis, prostatitis, urethritis, acute pyelonephritis, tuberculosis, schistosomiasis
- Malignancy: Renal cell carcinoma, transitional cell carcinoma, prostate cancer, Wilms tumor
- Trauma
- Glomerular disease
- Interstitial nephritis
- Polycystic kidney disease
- Papillary necrosis
- Medullary sponge kidney
- Miscellaneous: Loin pain–hematuria syndrome, arteriovenous malformation, chemical cystitis, caruncle, factitious

imaging studies.[16] Thirty-four patients were considered to have idiopathic loin pain–hematuria syndrome after nine with histologic evidence of immunoglobulin A nephropathy were excluded. Of these, 66% had glomerular basement membranes that were either unusually thick or thin on electron microscopy and 47% had a history of kidney stones, though none had obstructing stones at the time of imaging assessment. Evidence of glomerular hematuria was more common in biopsy samples of patients with loin pain–hematuria syndrome compared with those of healthy living kidney donors who also underwent renal biopsy. The investigators postulated that the structurally abnormal glomerular basement membranes in the majority of these patients may lead to rupture of the glomerular capillary walls, with consequent hemorrhage into the renal tubules. Tubular obstruction by red blood cells or potentially by microcrystals ensues. Local and global renal parenchymal edema follow, ultimately resulting in stretching of the renal capsule and in severe flank pain.

Loin pain–hematuria syndrome is a chronic condition requiring reassurance, careful management of analgesia, and ongoing psychological support. The condition usually remits after several years. Denervation of the kidney by autotransplantation is rarely successful. The extreme measure of nephrectomy has been used, but pain often recurs promptly in the contralateral kidney. Bilateral nephrectomy and renal replacement therapy has been reported as an approach of very last resort. Referral to a pain clinic can assist in providing psychiatric counseling, analgesia, and exclusion of other disorders. In one retrospective study, patients who eventually came to accept a nonsurgical approach along with pain-coping strategies that did not involve narcotic analgesics had the most successful outcomes.[17]

Asymptomatic Stone Disease

Even large staghorn calculi may be asymptomatic and discovered only during the investigation of unrelated abdominal or musculoskeletal symptoms. Obstructive uropathy caused by calculi also may be painless; therefore nephrolithiasis always should be considered in the differential diagnosis of unexplained renal failure.

In the outbreak of melamine-associated nephrolithiasis in Chinese infants, the majority of patients brought to a screening clinic had no symptoms or signs of stones, and the diagnosis of nephrolithiasis was made only by ultrasound in at-risk infants and toddlers.[9]

Clinical Evaluation of Stone Formers

All patients with recurrent nephrolithiasis merit metabolic evaluation to determine the cause of their kidney stones. Complete evaluation of patients who have formed only a single stone is controversial because of the undetermined cost-to-benefit ratio. A National Institutes of Health Consensus Development Conference on the Prevention and Treatment of Kidney Stones determined that all patients, even those with a single stone, should undergo a basic evaluation. Those with metabolically active stones (stones growing in size or number within 1 year), all children, non–calcium stone formers, and patients in demographic groups not typically prone to stone formation warrant a more complete evaluation, which includes a 24-hour urine collection made with the patient taking his or her typical diet.

BOX 57.2 The Basic Evaluation of Nephrolithiasis

- Stone history
  - Number of stones formed
  - Frequency of stone formation
  - Age at first onset
  - Size of stones passed or still present
  - Kidney involved (left, right, or both)
  - Stone type, if known
  - Need for urologic intervention such as ESWL or percutaneous nephrolithotomy
  - Response to surgical procedure
  - Association of stones with urinary tract infections
- Medical history
- Medications
- Family history
- Occupation and lifestyle
- Fluid intake and diet
- Physical examination
  - Evidence of systemic causes of stones (e.g., tophi)
- Laboratory data
  - Urinalysis
  - Urine culture
  - Stone analysis
- Blood chemistry
  - Sodium, potassium, chloride, bicarbonate
  - Creatinine, calcium, phosphorus, uric acid
  - Intact parathyroid hormone level if calcium elevated
- Radiologic evaluation
  - Abdominal radiograph (no contrast)
  - Noncontrast CT
  - Ultrasound

CT, Computed tomography; *ESWL,* extracorporeal shock wave lithotripsy; *IVU,* intravenous urography.

Basic Evaluation

The evaluation of stone formers includes a careful history and physical examination and requires specific data gathering on stone formation, diet, and specific laboratory studies, as shown in Box 57.2.

History. The history serves to uncover a systemic cause for nephrolithiasis. Any disease that can lead to hypercalcemia (including malignancy, hyperparathyroidism, and sarcoidosis) can result in hypercalciuria and increase the risk for calcium stone formation. A number of malabsorptive gastrointestinal disorders (including Crohn disease and sprue [celiac disease]) can result in calcium oxalate stone formation as a result of volume depletion and hyperoxaluria. Uric acid stones often occur in patients with a history of gout and, increasingly, in patients with insulin resistance.[8]

The stone history (see Box 57.2) includes the number and frequency of stones formed, patient age at incidence of first stone, size of stones, stone type (if known), and whether the patient required surgical removal of the calculi. This information indicates the severity of the stone disease and provides clues to the cause of the stone formation. For example, large staghorn calculi that do not pass spontaneously and recur despite frequent surgical intervention are more consistent with struvite than calcium oxalate stones. Stones that develop at a young age may be caused by cystinuria or primary hyperoxaluria. Stone response to intervention is also significant; cystine stones, for example, do not fragment well with lithotripsy. If stones recur frequently in a single kidney, a congenital abnormality in that kidney, such as megacalyx or medullary sponge kidney, should be explored.

Family history is important because a number of stone types have a genetic basis. Idiopathic hypercalciuria is most likely a polygenic disorder. Mutations in the claudins, which regulate calcium reabsorption in the thick ascending limb of the loop of Henle, cause familial hypercalciuria and nephrocalcinosis. A genome-wide association study in patients with kidney stones identified sequence variants in the gene encoding claudin 14 that were associated with hypercalciuria.

Cystinuria is usually autosomal recessive, and hyperuricosuria has been associated with rare inherited metabolic disorders. Nephrolithiasis and nephrocalcinosis can result from a variety of monogenic disorders, such as Dent disease (X-linked recessive nephrolithiasis), McCune-Albright syndrome, osteogenesis imperfecta type 1, and congenital lactate deficiency. The various genetic disorders can lead to hypercalciuria by increasing bone resorption, affecting intestinal absorption, by decreasing renal tubular reabsorption transport, or through other, as yet unknown, mechanisms.[4,14,18]

A number of medications are known to potentiate calcium stone formation (e.g., loop diuretics are calciuric) or may predispose to uric acid lithiasis (salicylates, probenecid) (Box 57.3). Certain drugs can precipitate into stones themselves, such as rapidly infused intravenous acyclovir, high-dose sulfadiazine, triamterene, and the antiretroviral agents indinavir and nelfinavir.[19] In addition, some medications, such as acetazolamide and topiramate (a medication used for seizures and migraine headaches), promote nephrolithiasis by inhibiting carbonic anhydrase activity. In this setting the metabolic acidosis that ensues, along with lower urine citrate, higher urine pH, and increased urinary calcium excretion, predisposes to calcium phosphate stone formation.

The social history should include details regarding occupation and lifestyle. Surgeons and real-estate agents, for example, may minimize fluid intake to avoid bathroom breaks during the workday. Those who engage in vigorous physical activities, such as running, may not rehydrate adequately to keep up with insensible losses, producing excessively concentrated urine and precipitation of stone crystals in those prone to nephrolithiasis.

A dietary history and review of fluid intake are essential in determining potential causes or contributors to stone formation. The patient should be asked about commonly consumed foods, with attention paid to sodium-containing foods, as well as quantities of calcium, animal protein, purine, and oxalate (Box 57.4). Dietary calcium intake should be reviewed, because many patients with nephrolithiasis are erroneously instructed to eliminate all calcium from their diet, a suggestion that can result not only in bone demineralization, particularly in women and children, but also in an increase in stone formation.[1-3,20] Sugar-sweetened soda appears to be associated with a greater risk for stone formation, whereas consumption of coffee, tea, beer, wine, and orange juice appears to be associated with a lower risk.[21] The exact mechanism of nephrolithiasis from soda is not known but is likely related to the high fructose content of soda, which may alter urinary composition and pH.

BOX 57.3 Medications Associated With Nephrolithiasis and Nephrocalcinosis

Calcium Stone Formation

- Loop diuretics
- Vitamin D
- Corticosteroids
- Calcium supplements
- Antacids (calcium and noncalcium antacids)
- Theophylline
- Acetazolamide*
- Amphotericin*
- Topiramate

Uric Acid Stone Formation

- Salicylates
- Probenecid
- Melamine (in contaminated infant formula and milk products)

Medications That May Precipitate Into Stones

- Triamterene
- Acyclovir (if infused rapidly intravenously)
- Indinavir
- Nelfinavir

*Associated with nephrocalcinosis.

BOX 57.4 Foods High in Oxalate and Purine

High-Oxalate Foods (Avoid in Setting of Hyperoxaluria)

- Green beans
- Beets
- Celery
- Green onions
- Leeks
- Leafy greens: Collard greens, dandelion greens, Swiss chard, spinach, escarole, mustard greens, sorrel, kale, rhubarb
- Cocoa
- Chocolate
- Black tea
- Berries: blackberries, blueberries, strawberries, raspberries, currants, gooseberries
- Orange peel
- Lemon peel
- Dried figs
- Summer squash
- Nuts, peanut butter
- Tofu (bean curd)

High-Purine Foods (Avoid in Setting of Hyperuricosuria)

- Organ meats: Sweetbreads, liver, kidney, brains, heart
- Shellfish
- Meat: Beef, pork, lamb, poultry
- Fish: Anchovies, sardines (canned), herring, mackerel, cod, halibut, tuna, carp
- Meat extracts: Bouillon, broth, consommé, stock
- Gravies
- Certain vegetables: Asparagus, cauliflower, peas, spinach, mushrooms, lima and kidney beans, lentils

Physical examination. Most patients with idiopathic hypercalciuria are healthy and have normal physical examination findings. Patients with hyperuricosuria and uric acid stone formation may display tophi. Central obesity is associated with a predisposition to metabolic syndrome and uric acid stones. Paraplegic patients with a chronic indwelling bladder catheter may be predisposed to chronic UTI and struvite stones.

Laboratory findings. Urine pH is generally high in patients with struvite and calcium phosphate stones but low in patients with uric acid and calcium oxalate stones. Bacteriuria with urine pH greater than 7.0 suggests struvite stones. Urine should be cultured, and because many bacteria produce urease even when urine bacterial colony counts are low, the microbiology laboratory should be instructed to type the organism even if there are fewer than 10^5 colony-forming units/ml. The specific gravity, if high, will confirm inadequate fluid intake in many patients. Hematuria may imply active stone disease with crystal or stone passage. Examination of the urine may reveal red blood cells along with characteristic crystals (Fig. 57.3).

Blood tests required in the basic evaluation are serum electrolytes (sodium, potassium, chloride, and bicarbonate), creatinine, calcium, phosphorus, and uric acid. If the serum calcium is elevated or at the upper limit of normal, especially if the serum phosphorus is low, a serum parathyroid hormone level should be measured. A low potassium or bicarbonate level may indicate a cause for hypocitraturia, such as distal renal tubular acidosis.

Stone analysis. Patients should be encouraged to retrieve any stone they excrete for chemical analysis, which may help define the underlying metabolic abnormality and guide therapy.

Imaging. Current imaging techniques used to evaluate stones include plain abdominal radiograph, unenhanced helical computed tomography (CT), and renal ultrasound.[22] Unenhanced CT is typically the diagnostic test of choice for acute ureteral colic, although a recent study suggested that renal ultrasound may be a better choice than CT.

Plain abdominal radiography performed with views of the kidneys, ureters, and bladder (KUB) may reveal opacifications in the areas of the kidneys and ureters that could be a result of calcium, cystine, or struvite stones (Fig. 57.4). Uric acid and xanthine calculi are radiolucent and will not be visible on plain films.

Unenhanced helical CT scanning, also known as spiral CT, or CT urography, has replaced contrast intravenous urography (IVU) as a

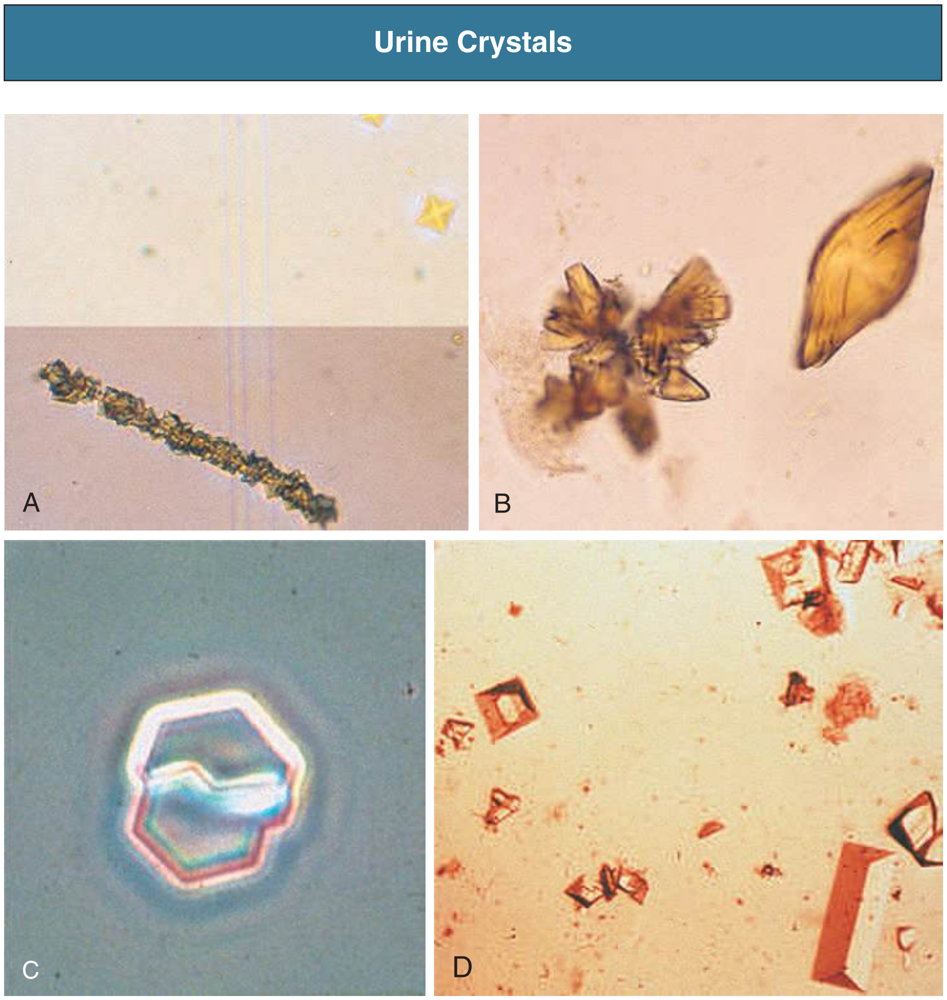

Fig. 57.3 Urine crystals. (A) Oxalate crystals: a pseudocast of calcium oxalate crystals accompanied by crystals of calcium oxalate dihydrate. (B) Uric acid crystals: complex crystals suggestive of acute uric acid nephropathy or uric acid nephrolithiasis. (C) A typical hexagonal cystine crystal; a single crystal provides a definitive diagnosis of cystinuria. (D) Coffin lid crystals of magnesium ammonium phosphate (struvite). (Courtesy Dr. Patrick Fleet, University of Washington, Seattle.)

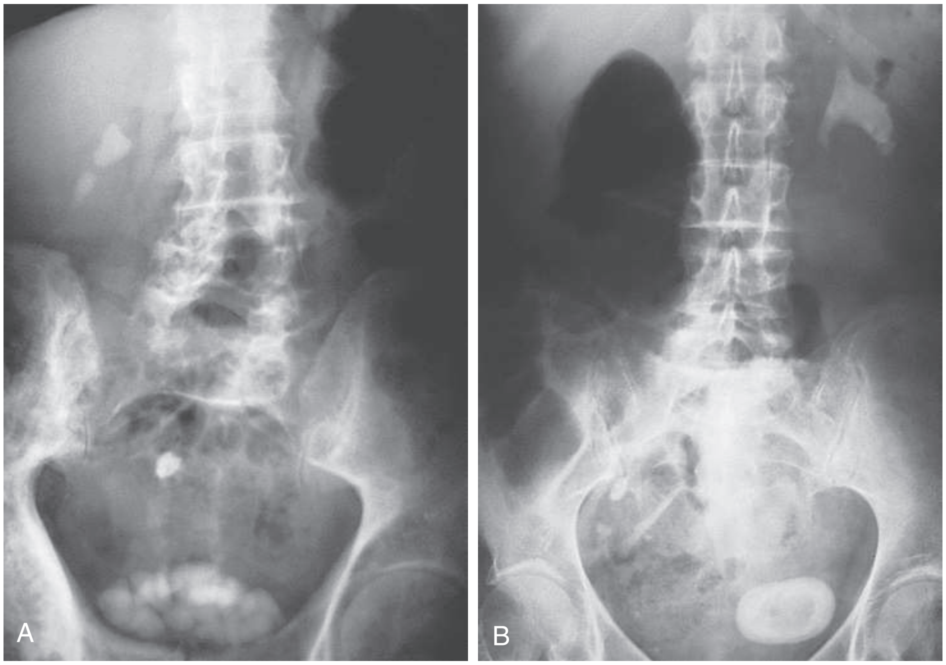

Fig. 57.4 **Radio-opaque renal calculi.** (A) X-ray film showing multiple cystine stones in the right kidney, right ureter, and bladder. (B) Struvite stones: left staghorn calculus and a single bladder stone.

diagnostic test for acute ureteral colic because it has a higher sensitivity and specificity for detecting ureteral stones and ureteral obstruction and avoids the need for contrast (see Fig. 57.5A). It is rapid, with results being available in minutes rather than hours, and this is an advantage in the emergency room setting. There are several disadvantages of CT imaging: radiation dose from a CT urography is approximately three times that of a conventional IVU; CT urography is more expensive and is associated with a high rate of incidental findings that could lead to inappropriate referral and treatment. In addition, an experienced radiologist, required for optimal interpretation of the images, may not be available at all times in urgent care facilities. CT urography should be avoided or limited in patients at risk for radiation exposure, such as children and pregnant women.

Renal ultrasound also provides high specificity in the evaluation of stones, and a recent study indicated that it may be a better choice than CT, especially for those patients who must avoid radiation exposure (Fig. 57.5B). In a multicenter, comparative effectiveness trial, 2759 patients who presented to the emergency department (ED) with suspected nephrolithiasis were randomized to undergo either initial ultrasound or abdominal CT. Ultrasound was associated with lower cumulative radiation exposure than initial CT. There were no significant differences in high-risk diagnoses with complications (e.g., abdominal aortic aneurysm with rupture, pneumonia with sepsis), serious adverse events, pain scores, return ED visits or hospitalizations between the ultrasound (whether assigned to either point-of-care in ED or to radiology department) and CT.

Periodic monitoring, if deemed necessary, should be obtained with a KUB and/or ultrasound scan rather than CT, whenever possible, to minimize radiation exposure. The combination of ultrasound and KUB is more sensitive in detecting stones than either test alone, while minimizing radiation compared with CT. Many patients with stones have recurrent disease and may require repeated imaging. Children and young adults are at higher risk for consequences from radiation exposure, and studies in this population should be limited. Especially when caring for patients who may father or subsequently carry offspring, every effort

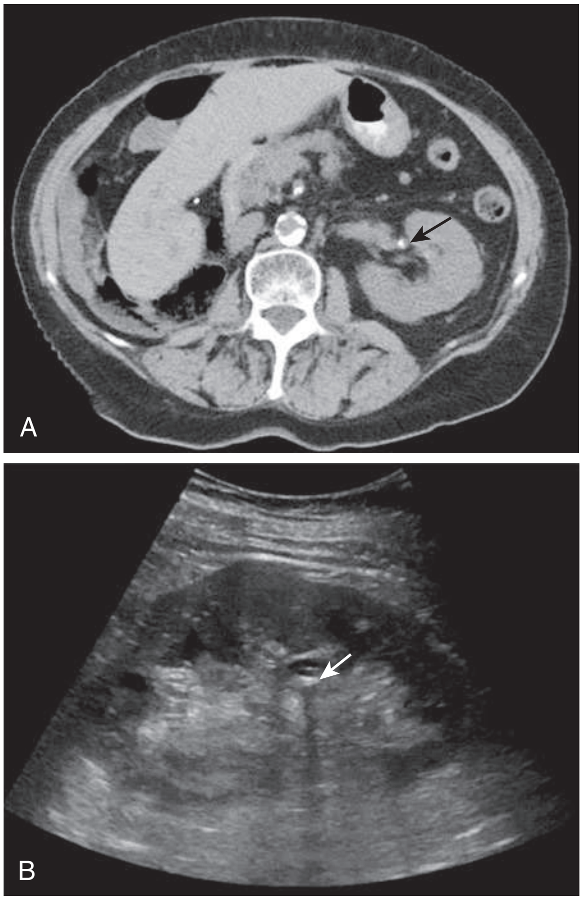

Fig. 57.5 **Renal calculi.** (A) Unenhanced CT scan showing a nonobstructing left kidney stone *(arrow)* in a patient with right nephrectomy. (B) Ultrasound of the left kidney (sagittal view) from the same patient showing a stone *(arrow).*

should be made to limit radiation exposure. In general, we do not order routine follow-up x-ray examinations and do not order x-ray examinations unless the results will alter subsequent care. If x-ray films are ordered, every effort should be made to limit radiation exposure, as the results of a noncontrast study alone are often sufficient to guide therapy.

Complete Evaluation

A complete evaluation should be undertaken in patients with multiple or metabolically active stones (i.e., stones that increase in size or number within a year), in all children, in patients from demographic groups not typically prone to stone formation, and in those with stones other than those containing calcium.

The complete evaluation should include a measure of urine volume and the quantity of calcium, oxalate, phosphorus, uric acid, sodium, citrate, and creatinine excreted in a 24-hour urine collection (Table 57.2). Urine creatinine is useful in assessing adequacy of the collection; men should excrete more than 15 mg/kg (132.6 μmol/kg), and women should excrete more than 10 mg/kg (88.4 μmol/kg) daily. Patients should be encouraged to perform the urine collection on a typical day while eating a typical diet, although many patients prefer to collect the urine on weekends when their diet and habits may differ from those during usual workdays. Specialized testing, such as urine collections during high- or low-dietary calcium intake is not recommended. Careful instructions should be given to avoid overcollection or undercollection. Patients should be instructed to discard the first morning urine at the start of the collection and collect all urine for the next 24 hours, including the first urine collection on the second morning.

A disadvantage of the standard 24-hour urine collection is that laboratories vary in the preservatives required to process the various constituents. Many require more than one collection to measure all the urinary constituents, reducing compliance and therefore the accuracy of the results.

TABLE 57.2 Optimal 24-Hour Urine Values in Recurrent Nephrolithiasis

24-Hour Urine Values	
Volume	>2-2.5 l
Calcium	<4 mg/kg (0.1 mmol/kg), ~300 mg (7.5 mmol) in men, ~250 mg (6.3 mmol) in women
Oxalate	<40 mg (0.36 mmol)
Uric acid	<750 mg (4.5 mmol) in women and <800 mg (4.7 mmol) in men (can be pH dependent)
Citrate	>320 mg (17 mmol)
Sodium	<2000 mg (<87 mmol)
Phosphorus	<1100 mg (35 mmol)
Creatinine	>10 mg/kg (88 μmol/kg) in women and >15 mg/kg (132 μmol/kg) in men, if specimen is a complete collection
Urine Supersaturation Values	
Calcium oxalate supersaturation	<5
Calcium phosphate supersaturation	0.5-2
Uric acid supersaturation	0-1

A better approach available in some laboratories is to undertake a 24-hour urine collection for quantification of supersaturation for the common solid phases of calcium oxalate, brushite (calcium phosphate), and uric acid (see Table 57.2). Urine for supersaturation analysis has been shown to correlate well with stone composition, and the risk for stone formation rises with increasing supersaturation. Determination of supersaturation is far more informative than evaluation of the individual urinary constituents.

Patients can bring their specimens to a local laboratory or may directly mail them to specialized laboratories that measure calcium, oxalate, citrate, uric acid, creatinine, sodium, potassium, magnesium, sulfate, phosphorus, chloride, urine urea nitrogen, and pH. Supersaturation is calculated with a computer program. Calculation of supersaturation from a 24-hour urine specimen will provide values lower than the peak postprandial supersaturation and peak nighttime supersaturation, either of which may initiate stone formation. Patients should stop taking any vitamin C or multivitamins containing more than 100 mg of vitamin C for at least 5 days before the urine collection because the antioxidants in the vitamin may interfere with the assay.

General Treatment

Intervention for stone removal may be required when pain, obstruction, and/or infection resulting from nephrolithiasis do not respond to conservative management. Surgical management of stones includes extracorporeal shock wave lithotripsy (ESWL) and both endoscopic and percutaneous surgical removal of stones, and is further discussed in Chapter 59. The risk for developing renal impairment varies with the type of stone, and this must be considered in planning management.

Medical Management

Patients who are seen by stone "specialists" often have a decrease in stone recurrence even without pharmacologic intervention.[23] This phenomenon, termed *the stone clinic effect*, is likely a result of modifications in diet and fluid intake. These nonpharmacologic measures include an increase in fluid intake, which increases urine volume; restriction of dietary sodium, which leads to a reduction of urine calcium excretion; restriction of animal protein, which also leads to a reduction of urine calcium excretion and an increase in excretion of the calcification inhibitor citrate; and ingestion of an age- and gender-appropriate amount of dietary calcium. Although dietary calcium restriction continues to be prescribed by many physicians, increasing evidence indicates that this is not beneficial and can actually increase the rate of stone formation (see later discussion of calcium stones).[3,20]

Fluid intake. An increase in urine volume to more than 2 to 2.5 liters daily has been proven to reduce the incidence of stones. Large urine volumes will reduce calcium oxalate supersaturation, as well as precipitation of other crystals. Increased fluid intake to augment urine volume is also a mainstay of therapy for patients with uric acid and cystine stones. The period of maximum risk for stone formation is at night, when urine concentration is physiologically increased. Patients should be encouraged to drink enough fluid in the evening to provoke nocturia and then drink further fluid before returning to bed.

Salt intake. Urine sodium excretion directly correlates with urine calcium excretion[1,2]; thus dietary salt restriction is associated with decreased urine calcium excretion. Patients should be instructed to limit daily sodium intake to 2 g (87 mmol sodium).

Dietary protein. Animal protein ingestion increases the frequency of renal stone formation by a number of mechanisms. Metabolism of certain amino acids leads to generation of sulfate ions, which render urinary calcium ions less soluble.[25,26] The metabolic acidosis that results from protein ingestion causes calcium release from bone and a consequent increase in the filtered load of calcium.[25,26] Acidosis also decreases tubular calcium reabsorption, resulting in hypercalciuria. Urinary citrate excretion is also pH dependent, with acidosis leading to a decrease in citrate excretion. The result of increased animal protein intake is an increase in urinary calcium excretion that is rendered less soluble because of concomitant sulfate excretion and hypocitraturia. Low urine pH, coupled with increased uric acid excretion from the metabolism of animal protein, can result in uric acid lithiasis. Stone formers should be encouraged to consume a moderate protein intake. Dietary fructose may also increase uric acid lithiasis.

Dietary calcium. Despite conventional wisdom, several studies have demonstrated a decrease in stone incidence when people consume diets adequate in calcium. [23,24] This beneficial effect has been attributed to intestinal binding of ingested oxalate (which is highly lithogenic) by dietary calcium. Although women have reduced stone formation while ingesting an age-appropriate amount of dietary calcium, this benefit may not extend to those taking calcium in the form of calcium supplements.[27] The data are inconsistent as to whether calcium supplements increase the risk for nephrolithiasis. Some have postulated that any increased risk may be a result of timing the supplemental calcium ingestion apart from meals, which would enhance calcium absorption without reducing oxalate absorption. In addition, the calcium supplements may dissociate rapidly, leading to rapid absorption, increased filtered calcium load, and transitory hypercalciuria, leading to increased supersaturation. We advise patients that it is best to obtain calcium from dairy products rather than supplements.

Recent studies have demonstrated that women ingesting calcium supplements have a great risk for cardiovascular disease and death, perhaps by promoting vascular calcification.[28] In one long-term study of more than 60,000 Swedish women, those with a dietary calcium intake exceeding 1400 mg/day had an increased risk for cardiovascular mortality with a hazard ratio of 1.49 (95% CI 1.09-2.02). The risk for all-cause mortality rose to 2.57 (95% CI 1.19-5.55) when any calcium tablet supplements were added to this high dietary intake.[29] A review of cardiovascular mortality in over 15 studies involving calcium supplementation versus placebo showed increased risk for myocardial infarction in those randomized to calcium supplements with a hazard ratio of 1.31 (95% CI 1.02-1.67) that rose to 1.85 (95% CI 1.28-2.67) in patients already taking more than 805 mg of dietary calcium daily.[28] In a 10-year follow-up of 5448 adults free of clinically diagnosed cardiovascular disease calcium supplements increased the risk for incident coronary artery calcification (relative risk 1.22 (95% CI 1.07-1.39)).[30] The Institute of Medicine in the United States recently adjusted the recommended allowance of calcium to 1000 mg/day for adults older than 19 years and 1200 mg for women over age 50 years.[31] We recommend that women take the appropriate amount of calcium in the form of food with limited supplement intake, except in cases of severe osteoporosis with insufficient dietary intake.

Support for the use of an age- and gender-appropriate amount of dietary calcium was provided by a randomized prospective study comparing the rate of stone formation in men assigned a low-calcium diet with those assigned a normal-calcium, low-sodium, and low–animal protein diet.[20] The men assigned the low-calcium diet were twice as likely to have recurrent stones over 5 years compared with those on the normal-calcium, low-sodium, and low–animal protein diet. Urinary calcium oxalate supersaturation also diminished more rapidly in those on the higher calcium diet and remained lower than that of men on the low-calcium diet for most of the 5-year study. This reduction in supersaturation was the result of a greater fall in urinary oxalate in the men eating the normal-calcium, low-sodium, and low–animal protein diet.[20,32]

Patients prescribed a low-calcium diet can avoid excessive hyperoxaluria when adequately instructed to also consume a low-oxalate diet.[33] Some contend that this approach may benefit patients with excessive intestinal absorption of calcium associated with severe hypercalciuria by allowing calcium restriction without the risk for significant osteopenia. We recommend, however, an age- and gender-appropriate calcium intake, best derived from a diet containing an adequate amount of dairy products. Because stone formation can be reduced with normal calcium intake and there is a risk for bone demineralization with calcium restriction, we consider the low-calcium diet to be obsolete.[18,29] Dietary calcium intake exceeding the age and gender recommendations and calcium supplements should be avoided in patients with calcium nephrolithiasis.

Vitamin D. Given the great degree of vitamin D deficiency and insufficiency in Northern latitudes, vitamin D supplementation is very common.[34] There is concern that this might exacerbate nephrolithiasis, given the role of vitamin D in mineral metabolism. In fact, studies have shown no association between vitamin D supplementation or serum 25-hydroxyvitamin D levels and calcium excretion, nor an increased rate of stone formation in hypercalciuric patients on vitamin D supplementation. It is reasonable to treat vitamin D deficiency (25-hydroxyvitamin D levels below 20 ng/ml) with supplemental vitamin D (we prefer cholecalciferol to ergocalciferol because of more robust biological activity and greater half-life) with no fear of worsening hypercalciuria or increasing stone formation.[35]

SPECIFIC TYPES OF STONES

Calcium Stones

Calcium-containing kidney stones constitute approximately 70% of all stones formed. Most calcium stones are composed of calcium oxalate, either alone or in combination with calcium phosphate or uric acid. A small percentage of stones are composed entirely of calcium phosphate.[1] Most calcium stones do not exceed 1 to 2 cm in width. Surgical intervention is often required for stones greater than 5 mm.

Calcium-based stones most often develop as a result of hypercalciuria. Other causes of calcium stones are hyperoxaluria, hyperuricosuria, hypocitraturia, renal tubular acidosis, certain medications, and congenital abnormalities of the genitourinary tract (Fig. 57.6). Specific therapy for patients with calcium stones depends on the underlying metabolic abnormalities detected on evaluation. General therapy as outlined earlier always should be instituted; however, more definitive treatment is often required to significantly decrease the rate of recurrent stone formation.

Hypercalciuria

Etiology. Hypercalciuria for which a causative metabolic abnormality cannot be determined is called *idiopathic hypercalciuria.* Previously, hypercalciuric patients were divided into those with excessive renal calcium excretion (renal leak) and those who absorbed excessive amounts of calcium via the gastrointestinal tract (absorptive hypercalciuria). However, it is apparent that hypercalciuric patients generally do not have a transport defect limited to a single site; they appear to have a systemic dysregulation of calcium transport at the major calcium transporting sites, the intestine, kidney, and bone. In both hypercalciuric rats and in humans placed on a low-calcium diet, there is a continuous, wide spectrum of calcium excretion. Hypercalciuric patients may appear to have a renal leak on one examination and absorptive hypercalciuria on another.[1,2] Some patients excrete more calcium than they consume, indicating a negative total body calcium balance. This calcium must be derived from the mineral phases of bone, which contain by far the largest repository of calcium in the body. The cause of this systemic disorder in calcium transport has, in hypercalciuric stone–forming rats and perhaps in humans, been linked to an increased number of receptors for vitamin D in the major calcium transporting organs (intestine, kidneys, and

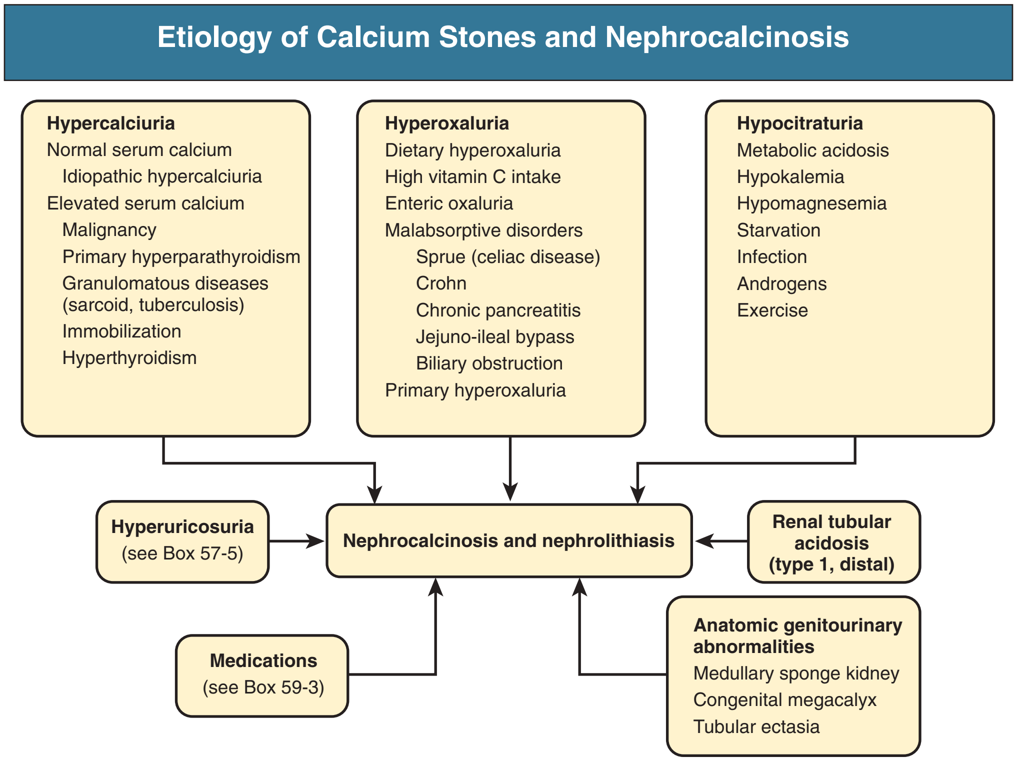
Etiology of Calcium Stones and Nephrocalcinosis
Hypercalciuria
Normal serum calcium
Idiopathic hypercalciuria
Elevated serum calcium
Malignancy
Primary hyperparathyroidism
Granulomatous diseases (sarcoid, tuberculosis)
Immobilization
Hyperthyroidism
Hyperoxaluria
Dietary hyperoxaluria
High vitamin C intake
Enteric oxaluria
Malabsorptive disorders
Sprue (celiac disease)
Crohn
Chronic pancreatitis
Jejuno-ileal bypass
Biliary obstruction
Primary hyperoxaluria
Hypocitraturia
Metabolic acidosis
Hypokalemia
Hypomagnesemia
Starvation
Infection
Androgens
Exercise
Hyperuricosuria (see Box 57-5)
Nephrocalcinosis and nephrolithiasis
Renal tubular acidosis (type 1, distal)
Medications (see Box 59-3)
Anatomic genitourinary abnormalities
Medullary sponge kidney
Congenital megacalyx
Tubular ectasia

Fig. 57.6 Etiology of calcium stones and nephrocalcinosis.

bone).[36-38] Metabolic disorders leading to an elevation in serum calcium, parathyroid hormone, or 1,25(OH)$_2$D (1,25-dihydroxyvitamin D) also may result in hypercalciuria.

Treatment. For hypercalciuria the usual first-line therapy is a thiazide diuretic, which acts to reduce urinary calcium. In the United States, chlorthalidone 25 to 50 mg is the drug of choice because it requires only once-daily administration. Indapamide 1.25 to 2.5 mg/day does not tend to raise serum lipids as much as other thiazides and may be preferred for patients with cardiac risk factors or elevated serum lipids. On commencing these medications, patients should be instructed to increase their dietary potassium intake, and a serum potassium level should be checked 7 to 10 days later. If serum potassium is low, oral potassium supplementation should be initiated. Potassium citrate is generally preferred over potassium chloride. However, most patients find potassium citrate liquid preparations unpalatable. A wax matrix tablet of potassium citrate is well tolerated and is available in some countries. In general, patients are able to maintain a normal serum potassium level with potassium citrate 20 to 40 mmol/day. The serum potassium and bicarbonate levels should be rechecked 7 to 10 days later for further dosage adjustment. Because citrate is a base, potassium citrate may excessively raise the serum bicarbonate level and urinary pH, which could promote calcium phosphate stone formation. Urinary pH and supersaturation must be carefully monitored, and a change to potassium chloride may be required.

The 24-hour urine calcium, sodium, and citrate should be rechecked after several weeks. If the calcium excretion remains elevated, the thiazide dose should be increased. However, if the sodium excretion also remains high, patients should be encouraged to limit their sodium intake further because they will not have an adequate response to the diuretic on a high-sodium diet. If serum potassium remains low despite supplementation or the calcium excretion remains high despite increased thiazide dosing, addition of a potassium-sparing diuretic may be required to increase serum potassium. Amiloride with a starting dose 5 mg/day is the preferred treatment for thiazide-induced hypokalemia.[1,2] (Triamterene should not be used because it can precipitate into stones.)

Dietary recommendations. See the discussion of general treatment.

Hyperoxaluria

Etiology. Elevated urinary oxalate results from excessive dietary intake (dietary oxaluria), gastrointestinal disorders that can lead to malabsorption (enteric oxaluria), or an inherited enzyme deficiency that results in excessive metabolism of oxalate (primary hyperoxaluria) (see Fig. 57.6).[39]

Dietary excess of oxalate generally does not raise urinary oxalate above 60 mg/24 h (0.54 mmol/24 h). Enteric oxaluria may occur when malabsorption results in excessive colonic absorption of oxalate, as a result of sprue (celiac disease), Crohn disease, chronic pancreatitis, or short bowel syndrome or after bariatric surgery. The anion exchange transporter Slc26a6 appears responsible for intestinal oxalate secretion, and mice with targeted inactivation of this transporter have hyperoxaluria.[40] It is not yet known whether patients with enteric hyperoxaluria have mutations in Slc26a6. Urinary oxalate is generally more than 60 mg/24 h and can exceed 100 mg/24 h (0.54 and 0.9 mmol/24 h). In primary hyperoxaluria, the tremendous oxalate production results in widespread calcium oxalate deposition throughout the body at an early age. This infiltration of calcium oxalate into organs can result in cardiomyopathy, bone marrow suppression, and renal failure. Urinary oxalate values may range from 80 to 300 mg/24 h (0.72 to 2.70 mmol/24 h).

There are three types of primary hyperoxaluria with unique enzymatic defects in the liver glyoxylate pathway. In type 1, the defective enzyme is alanine–glyoxylate aminotransferase, encoded by the gene *AGXT* on chromosome 2; this accounts for approximately 80% of cases. Type 2 tends to be a milder disorder and is caused by mutations in the *GRHPR* gene on chromosome 9, which results in failure of glyoxylate reduction to glycolate; this accounts for approximately 10% of the cases. Type 3 is a result of mutations in the gene that encodes the mitochondrial 4-hydroxy-2-oxoglutarate aldolase enzyme, which catalyzes the cleavage of 4-hydroxy-2-oxoglutarate to pyruvate and glyoxylate and accounts for about half of the remaining cases.[41]

Treatment of dietary and enteric hyperoxaluria. Treatment of dietary oxaluria consists of dietary oxalate restriction. Patients should be given a list of foods that have high oxalate content to avoid or eat in moderation (see Box 57.4). Calcium containing food may be included at each meal to bind intestinal oxalate and prevent its absorption.

Specific therapy for the malabsorptive disorder, such as a gluten-free diet for patients with sprue, is the first-line treatment for enteric hyperoxaluria. More generalized therapy for steatorrhea, such as a low-fat diet, cholestyramine, and administration of medium-chain triglycerides, may reduce fat malabsorption as well as oxalate absorption and subsequent excretion. The low-oxalate diet and mealtime calcium carbonate prescribed for patients with dietary oxaluria is also helpful for these patients. The diarrhea associated with these disorders may result in low urine volumes, hypokalemia, hypocitraturia, and hypomagnesuria. Patients should therefore be advised to increase their fluid intake and take potassium citrate (in this case, the liquid, although unpalatable, is better absorbed than the tablets), as well as a magnesium supplement. Magnesium also serves as a urinary stone inhibitor and can be given as magnesium gluconate 0.5 to 1 g once or twice a day or as magnesium oxide 400 mg every 12 hours.

Treatment of primary hyperoxaluria. Primary hyperoxaluria type 1 (PH1) is a severe disorder that can be cured only with liver transplantation to replace the defective hepatic enzyme. Pyridoxine (vitamin B_6) in doses ranging from 2.5 to 15 mg/kg/24 h may reduce oxalate production in patients with PH1. Efforts should be made to render the calcium and oxalate more soluble in the urine by raising the urinary pH (to at least 6.5) and giving supplemental citrate and magnesium. Orthophosphate is also an effective inhibitor of urinary calcium oxalate precipitation and can be safely administered in patients with a glomerular filtration rate (GFR) exceeding 50 ml/min. Because oxalate is poorly excreted in CKD and is not removed well by dialysis, renal transplantation serves not only to improve renal function, but also to improve oxalate excretion and diminish systemic oxalosis.[14]

Oxalobacter formigenes primarily uses oxalate for cellular metabolism.[42] Calcium oxalate stone formers who are colonized with *O. formigenes* have lower urine oxalate levels than those who are not colonized.[43] A small clinical trial involving administration of *O. formigenes* resulted in a modest decrease in urinary oxalate in some patients.[42] Further studies with larger numbers of patients and an end-point of reduction of recurrent stone formation will be necessary before this novel approach becomes accepted therapy.

Hypocitraturia

Citrate inhibits stone formation. A number of conditions reduce urinary citrate excretion, predisposing to stone formation. Excessive protein intake, hypokalemia, metabolic acidosis, exercise, hypomagnesemia, infections, androgens, starvation, and acetazolamide have all been implicated in decreased urinary citrate excretion. Therapy involves treatment of the underlying condition and potassium citrate supplementation. The potassium salt is preferred to sodium citrate because sodium promotes renal calcium excretion. Potassium citrate 15 to 25 mmol two to three times daily is required, and tablets are considered by most patients to be more palatable than the liquid preparation. In patients with renal impairment, serum potassium should be monitored carefully and dose reduction may be needed if hyperkalemia develops.[14]

Distal Renal Tubular Acidosis

Patients with distal (type 1) renal tubular acidosis have impaired distal tubular excretion of hydrogen ions with non–anion gap metabolic acidosis and alkaline urine. The acidosis causes calcium and phosphate to be released from bone with an ensuing increase in renal excretion of these ions. The acidosis also leads to an increase in citrate reabsorption by the proximal tubule. The end result is a high urinary pH, hypocitraturia (urinary citrate generally <100 mg/24 h [0.53 mmol/24 h]), and increased renal excretion of calcium and phosphate, all of which increase the propensity for calcium phosphate precipitation. Nephrocalcinosis in this setting is not uncommon because calcium precipitates with phosphorus in the alkaline tubular fluid. The metabolic acidosis and hypocitraturia should be treated with a combination of sodium citrate (or bicarbonate) and potassium citrate (or bicarbonate). Often large amounts, 1 to 2 mmol/kg/day in 2 or 3 divided doses, are required to neutralize the acidosis.[1] Citrate is generally preferred to bicarbonate by patients because it does not produce carbon dioxide on contact with stomach acid with resultant gastrointestinal bloating. However, citrate is usually more expensive than bicarbonate.

Hyperuricosuria

Calcium oxalate crystals often nucleate around other crystal types such as uric acid. Hyperuricosuria contributes to nephrolithiasis in 10% to 15% of calcium stones. Patients with hyperuricosuric calcium oxalate nephrolithiasis have hyperuricosuria with normal urinary calcium and oxalate, but often a higher urinary pH (>5.5) than patients with pure uric acid stones. Therapy for hyperuricosuria consists of increased fluid intake and reduced dietary purine intake. If uric acid excretion remains elevated, allopurinol should be initiated at 100 to 300 mg/day.[1]

Uric Acid Stones

Epidemiology

The prevalence of uric acid stones depends greatly on geographical location. In the United States, uric acid stones constitute 5% to 10% of all stones formed, whereas in Mediterranean and Middle Eastern countries uric acid stones may constitute up to 75% of stones. The stones are radiolucent and therefore poorly visible on plain radiographs. They are detectable on ultrasound and CT and as filling defects on IVU (Fig. 57.7).

Etiology and Pathogenesis

Causes of hyperuricosuria include excessive dietary purine or protein intake, disorders associated with cellular breakdown (tumor lysis syndrome, myeloproliferative disorders, hemolytic anemia), gout, uricosuric medications, certain inborn errors of metabolism, and possibly excessive fructose intake.

Three major factors influence uric acid stone formation: low urine pH, low urine volume, and elevated urinary uric acid levels (Box 57.5). Of the three, low urine pH is the principal metabolic disorder found in patients with uric acid nephrolithiasis. Uric acid is poorly soluble at pH below 5.5. Solubility increases with urine alkalinity such that at urine pH 6.5, urine can contain over six times the quantity of uric acid present at pH 5.3, without exceeding supersaturation. The rising incidence of obesity and insulin resistance in the United States led to a parallel increase in uric acid lithiasis. The urinary acidosis is likely a result of impaired ammoniagenesis, which results in excessive excretion of unbuffered acid and a very low urine pH.[8,44] The geographical and ethnic variations in the incidence of uric acid stones may be due to diet, caused by environmental factors, or the result of genetic susceptibility in some populations.[8]

Treatment

Treatment of uric acid stones involves increasing urine pH and volume as well as decreasing uric acid excretion. Alkaline urine not only can prevent uric acid stone formation, but also may result in stone

Radiolucent Urate Calculi

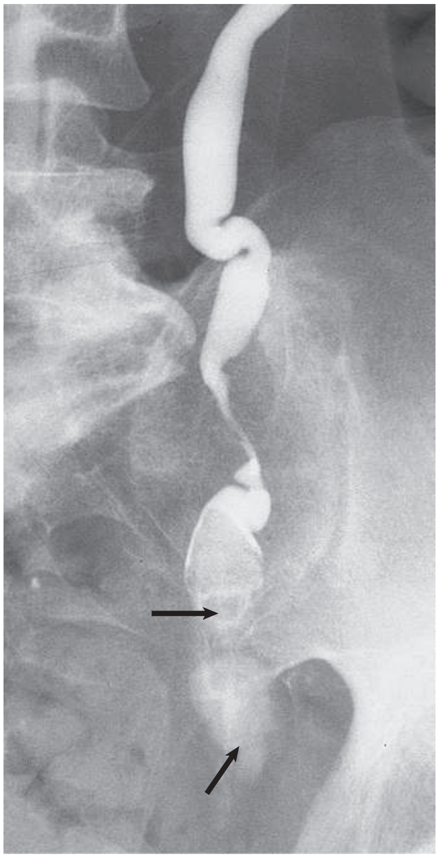

Fig. 57.7 **Radiolucent urate calculi.** Antegrade pyelogram showing multiple radiolucent uric acid stones *(arrows)* obstructing the lower ureter.

dissolution. To raise urine pH, potassium citrate is recommended. While sodium bicarbonate alkalinizes the urine and enhances uric acid solubility, the added sodium increases sodium urate formation, which serves as a nidus for calcium oxalate precipitation. Potassium citrate 40 to 50 mmol/day in divided doses is given, increasing the dose as necessary to achieve a urine pH of 6.5 to 7.0. Patients should monitor pH with urine dipsticks at various times of the day and adjust the dosage accordingly. If urine pH remains low despite potassium citrate exceeding 100 mmol/day, or if that dose results in hyperkalemia, acetazolamide may be added. This carbonic anhydrase inhibitor produces an alkaline urine similar to that seen in renal tubular acidosis. Patients should be cautioned not to exceed urine a pH of 7.0 because this may result in calcium phosphate precipitation.

A low-purine and low–animal protein diet is also useful in raising urinary pH and decreasing uric acid excretion (see Box 57.4). If uric acid excretion remains high despite dietary intervention, as in patients with disorders of cellular catabolism, allopurinol should be prescribed, 100 mg increasing to 300 mg/day as needed to keep urinary uric acid excretion below 750 mg/24 h (4.5 mmol/24 h). See Box 57.4 for high-purine foods to avoid.[45]

BOX 57.5 Factors Associated With Uric Acid Stone Formation

Low Urine pH (≤5.5)

- High–animal protein diet
- Diarrhea
- Insulin resistance (high body mass index, metabolic syndrome, type 2 diabetes)

Low Urine Volume

- Inadequate fluid intake
- Excessive extrarenal fluid losses
  - Diarrhea
  - Insensible losses (e.g., perspiration)

Hyperuricosuria

- Excessive dietary purine intake
- Hyperuricemia
  - Gout
  - Intracellular-to-extracellular uric acid shift
  - Myeloproliferative disorders
  - Tumor lysis syndrome
- Inborn errors of metabolism
  - Lesch-Nyhan syndrome
  - Glucose-6-phosphatase deficiency

Medications

- See Box 57.3.

BOX 57.6 Factors Associated With Struvite Stone Formation*

- Urease-producing bacteria
  - *Proteus*
  - *Haemophilus*
  - *Yersinia* spp.
  - *Staphylococcus epidermidis*
  - *Pseudomonas*
  - *Klebsiella*
  - *Serratia*
  - *Citrobacter*
  - *Ureaplasma*
- Elevated urinary pH

**Escherichia coli* is not a urease producer.

Struvite Stones

Struvite stones are also referred to as *infection stones* or *triple phosphate stones*. The stones grow rapidly to a large size, can reduce renal function in the affected kidney, and are difficult to eradicate. Because of the significant morbidity in patients with struvite stones, they also have been termed *stone cancer*. Most staghorn calculi, large stones that penetrate more than one renal calyx, are composed of struvite. Their formation requires the presence of urease-producing bacteria in the urine (Box 57.6).[46]

Etiology and Pathogenesis

Struvite stones are composed of magnesium ammonium phosphate and calcium carbonate apatite. They form when urease production by certain urinary bacteria breaks down urea to ammonium (NH_4^+) and a carboxyl (OH^-) group. The urine becomes quite alkaline; urinary phosphate becomes insoluble and forms a solid phase with magnesium, calcium, and the ammonium. Women are more prone to struvite nephrolithiasis than men because of an increased propensity for UTI. Others predisposed to developing struvite stones through infections or urinary stasis include patients with indwelling urinary catheters, neurogenic bladders, genitourinary tract anomalies, and spinal cord lesions. An alkaline urine (pH 7.0), urine culture of urease-producing bacteria, and large stones suggest the diagnosis of struvite nephrolithiasis.[46]

A number of gram-negative and gram-positive bacteria have been implicated in urease production and consequent struvite formation, with the most common being *Proteus* spp. (see Box 57.6). *Escherichia coli,* which is frequently present in urine cultures, is not a urease producer. If there is a strong suspicion for struvite stones but no organism is detected in the urine, a specific culture request for *Ureaplasma urealyticum* should be considered, because it does not grow on routine culture media.

Treatment

Struvite stones require aggressive medical and surgical management. Antibiotic therapy is important to reduce further stone growth and for stone prevention. Bacteria will remain in the stone interstices, however, and stones will continue to grow unless chronic antibiotic suppression is maintained or the calculi are completely eradicated. Given the need for complete stone removal to effect a cure, early urologic intervention is advised. Stones smaller than 2 cm may respond well to ESWL; however, larger stones will likely require percutaneous nephrolithotomy, often in combination with ESWL (see Chapter 59). Any stone fragments retrieved should be cultured and culture-specific antibiotics continued. Once the urine is sterile, usually approximately 2 weeks after initiation of therapy, the dose is halved. Monthly urine cultures should be obtained, and if they remain sterile for 3 consecutive months, antibiotics may be discontinued, although surveillance urine cultures should continue monthly for a full year.[47]

Adjunct medical therapies include urease inhibitors and chemolysis. The most commonly used urease inhibitor is acetohydroxamic acid. By inhibiting urease, these agents retard stone growth and prevent new stone formation. Unfortunately, they have numerous side effects, including deep venous thrombosis and hemolytic anemia, that limit their use, although these resolve on discontinuation of the drug. In addition, they require adequate renal clearance to be effective and therefore are not useful in patients with CKD (estimated GFR <60 ml/min).[46] Chemolysis involves irrigation of the kidney via a nephrostomy tube or the ureter with a solution designed to dissolve the stones. The most common solution is 10% hemiacidrin, which contains carbonic acid, citric acid, D-gluconic acid, and magnesium at pH 3.9. Lavage chemolysis is controversial because it has previously been associated with a high mortality rate, but it is now considered safe with appropriate monitoring for UTI, assessment of obstruction to flow by intrapelvic pressure measurement, and monitoring of serum magnesium levels. Although not a treatment of choice for large stones, it may be useful when surgical techniques have been effective but have left residual stone fragments.

Cystine Stones

Cystinuria is an autosomal disorder in which there is a tubular defect in dibasic amino acid transport, resulting in increased cystine, ornithine, lysine, and arginine excretion. It is also discussed in Chapter 48. The pattern of inheritance may be autosomal recessive or autosomal dominant with incomplete penetrance. The stone disease is usually clinically manifested by the second and third decades of life. Because of the high sulfur content of the cystine molecule, the stones are apparent on plain radiographs (see Fig. 57.4A) and often will manifest as staghorn calculi or multiple bilateral stones.

Cystine is poorly soluble, only approximately 300 mg/l (1.25 mmol/l) at a neutral pH. Normal cystine excretion of approximately 30 to 50 mg (0.12 to 0.21 mmol) per day is readily soluble in the usual daily urine output of approximately 1 liter. However, homozygote cystinurics often excrete 250 to 1000 mg (1.04 to 4.20 mmol) of cystine per day, with heterozygotes excreting an intermediate amount. Treatment is directed at decreasing the urinary cystine concentration below the limits of solubility. Because the dietary precursor of cystine, methionine, is an essential amino acid, it is impractical to significantly reduce intake. Increasing urine volume so that cystine remains below the limits of solubility sometimes requires 4 liters of urine per day. A low-sodium diet has been reported to reduce urine cystine excretion, although the mechanism by which this occurs is not clear.[48] Increasing urine pH above 7.5 will increase cystine solubility, but this is difficult to achieve on a long-term basis. Tiopronin 800 mg/day in 3 divided doses or D-penicillamine with a starting dose 250 mg/day and maximum dose of 2 g/day will both bind cystine and reduce urinary supersaturation; however, side effects may limit their use. The angiotensin-converting enzyme inhibitor captopril may be effective by forming a thiol-cysteine disulfide bond that is more soluble than cystine.[49]

Stones Associated With Melamine Exposure

By late 2008, more than 50,000 Chinese children younger than 3 years had been reported to have kidney stones associated with contaminated milk products. Powdered milk and infant formulas were noted to contain melamine, a nitrogenous substance synthesized from urea that increases the apparent protein content of the product.[9] Risk factors for nephrolithiasis after melamine exposure may include volume depletion, small body size, uricosuria, and low urine pH.

Although affected children often presented with dysuria and hematuria, many children who were subsequently screened were asymptomatic despite kidney stones identified on ultrasound.[9] On urinalysis, some children exhibited fan-shaped crystals. The kidney stones formed were radiolucent and fragile. Many were composed of a combination of uric acid with melamine and were amenable to dissolution by hydration and alkalinization. In animal studies of melamine exposure, the distal tubular crystal deposition may lead to tubulointerstitial inflammation and fibrosis. Whether a similar process may occur in humans is unknown.

NEPHROCALCINOSIS

Nephrocalcinosis refers to augmented calcium content within the kidney.[50] This disorder may be symmetric or may involve only a single kidney.

Etiology and Pathogenesis

Medullary Nephrocalcinosis

Medullary nephrocalcinosis in which the calcification tends to occur in the area of the renal pyramids accounts for the majority of cases of nephrocalcinosis. It is typically associated with elevated urinary calcium, phosphate, and oxalate, or it can occur with alkaline urine (Box 57.7). Any disorder that can lead to hypercalcemia and/or hypercalciuria may be implicated. Instead of stone formation, smaller parenchymal calcifications deposit in the medulla, and they are usually bilateral and relatively symmetric (Fig. 57.8). Some metabolic disorders, particularly oxalosis caused by primary hyperoxaluria, can result in both medullary and cortical nephrocalcinosis[49] (Fig. 57.9).

In adults, the most common causes of medullary nephrocalcinosis are primary hyperparathyroidism, distal renal tubular acidosis, and medullary sponge kidney, as well as medications, including acetazolamide, amphotericin, and triamterene (see Box 57.3).

In children, a similar range of disorders can be seen, but the most common associations are with furosemide therapy and the hereditary disorders associated with hypercalciuria.[18] Furosemide, when used in premature neonates and older infants with congestive heart failure,

BOX 57.7 Causes of Nephrocalcinosis

Medullary

Disturbed Calcium Metabolism

- Hyperparathyroidism
- Sarcoidosis
- Milk-alkali syndrome
- Rapidly progressive osteoporosis
- Idiopathic hypercalciuria

Other Tubular Disease

- Distal (type 1) renal tubular acidosis
- Oxalosis*
- Dent disease (X-linked hypercalciuric nephrolithiasis)
- X-linked hypophosphatemic rickets
- Bartter syndrome
- Hypomagnesemia-hypercalciuria syndrome

Anatomic Disease

- Medullary sponge kidney
    - Papillary necrosis

Medications

- Acetazolamide
- Amphotericin
- Triamterene

Cortical

- Cortical necrosis
- Transplant rejection
- Chronic glomerulonephritis
- Trauma
- Tuberculosis
- Oxalosis*

*Oxalosis typically causes both cortical and medullary nephrocalcinosis.

Medullary Nephrocalcinosis

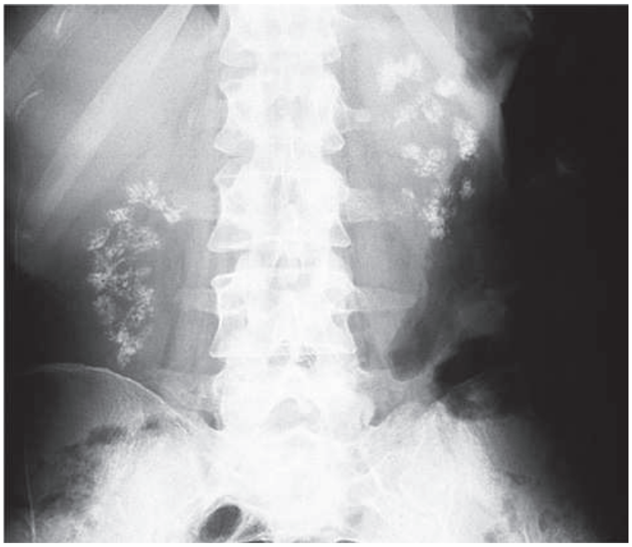

Fig. 57.8 **Medullary nephrocalcinosis.** Plain radiograph showing bilateral metastatic medullary nephrocalcinosis in a patient with distal renal tubular acidosis.

Nephrocalcinosis

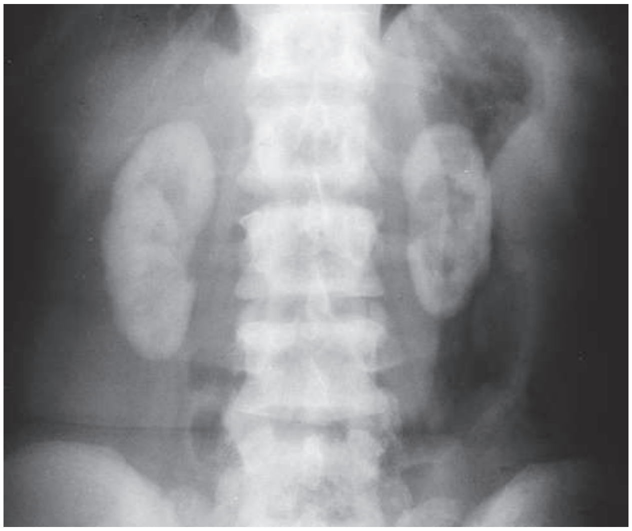

Fig. 57.9 **Nephrocalcinosis.** Dense cortical and medullary calcification in the shrunken kidneys of a patient with oxalosis and long-standing renal failure.

can result in nephrocalcinosis with or without hypercalciuria. The lesions often resolve with discontinuation of therapy. A normal ratio of calcium to creatinine at the time of diagnosis of nephrocalcinosis (~0.40 [mg/mg] in premature infants) appears to be a good predictor of resolution.

There are many uncommon hereditary disorders associated with nephrocalcinosis, including Dent disease, X-linked hypophosphatemic rickets, hypomagnesemia-hypercalciuria syndrome, and Bartter syndrome.

Dent disease is an X-linked recessive disorder of proximal tubules characterized by low-molecular-weight proteinuria with hypercalciuria and nephrocalcinosis.[51] In most cases, it is due to mutations that inactivate a voltage-gated chloride transporter called *CLC-5*. A number of mutations affecting the *CLCN5* gene on the X chromosome have been identified that lead to inactivation of CLC-5. The result is a clinical syndrome typically affecting young boys and usually including hypercalciuria, nephrocalcinosis, nephrolithiasis, and hematuria, as well as low-molecular-weight proteinuria, glycosuria, aminoaciduria, hypophosphatemia, renal failure, and rickets. Dent disease is further discussed in Chapter 48.

In X-linked hypophosphatemic rickets, the recommended treatment, with phosphate repletion and vitamin D, may itself result in hypercalcemia, hypercalciuria, and nephrocalcinosis. Thus only enough phosphate and vitamin D should be prescribed to allow bone growth and prevent symptomatic hypophosphatemia.

Another cause of medullary nephrocalcinosis in children is primary hypomagnesemia-hypercalciuria syndrome.[2,11] This rare autosomal recessive condition results from defective production of the cellular tight-junction protein paracellin-1. This claudin family protein is necessary for adequate calcium and magnesium reabsorption in the thick ascending limb of the loop of Henle. Children typically present with symptoms of UTI (often with nephrolithiasis), polyuria, tetanic seizures (caused by hypomagnesemia), and muscle cramps and weakness. Hypercalciuria, hypermagnesuria, and a urinary concentrating defect also occur. Patients often have renal impairment and may require renal

Cortical Nephrocalcinosis

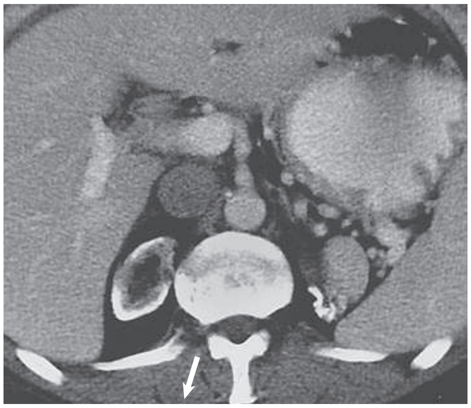

Fig. 57.10 **Cortical nephrocalcinosis.** Noncontrast CT showing cortical nephrocalcinosis *(arrows)* in the right kidney after cortical necrosis.

replacement therapy by the third decade of life. Sensorineural hearing disorders and ocular impairment may accompany the renal manifestations in a subset of patients.

Cortical Nephrocalcinosis

Cortical nephrocalcinosis is usually the result of dystrophic calcification, which follows parenchymal tissue destruction, rather than the precipitation of excessive urinary constituents. It is secondary to infarction, neoplasm, and infection. It is typically asymmetric and is usually localized to the renal cortex (Fig. 57.10). Causes of cortical nephrocalcinosis include transplant rejection, cortical necrosis, tuberculosis, ethylene glycol toxicity, and chronic glomerulonephritis.

Clinical Manifestations

Patients who do not have nephrolithiasis associated with nephrocalcinosis are often asymptomatic. Ultrasound and CT scanning are sensitive diagnostic tests for both cortical and medullary nephrocalcinosis, demonstrating the parenchymal calcifications before they can be visualized on plain radiographs. The extent of calcification correlates poorly with renal function.

Treatment

Similarly to nephrolithiasis, treatment of nephrocalcinosis relies on therapy for the underlying disease, as well as measures to reduce hypercalcemia, hyperphosphatemia, and oxalosis, if possible. The goal of treatment is usually to prevent further deposits, because therapy cannot eradicate existing calcium deposits.

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SELF-ASSESSMENT QUESTIONS

1. A 49-year-old paraplegic man is referred for evaluation of nephrolithiasis. He has a suprapubic catheter and has had frequent urinary tract infections. He has reduced kidney function and is noted to have large staghorn calculi in both kidneys. On urinalysis he has many white blood cells and bacteria. Urine culture grows *Proteus.* All statements regarding this patient's kidney stones are true *except:*
   A. His current stones can be treated with a course of antibiotics.
   B. Stone formation is facilitated by the effects of urease-producing bacteria.
   C. His stones are formed by a combination of phosphate with three cations.
   D. Stone formation is potentiated by an elevated urine pH.
   E. His current stones require surgical management.
2. A 35-year-old woman presents with her fourth kidney stone. Her father and brother have had stones as well. She was informed that her stones are composed of calcium. She tries to drink as much fluid as possible. Urine calcium excretion is elevated, but serum calcium is normal. All of the following dietary measures may be recommended for kidney stone prevention in this patient *except:*
   A. Low-sodium diet
   B. Reduction in animal protein intake
   C. Reduction in dietary calcium intake
   D. Low-oxalate diet
3. A 52-year-old obese man presents with flank pain and gross hematuria. Computed tomography (CT) reveals an obstructing left kidney stone and two other nonobstructing kidney stones in the right kidney measuring 0.5 mm. He passes the left kidney stone, which is found on analysis to be a uric acid stone. He was recently started on metformin for diabetes mellitus, his body mass index is 33, and he has normal kidney function; 24-hour urine reveals urine pH 5.3, volume 1.5 liter, and uric acid excretion of 500 mg. Which of the following is a *true* statement regarding this patient's kidney stones?
   A. The patient's right kidney stones can be followed by serial abdominal x-ray examination of the kidneys.
   B. The patient's insulin resistance may be contributing to his stone disease.
   C. The patient should be treated with allopurinol.
   D. Potassium citrate would not be beneficial.
   E. The patient is drinking an adequate amount of fluid.

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Urinary Tract Obstruction

Kevin M. Gallagher, Jeremy Hughes

DEFINITIONS

Obstructive uropathy refers to the structural or functional changes in the urinary tract that impede normal urine flow. *Obstructive nephropathy* refers to the renal disease caused by impaired flow of urine or tubular fluid. *Hydronephrosis* refers to dilation of the urinary tract. *Hydronephrosis* is not synonymous with *obstructive uropathy* because the former can occur without functional obstruction to the urinary tract and can be absent in established obstruction. Obstructive uropathy and nephropathy frequently coexist, and their management requires close collaboration between nephrologists and urologists. Some surgical aspects of obstruction to the urinary tract are discussed in Chapter 59.

Obstructive uropathy is classified according to the site, degree, and duration of the obstruction. Acute or chronic obstruction can occur anywhere in the urinary tract and includes intrarenal causes (casts, crystals) and extrarenal causes. Acute or chronic obstruction is further subdivided into upper urinary tract obstruction (usually unilateral obstruction occurring above the vesicoureteral junction) and lower urinary tract obstruction (usually bilateral obstruction located below the vesicoureteral junction). Complete obstruction of the urinary tract is termed *high grade,* whereas partial or incomplete obstruction is termed *low grade*.

Unilateral obstruction in a patient with two normal kidneys will not result in significant renal impairment because the contralateral kidney compensates. However, bilateral obstruction or the obstruction of a single functioning kidney will result in renal failure. In acute urinary tract obstruction, changes are mainly functional, whereas structural damage to the kidney results from more chronic obstruction. The kidney with acute functional changes may recover after effective release of the obstruction, but structural changes may be permanent and lead to chronic kidney disease (CKD). Urinary tract obstruction is a major cause of renal impairment worldwide in children and adults.

ETIOLOGY AND PATHOGENESIS

The causes of obstructive uropathy affecting the upper and lower urinary tracts are summarized in Boxes 58.1 and 58.2.

Congenital Urinary Tract Obstruction

Congenital urinary tract obstruction occurs most frequently in males, most commonly as a result of posterior urethral valves or pelviureteral junction (PUJ) obstruction. If obstruction occurs early during development, the kidney fails to develop and becomes dysplastic. If the obstruction is bilateral, there is a high mortality rate as a result of severe renal failure. If the obstruction occurs later in gestation and is low grade or unilateral, hydronephrosis and nephron loss will still occur, but renal function may be sufficient to allow survival, and such patients may not present until later in childhood. PUJ obstruction, if it is mild, may not manifest until adulthood and in some patients may be an incidental finding (Fig. 58.1). However, with increased use and improved sensitivity of antenatal scanning, congenital abnormalities of the urinary tract are now frequently identified early, allowing prompt postnatal (and in some cases antenatal) intervention to relieve the obstruction and hence preserve renal function. Congenital causes of obstruction are discussed further in Chapter 50.

Acquired Urinary Tract Obstruction

Acquired urinary tract obstruction may affect either the upper or lower urinary tract and can result from either intrinsic or extrinsic causes. Intrinsic causes of obstruction may be intraluminal or intramural.

Intrinsic Obstruction

Intraluminal obstruction. Intraluminal obstruction may result from tubular intrarenal obstruction, such as the deposition of uric acid crystals in the tubular lumen after treatment of hematologic malignancies (tumor lysis syndrome). It also may occur with the precipitation of Bence Jones protein in myeloma and with the precipitation or crystal formation of certain drugs, including sulfonamides, acyclovir, methotrexate, and indinavir. Uncommonly, patients with an underlying glomerulonephritis such as immunoglobulin A (IgA) nephropathy may develop severe glomerular hematuria with tubular obstruction from erythrocytes and acute kidney injury (AKI) that typically resolves with time.

Extrarenal intraluminal obstruction in young adults is most commonly caused by renal calculi (see Chapter 57). Calcium oxalate stones are the most common and typically cause intermittent acute unilateral urinary tract obstruction but rarely result in marked CKD. Less common causes of urinary lithiasis, such as struvite stones, uric acid stones, and cystinuria are often bilateral and hence more likely to cause long-term CKD. Renal calculi lodge more commonly in the calyx, PUJ, or vesicoureteral junction and at the level of the pelvic brim. Surgical management of stones is discussed in Chapter 59. Intraluminal obstruction also can result from a sloughed papilla after papillary necrosis or blood clots after macroscopic hematuria ("clot colic"). Papillary necrosis may occur in diabetes mellitus, sickle cell trait or disease, analgesic nephropathy, renal amyloidosis, and acute pyelonephritis. Clot colic can occur with bleeding from renal tumors or arteriovenous malformations, after renal trauma or surgery, and in patients with polycystic kidney disease.

Intramural obstruction. Intramural obstruction can result from either functional or anatomic changes. Functional disorders include adynamic ureteral segments (usually at the junction of the ureter with

BOX 58.1 Causes of Lower Urinary Tract Obstruction*

Urethral Anatomic Causes

- Urethral strictures: Trauma, *postinstrumentation,* infections such as gonococcal urethritis, nongonococcal urethritis, tuberculosis
- *Posterior Urethral Valves*
- Stones
- Blood clots
- Periurethral abscess
- Phimosis
- Paraphimosis
- Meatal stenosis

Urethral Functional Causes

- Anticholinergic drugs, antidepressants, levodopa

Prostate

- *Benign prostatic hypertrophy*
- *Prostatic carcinoma*

Bladder Anatomic Causes

- *Bladder cancer*
- *Schistosomiasis* (*Schistosoma haematobium* infection)
- Bladder calculi
- Bladder trauma, pelvic fracture

Bladder Functional Causes

- *Neurogenic bladder:* Spinal cord defects or trauma, diabetes, multiple sclerosis, Parkinson disease, cerebrovascular accidents

*The most common causes are in italics.

BOX 58.2 Causes of Upper Urinary Tract Obstruction*

Intrinsic Causes

Intraluminal

- Intratubular deposition of crystals (uric acid, drugs)
- *Stones*
- Papillary tissue
- Blood clots
- Fungal ball

Intramural

- Functional: Pelviureteral or vesicoureteral junction dysfunction
- Anatomic: Tumors (benign or malignant)
- Infections, granulomas, strictures

Extrinsic Causes

Reproductive System

- Cervix: *Carcinoma*
- Uterus: *Pregnancy, tumors,* prolapse, endometriosis, pelvic inflammatory disease
- Ovary: Tumor, cysts
- Prostate: *Carcinoma*

Vascular System

- Aneurysms: Aorta, iliac vessels
- Aberrant arteries: Pelviureteral junction
- Venous: Ovarian veins, retrocaval ureter

Gastrointestinal Tract

- Crohn's disease
- Pancreatitis
- Appendicitis
- Diverticulitis
- Tumors

Retroperitoneal Space

- Lymph nodes
- Fibrosis: Idiopathic, drugs, inflammatory or IgG4-related disease
- Tumors: Primary or metastatic
- Hematomas
- Radiation therapy

Surgical Disruption or Ureteral Ligation

*The most common causes are in italics.

the pelvis or bladder) and neurologic disorders. The latter may result in a contracted (hypertonic) bladder or a flaccid (atonic) bladder, depending on whether the lesion affects upper or lower motor neurons, and may lead to impaired bladder emptying with vesicoureteral reflux. Bladder dysfunction is very common in patients with multiple sclerosis and after spinal cord injury and is also seen in diabetes mellitus, in Parkinson disease, and after cerebrovascular accidents. Some drugs (anticholinergics, levodopa) can alter neuromuscular activity of the bladder and result in functional obstruction, especially if there is preexisting bladder outflow obstruction (e.g., prostatic hypertrophy).

Anatomic causes of intramural obstruction of the upper urinary tract include transitional cell carcinoma of the renal pelvis and ureter and ureteral strictures secondary to radiotherapy or retroperitoneal surgery. Rarely, obstruction may result from ureteral valve malfunction, polyps, or strictures after therapy for tuberculosis. Intramural obstruction of the lower urinary tract can result from urethral strictures, which are usually secondary to chronic instrumentation or previous urethritis, or malignant and benign tumors of the bladder. Infection with *Schistosoma haematobium* when the ova lodge in the distal ureter and bladder is a common cause of obstructive uropathy worldwide; up to 50% of chronically infected patients develop ureteral strictures and fibrosis, with calcifications and contraction of the bladder.

Extrinsic Obstruction

The most common cause of extrinsic compression in women is pressure from a gravid uterus on the pelvic rim; the right ureter is more commonly affected. It is usually asymptomatic, and the changes resolve rapidly after delivery. Rarely, bilateral obstruction and AKI may occur. Ureteral dilation frequently may be seen in pregnancy as a result of hormonal effects (especially progesterone) on smooth muscle, but this does not indicate functional obstruction (see Chapter 42, Fig. 42.1). Carcinoma of the cervix also may cause extrinsic obstruction secondary to direct extension of the tumor to involve the urinary tract. Other pelvic pathologic processes that can cause ureteral compression include benign and malignant uterine and ovarian masses, endometriosis, and pelvic inflammatory disease. Compression of the ureters outside the bladder also may occur with uterine prolapse. Rarely, inadvertent ureteral ligation may occur during surgical procedures, particularly those related to obstetrics and gynecology. Unilateral ligation may go undetected, but AKI will result from bilateral ligation.

In men, the most common cause of extrinsic obstruction of the lower urinary tract is benign prostatic hypertrophy. Carcinoma of the prostate can result in obstruction either from direct tumor extension to the bladder outlet or ureters or from metastatic spread.

Retroperitoneal pathology may result in extrinsic obstruction of the ureters, as can metastases or extension of tumors from the cervix,

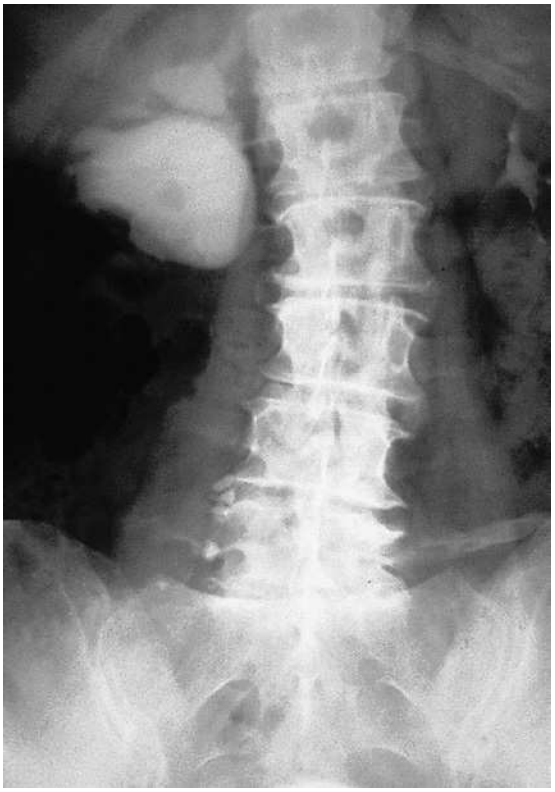


Fig. 58.1 **Intravenous urogram demonstrating pelviureteral junction obstruction.** The study was performed in a previously asymptomatic adult to investigate nonspecific right loin pain. There is unilateral dilation of the pelvicalyceal system. The ureter has not been visualized.

prostate, bladder, colon, ovary, and uterus. Primary tumors of the retroperitoneum, such as lymphomas and sarcomas, commonly cause obstruction. Obstruction also can result from inflammatory conditions affecting the retroperitoneum, such as Crohn's disease and large bowel diverticulitis. In Crohn's disease the obstruction is usually right sided as a result of ileocecal disease. Less common pathologic processes include retroperitoneal fibrosis, in which thick fibrous tissue extends out from the aorta to encase the ureters and draw them medially (Fig. 58.2). Retroperitoneal fibrosis may be idiopathic but can result from inflammatory aortic aneurysms, certain drugs (e.g., β-blockers, bromocriptine, and methysergide), previous irradiation, trauma or surgery, and granulomatous disease (e.g., tuberculosis, sarcoidosis). Retroperitoneal fibrosis is also associated with IgG4-related disease (see Chapter 62), which typically presents with autoimmune pancreatitis, and elevated serum IgG4 levels suggests this diagnosis.[1] IgG4-related disease may be diagnosed after retroperitoneal biopsy material with an IgG4-positive plasma cell infiltrate, fibrosis with a whorled cartwheel appearance, and an obliterative venous phlebitis evident.[2] Ureteral compression may be a result of vascular abnormalities, including aneurysmal dilation of the aorta or iliac vessels, aberrant vessels such as an aberrant anterior crossing accessory renal artery causing PUJ obstruction in adults, and anatomic variations in the location of the ureter (retrocaval ureter).

Pathophysiology

Obstruction of the renal tract causes profound functional and structural changes of the kidney. Initially, changes are predominantly functional and potentially reversible, but with time, chronic and irreversible structural changes occur. Our understanding of the consequences of urinary tract obstruction stems mainly from the study of animal models.[3] Although many studies have focused on the effects of complete ureteral obstruction in rodents, investigators have also examined models of chronic complete, partial, or reversible obstruction in adult and neonatal animals.[3] Available experimental data show little species-to-species variation in the response to acute obstruction, suggesting that similar changes are likely to occur in humans. The complex effects of urinary tract obstruction on the kidney affect both glomerular hemodynamics and tubular function.

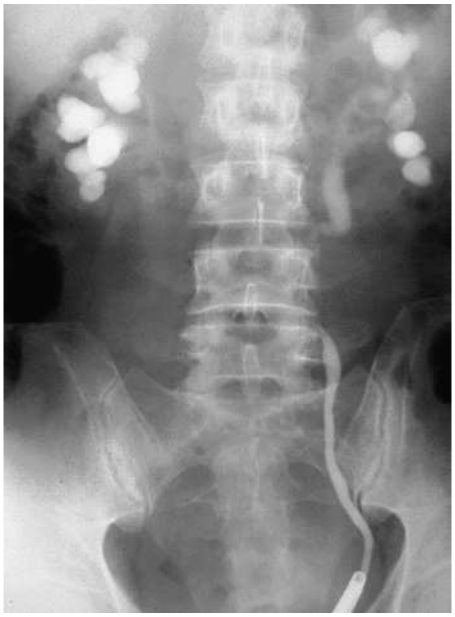


Fig. 58.2 **Retrograde pyelogram showing idiopathic retroperitoneal fibrosis.** Dilation of the pelvicalyceal system is clearly demonstrated. The ureters, however, are not dilated, and the left ureter can be seen displaced medially as a result of being encased in thick fibrous tissue.

Changes in Glomerular Function

Glomerular filtration rate (GFR) declines progressively after the onset of complete ureteral obstruction. After complete ureteral obstruction, there is an initial rise in proximal tubular pressure. This is accompanied by afferent arteriolar dilation as a result of the generation of vasodilatory prostaglandins. Although this increases glomerular capillary hydraulic pressure, it does not offset the rise in tubular pressure, and there is a decrease in the hydraulic pressure gradient across glomerular capillaries, resulting in a dramatic decline in GFR. The relative changes in ureteral pressure, renal plasma flow, and GFR are summarized in Fig. 58.3. With ongoing obstruction, there is a progressive fall in renal blood flow secondary to the generation of angiotensin II (Ang II) and thromboxane A_2, the release of vasopressin (antidiuretic hormone), and decreased nitric oxide production. An interstitial leukocyte infiltrate develops, predominantly macrophages, and promotes the late structural changes that occur after obstruction as macrophage depletion limits experimental interstitial fibrosis.[4]

The extent to which glomerular function recovers after the release of ureteral obstruction depends on the duration of the obstruction. Whole-kidney GFR may return to normal after short-term obstruction (days), whereas recovery may be incomplete after prolonged obstruction.

Changes in Tubular Function

Abnormalities in tubular function are common in urinary tract obstruction and manifest as altered renal handling of electrolytes and changes in the regulation of water excretion. The degree and nature of the tubular defects after obstruction depend in part on whether the obstruction is bilateral or unilateral. These differences could result from the

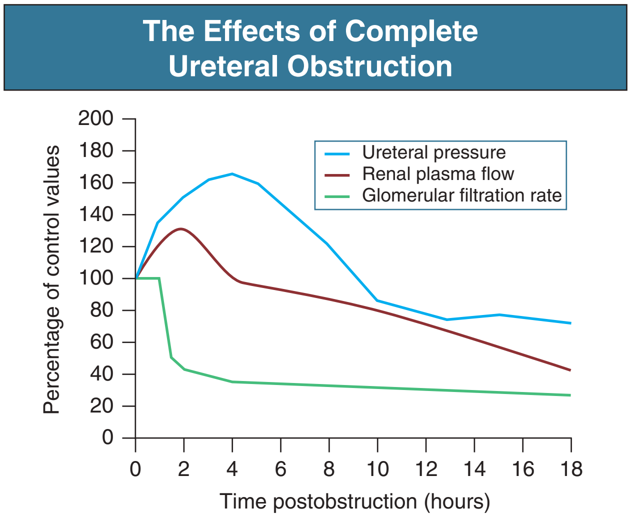


Fig. 58.3 The effects of complete ureteral obstruction. The relative changes in ureteral pressure, renal plasma flow, and glomerular filtration rate are shown using data from experimental studies of unilateral ureteral obstruction in rats.

dissimilar hemodynamic responses, different intrinsic changes within the nephron, or differences in extrinsic factors (e.g., volume expansion and accumulation of natriuretic substances in bilateral obstruction) between the two states.

After ureteral obstruction, the ability to concentrate the urine is markedly impaired, with maximum values of 350 to 400 mOsm/kg reported in the rat. Causative factors include a loss of medullary tonicity and reduced expression of sodium transporters. Also, the collecting duct is unresponsive to vasopressin because of reduced expression of renal aquaporins that results from both cyclooxygenase-2 activity and Ang II.

Rats exhibit reduced expression of multiple acid-base transporters after ureteral obstruction,[5] and patients with urinary tract obstruction often have urinary acidification defects. These defects may be detected only by exogenous acid loading, but hyperchloremic acidosis caused by impaired distal acid secretion, hyporeninemic hypoaldosteronism (type IV renal tubular acidosis), and a combination of these findings has been described. This acidifying defect results from a marked increase in bicarbonate excretion or from a distal acidification defect, possibly as a result of abnormalities of the H^+-ATPase activity of intercalated cells of the collecting duct after ureteral obstruction.

Obstruction also alters renal potassium handling. In the presence of a normal functioning contralateral kidney, potassium excretion is reduced after relief of obstruction, either in proportion to or perhaps even greater than the fall in GFR (i.e., fractional excretion of potassium is unaltered or slightly reduced). There is a defect in the distal potassium secretory mechanism after unilateral obstruction that may be secondary to reduced responsiveness of that nephron segment to aldosterone. By contrast, after release of bilateral ureteral obstruction, there is a marked increase in both net and fractional potassium excretion. The major mechanism by which potassium losses occur in this setting is an increased delivery of sodium to the distal tubule, resulting in increased sodium-potassium exchange.

Recovery of tubular function after release of obstruction is slow and may remain abnormal even after whole-kidney GFR has returned to normal. In rats, acidification and potassium-handling abnormalities persist for at least 14 days and urinary concentrating ability is abnormal for up to 60 days after the release of 24 hours of unilateral ureteral obstruction. These observations are consistent with persistent alterations in distal tubular and collecting duct function or a loss in functioning juxtaglomerular nephrons after the release of the obstruction.

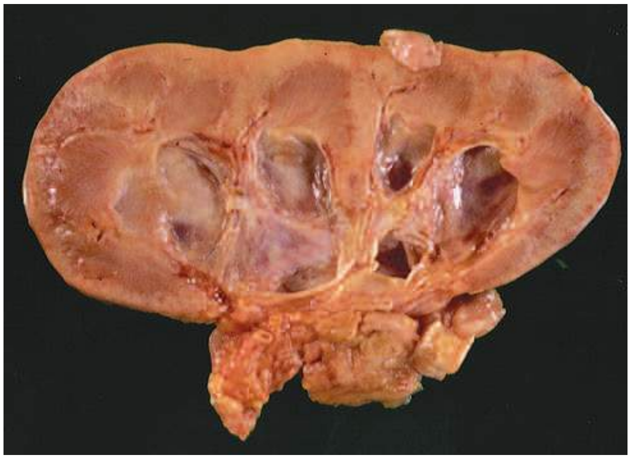


Fig. 58.4 Autopsy specimen of a kidney showing the early effects of ureteral obstruction. The kidney is enlarged and edematous with pelvicalyceal dilation. There is good preservation of the renal parenchyma.

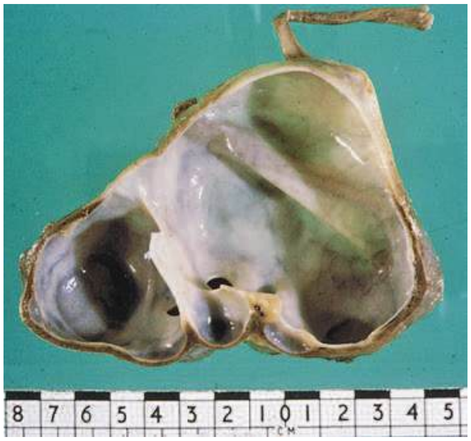


Fig. 58.5 Chronic ureteral obstruction. Surgical specimen of a kidney showing gross dilation of the pelvicalyceal system and the reduction of the renal cortex to a thin fibrotic rim of tissue. There would have been no prospect for any significant functional recovery in this kidney after the relief of the obstruction.

HISTOPATHOLOGIC CHANGES

The morphologic alterations in renal architecture are similar irrespective of the cause of the obstruction. Initially, there is renal enlargement and edema with pelvicalyceal dilation (Fig. 58.4). Tubular dilation that predominantly affects the collecting duct and distal tubular segments is seen microscopically, although cellular flattening and atrophy of proximal tubular cells also can occur. Glomerular structures are usually preserved initially, although the Bowman space may be dilated and some periglomerular fibrosis may ultimately develop.

Inadequately treated urinary tract obstruction eventually causes irreversible structural changes to the renal tract. The renal pelvis becomes widely dilated, with the renal papillae either flattened or hollowed out. The cortex and medulla become grossly thinned, such that the kidney becomes a thin rim of renal tissue surrounding a large saccular pelvis (Fig. 58.5). Histologic examination demonstrates tubulointerstitial fibrosis and profound nephron loss. Tubular proliferation and apoptosis, interstitial myofibroblast accumulation, increased extracellular matrix

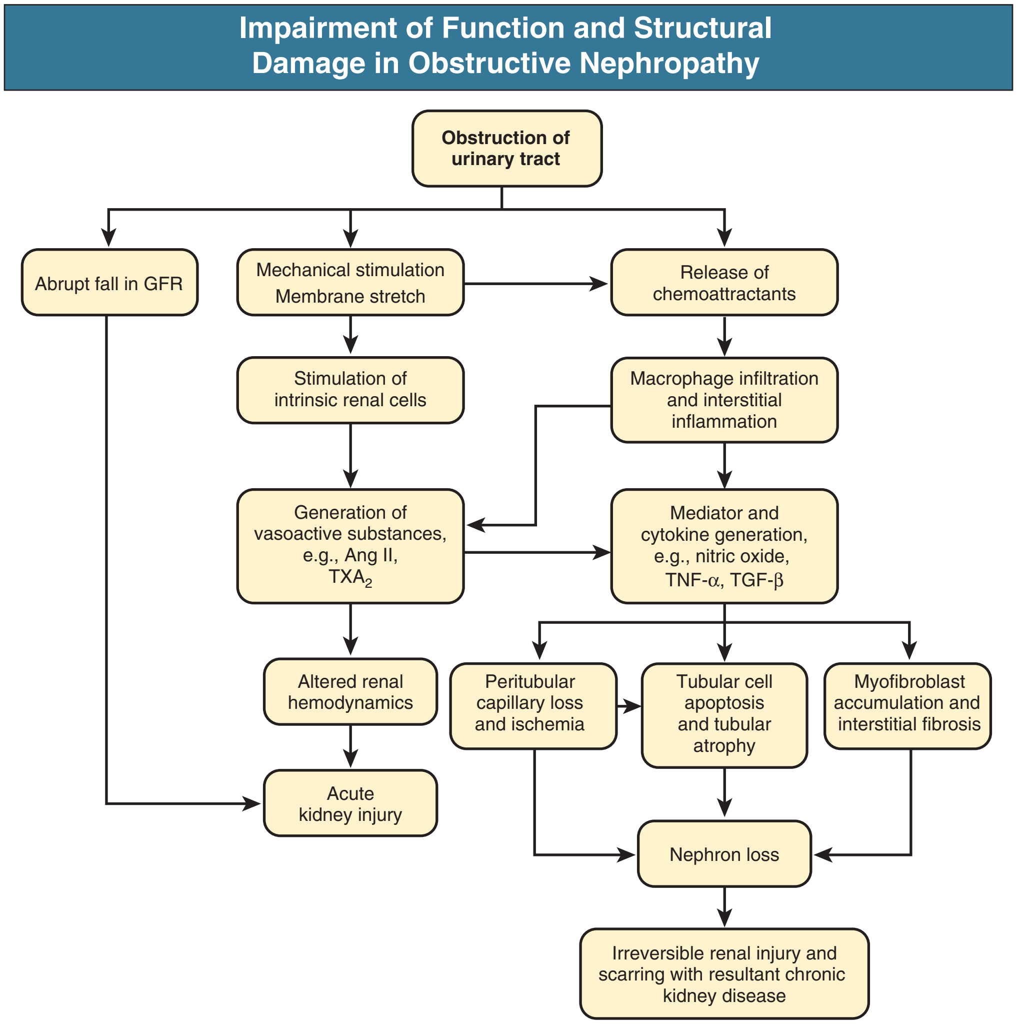

Impairment of Function and Structural Damage in Obstructive Nephropathy
Obstruction of urinary tract
Abrupt fall in GFR
Mechanical stimulation Membrane stretch
Release of chemoattractants
Stimulation of intrinsic renal cells
Macrophage infiltration and interstitial inflammation
Generation of vasoactive substances, e.g., Ang II, TXA2
Mediator and cytokine generation, e.g., nitric oxide, TNF-α, TGF-β
Altered renal hemodynamics
Peritubular capillary loss and ischemia
Tubular cell apoptosis and tubular atrophy
Myofibroblast accumulation and interstitial fibrosis
Acute kidney injury
Nephron loss
Irreversible renal injury and scarring with resultant chronic kidney disease

Fig. 58.6 Events leading to acute impairment of renal function and chronic structural damage in obstructive nephropathy. *Ang II,* Angiotensin II; *GFR,* glomerular filtration rate; *TGF-β,* transforming growth factor-β; *TNF-α,* tumor necrosis factor α; *TXA_2,* thromboxane A_2.

deposition, and tubular atrophy occur. Ischemia as a result of the decreased renal blood flow and the rarefaction of peritubular capillaries contributes to the parenchymal damage after obstruction. In both genetic and interventional studies, an important pathologic role for Ang II and transforming growth factor-β (TGF-β) has been established.[3]

Infiltrating macrophages release profibrogenic factors (e.g., TGF-β, galectin-3) and play a pivotal role in the chronic tissue injury and fibrosis that result from prolonged ureteral obstruction[4,6] (Fig. 58.6). Local Ang II generation also may stimulate tubular cell production of TGF-β. Treatments shown to ameliorate chronic interstitial damage in experimental obstructive uropathy include ARBs, pentoxifylline, simvastatin, and growth factors (such as bone morphogenetic protein 7, hepatocyte growth factor, and epidermal growth factor); beneficial effects include a reduction in tubulointerstitial inflammation, tubular cell apoptosis, and fibrosis.[3] However, it is pertinent that differences have been noted in the responses of adult and neonatal rodents to experimental therapeutic interventions and it is unclear whether such differences might occur in humans.

EPIDEMIOLOGY

Obstructive uropathy is a common entity and can occur at all ages, with the prevalence of hydronephrosis at autopsy being 3.5% to 3.8%, although this underestimates the true incidence because these figures exclude transient obstruction. The frequency and cause of obstruction vary in both sexes with age. Antenatal ultrasound has significantly increased the detection rate of lower urinary tract obstruction in the fetus.[7] In children younger than 10 years, obstruction is more common in boys; congenital urinary tract anomalies, such as urethral valves and pelviureteral obstruction, account for most cases. In North America, obstructive uropathy is a common cause of end-stage renal disease (ESRD) in children and accounts for 8.5% of cases.[8] In addition, congenital obstructive uropathy accounts for 0.7% of all patients (median age, 31 years) maintained with renal replacement therapy, demonstrating the continued impact of this disease into adult life.[9] In adults younger than 20 years, the frequency of urinary tract obstruction is similar in males and females. Beyond 20 years of age, obstruction becomes more common in females, mainly because of pregnancy and gynecologic malignancy. The peak incidence of renal calculi occurs in the second and third decades of life, with a threefold increased incidence in men. After the age of 60 years, obstructive uropathy occurs more frequently in men secondary to benign prostatic hypertrophy and prostatic carcinoma. About 30% of men older than 50 years have some symptoms of bladder outflow obstruction. In Europe, acquired urinary tract obstruction accounts for 3% to 5% of the cases of ESRD in patients older than 65 years, with most resulting from prostatic disease.[10] In the

United States, the number of patients receiving renal replacement therapy as a result of acquired obstruction continues to increase, accounting for 1.4% of prevalent patients, although the rise is not as rapid as with other causes of ESRD.[9]

CLINICAL MANIFESTATIONS

Obstruction of the urinary tract can present with a wide range of clinical symptoms, depending on the site, degree, and duration of obstruction. The clinical manifestations of upper and lower urinary tract obstruction differ. Symptoms can be caused by mechanical obstruction of the urinary tract (usually pain) or can result from the complex alterations in glomerular and tubular function that may occur in obstructive nephropathy. The latter commonly manifests as alterations in urine volume and as renal failure, which can be acute or chronic. For example, patients with complete obstruction present with anuria and AKI, whereas those with partial obstruction may present with polyuria and polydipsia secondary to acquired vasopressin resistance. Alternatively, there may be a fluctuating urine output, alternating from oliguria to polyuria. However, obstructive uropathy and hence obstructive nephropathy can occur without symptoms and with minimal clinical manifestations. Therefore obstruction of the urinary tract must be considered in the differential diagnosis of any patient with renal impairment.

Pain

Pain is a frequent complaint in patients with obstructive uropathy, particularly in those with ureteral calculi. The pain is believed to result from stretching of the collecting system or the renal capsule. The location of the pain may help determine the site of obstruction. With upper ureteral or pelvic obstruction, flank pain and tenderness typically occur, whereas lower ureteral obstruction causes pain that radiates to the groin, the ipsilateral testicle, or the labia. Acute high-grade ureteral obstruction may be accompanied by a steady and severe crescendo flank pain radiating to the labia, the testicles, or the groin (classic renal colic). The acute attack may last less than half an hour or as long as a day. By comparison, patients with chronic slowly progressive obstruction may have no pain or minimal pain; in such patients, any pain that does occur is rarely colicky. In PUJ obstruction, pain may occur only after fluid loading to promote a high urine flow rate.

Lower Urinary Tract Symptoms

Obstructive lesions of the urethra or bladder neck or bladder disease may cause a decrease in the force or caliber of the urine stream, intermittency, postmicturition dribbling, hesitancy, or nocturia. Urgency, frequency, and urinary incontinence can result from incomplete bladder emptying. Indeed, the development of nocturnal incontinence suggests chronic urinary retention that may be associated with painless renal failure. Such symptoms commonly result from prostatic hypertrophy and are frequently referred to as *prostatism*, but they are not pathognomonic of this condition.

Urinary Tract Infections

Urinary stasis resulting from obstruction predisposes to urinary tract infections (UTIs), and patients may develop cystitis with dysuria and frequency or pyelonephritis with loin pain and systemic symptoms. Infection occurs more often in patients with lower urinary tract obstruction than in those with upper urinary tract obstruction.

UTI in men or young children of either sex, recurrent or persistent infections in women, infections with unusual organisms such as *Pseudomonas* spp., and a single attack of acute pyelonephritis require further investigation to exclude obstruction. Also, the presence of obstruction makes effective eradication of the infection difficult. Infections of the urinary tract with a urease-producing organism such as *Proteus mirabilis* predispose to stone formation. These organisms generate ammonia, which results in urine alkalinization and favors the development of magnesium ammonium phosphate (struvite) stones. Struvite calculi can fill the entire renal pelvis to form a staghorn calculus that eventually leads to loss of the kidney if it is untreated. Thus stone formation and papillary necrosis also can be consequences of urinary tract obstruction as well as causes of obstruction.

Hematuria

Calculi may cause trauma to the urinary tract uroepithelium and result in either macrohematuria or microhematuria. Any neoplastic lesion that obstructs the urinary tract, especially uroepithelial malignancies, may bleed, resulting in macrohematuria. Urinary tract bleeding may result in obstruction, giving rise to clot colic when it is in the ureter or clot retention when it is in the bladder.

Changes in Urine Output

Complete bilateral obstruction or unilateral obstruction of a single functioning kidney such as a renal transplant will result in anuria. However, when the lesion results in partial obstruction, urine output may be normal or increased (polyuria). A pattern of alternating oliguria and polyuria or the presence of anuria strongly suggests obstructive uropathy.

Abnormal Physical Findings

Physical examination can be completely normal. Some patients with upper urinary tract obstruction may have flank tenderness. Long-standing obstructive uropathy may result in an enlarged palpable kidney in children. Lower urinary tract obstruction causes a distended, palpable, and occasionally painful bladder. A rectal examination and, in women, a pelvic examination should be performed because they may reveal a local malignancy or prostatic enlargement.

Acute or chronic hydronephrosis, either unilateral or bilateral, may cause hypertension secondary to impaired sodium excretion with expansion of extracellular fluid volume or from the abnormal release of renin. On occasion, in patients with partial urinary tract obstruction, polyuria, and volume depletion lead to hypotension.

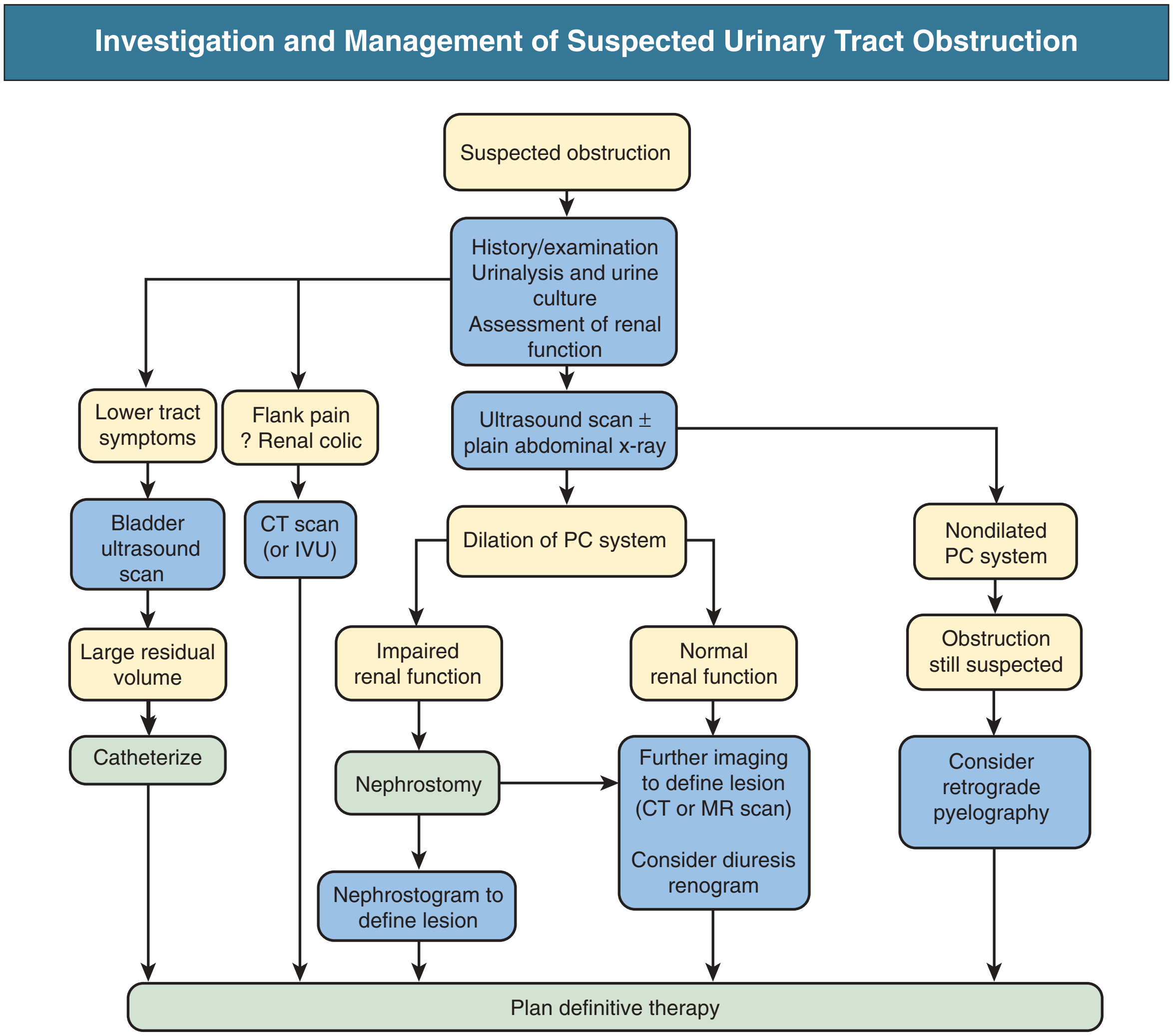
Abnormal Laboratory Findings

Urinalysis may show hematuria, bacteriuria, pyuria, crystalluria, and low-grade proteinuria, depending on the cause of obstruction. However, urinalysis may be completely negative despite advanced obstructive nephropathy. In the acute phase of obstruction, urinary electrolyte values are similar to those seen in a prerenal state, with a low urinary sodium concentration (<20 mmol/l), a low fractional excretion of sodium (<1%), and a high urinary osmolality (>500 mOsm/kg). However, with more prolonged obstruction, a decreased ability to concentrate the urine and an inability to reabsorb sodium and other solutes occur. These changes are particularly marked after the release of chronic obstruction and give rise to the syndrome commonly referred to as postobstructive diuresis.

Increases in serum urea and creatinine are the most significant laboratory abnormalities in patients with obstructive uropathy. Electrolyte abnormalities may occur, including hyperchloremic hyperkalemic (type 4) metabolic acidosis or hypernatremia from acquired nephrogenic diabetes insipidus. The development of obstruction in patients with underlying CKD may accelerate the rate of progression. ESRD may occasionally be caused by chronic obstructive uropathy that had been asymptomatic.

Obstruction in Neonates or Infants

With the advent of routine antenatal scanning, the diagnosis of hydronephrosis and genitourinary abnormalities is now frequently made


Investigation and Management of Suspected Urinary Tract Obstruction

Suspected obstruction
History/examination Urinalysis and urine culture Assessment of renal function
Lower tract symptoms
Flank pain ? Renal colic
Ultrasound scan ± plain abdominal x-ray
Bladder ultrasound scan
CT scan (or IVU)
Dilation of PC system
Nondilated PC system
Large residual volume
Impaired renal function
Normal renal function
Obstruction still suspected
Catheterize
Nephrostomy
Further imaging to define lesion (CT or MR scan)
Consider diuresis renogram
Consider retrograde pyelography
Nephrostogram to define lesion
Plan definitive therapy

Fig. 58.7 **Investigation and management of suspected urinary tract obstruction.** A full history and examination should be performed, together with urinalysis, urine microscopy and culture, and measurement of renal function and serum electrolytes. Ultrasound is a useful first-line investigation for any patient with suspected urinary tract obstruction. Computed tomography *(CT)* is now the preferred imaging technique when renal calculi are suspected. Either CT or magnetic resonance *(MR)* urography can accurately diagnose both the site and cause of obstruction in most cases. If there is renal impairment, a nephrostomy or stenting allows the effective relief of the obstruction and time for renal function to recover while definitive therapy is planned. *IVU,* Intravenous urography; *PC,* pelvicalyceal.

antenatally; however, unsuspected obstructive uropathy may present in the postnatal period with failure to thrive, voiding difficulties, fever, hematuria, or symptoms of renal failure. Oligohydramnios at the time of delivery should raise the suspicion of obstructive uropathy, as should the presence of congenital anomalies of the external genitalia. Nonurologic anomalies such as ear deformities, a single umbilical artery, imperforate anus, or a rectourethral or rectovaginal fistula should prompt investigation for urinary tract obstruction. Any infant with neurologic abnormalities may have a neurogenic bladder with associated obstructive uropathy.

DIAGNOSIS

Prompt diagnosis of urinary tract obstruction is essential to allow timely treatment. Symptoms such as renal colic may suggest the diagnosis and prompt appropriate investigation. However, urinary tract obstruction should be considered in any patient with unexplained acute or chronic kidney impairment. The diagnostic approach must be tailored to the clinical presentation (Fig. 58.7), but a careful history and thorough physical examination are mandatory in all patients.

Urinalysis may provide valuable diagnostic information. Hematuria suggests that the obstructing lesion is a calculus, sloughed papilla, or tumor. Bacteriuria suggests urinary stasis, especially in men or pregnant women, but it also may be a complication of chronic obstruction. The presence of crystals in the urine sediment (cystine or uric acid) may be an indication of the type of stone causing the ureteral obstruction or the intrarenal obstruction resulting in AKI. Laboratory studies must include assessment of renal function and serum electrolytes.

Imaging

Because the sites, causes, and consequences of obstruction to the renal tract are so variable, no single imaging investigation can diagnose or exclude renal tract obstruction with certainty. Therefore if the clinical suspicion of obstruction is high, the patient may require investigation with multiple imaging techniques.

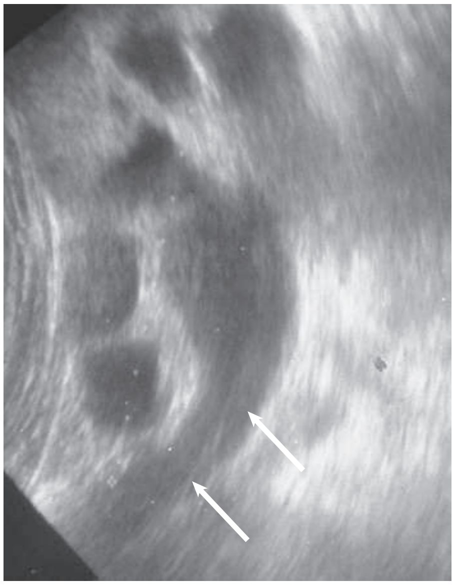


Fig. 58.8 Renal ultrasound scan of a patient with obstruction of the urinary tract causing hydronephrosis. The kidney is hydronephrotic with dilation of the pelvicalyceal system; dilation of the upper ureter is also clearly seen *(arrows).*

Ultrasound is the most widely used imaging modality, but computed tomography (CT) scanning and magnetic resonance (MR) urography are increasingly used to accurately diagnose both the site and cause of obstruction. Although much less commonly used, older imaging techniques, such as intravenous urography (IVU), can be used to evaluate patients with obstructive uropathy. The role of imaging techniques is shown in Fig. 58.7 and discussed further in Chapter 5.

Ultrasound

Ultrasound can define renal size and demonstrate calyceal dilation[11] but depends on the expertise of the operator (Fig. 58.8). Although it is sensitive for detection of hydronephrosis, ultrasound often will not determine its cause. Pathologic change within the ureter is difficult to demonstrate, and tiny stones will not generate acoustic shadows. However, unilateral hydronephrosis suggests obstruction of the upper urinary tract by stones, blood clots, or tumors. Bilateral hydronephrosis is more likely to result from a pelvic problem obstructing both ureters or obstruction of the bladder outlet, in which case the bladder will also be enlarged. Ultrasound should be combined with radiographic examination of the kidneys, ureters, and bladder (KUB) to ensure that ureteral stones or small renal stones are not overlooked.

Ultrasound produces false-negative results in cases of nondilated obstructive uropathy.[11] Immediately after acute obstruction (within 24 hours), the relatively noncompliant collecting system may not have dilated, so ultrasound examination findings may be normal. Furthermore, if urine flow is low, as in severe dehydration or renal failure, there may be little dilation of the urinary tract. Dilation also may be absent in slowly progressive obstruction when the ureters are encased by fibrous tissue (as in retroperitoneal fibrosis) or by tumor, and in some renal transplants in which there is dense surrounding scar tissue. The acoustic shadow of a staghorn calculus also can mask dilation of the upper urinary tract. In view of this it is advisable to repeat the renal ultrasound if suspicion of obstruction is high. The sensitivity of ultrasound for diagnosis of obstruction can be improved by measuring the resistive index with color Doppler sonography. A resistive index above 0.7 reflects the increased vascular resistance present in obstruction and can assist discrimination between obstructed and nonobstructed kidneys,[11] though the resistive index can be increased in other conditions.[12] Such ultrasound techniques are particularly useful when it is especially important to minimize radiation exposure, for example, in pregnant women and children, and in the follow-up of patients requiring repeated imaging, such as after extracorporeal shock wave lithotripsy.

Even in experienced hands, ultrasound may have a significant false-positive rate, especially if minimal criteria are adopted to diagnose obstruction. In addition, the echogenicity produced by multiple renal cysts may be mistaken for hydronephrosis.

Ultrasound scanning can be used to assess bladder emptying and should be undertaken in patients with lower urinary tract symptoms, being performed at the bedside if necessary. The normal postmicturition residual volume is less than 50 ml (<100 ml is usually acceptable in patients older than 65 years), and a large postmicturition residual volume suggests bladder outflow obstruction, which should prompt further urologic investigation and treatment.

The investigation of neonates with hydronephrosis diagnosed antenatally depends on the grade of hydronephrosis identified. Neonates with grade 1 or 2 hydronephrosis (no calyceal dilation) undergo ultrasound scanning; neonates with grade 3 or 4 hydronephrosis (indicating increasingly severe pelvicalyceal dilation) require both ultrasound scanning and voiding cystourethrography.[13] This combination can distinguish megaureter resulting from obstruction or reflux and enable the diagnosis of posterior urethral valves and UPJ obstruction. Recent work suggests that using measurements of both calyceal dilation and the anteroposterior diameter of the renal pelvis at the first postnatal ultrasound may be able to distinguish those children who will require surgery, but this grading system will require further validation.[14]

Plain Abdominal Radiography

A plain abdominal radiograph (or KUB) allows an assessment of kidney size and contour and frequently demonstrates renal calculi because about 90% of calculi are radiopaque.

Intravenous Urography

IVU was formerly the first-choice investigation for suspected upper urinary tract obstruction. In patients with normal renal function, it can usually define both the site and the cause of the obstruction. However, the excretion of contrast material may be poor or delayed in patients with low GFR because of a decreased filtered load of the contrast agent, which is potentially nephrotoxic. IVU is no longer a first-line investigation to diagnose urinary tract obstruction, especially in patients with impaired renal function.

Computed Tomography

Non–contrast-enhanced spiral CT scanning is used increasingly as the primary imaging modality for the evaluation of patients with acute flank pain[15] and uses a low-dose protocol compared with conventional CT scanning of abdomen and pelvis.[16] Stones are easily detected because of their high density; CT can provide an accurate and rapid diagnosis of an obstructing ureteral calculus, with a stone being found more commonly in men.[17] In addition, it provides useful information about the site and nature of the obstructing lesion, especially when this is extrinsic to the urinary tract (Fig. 58.9; see also Chapter 59, Fig. 59.1), though a higher dose CT scan may be required for a full diagnostic study. CT demonstrates retroperitoneal disease, such as paraaortic and paracaval lymphadenopathy; retroperitoneal fibrosis is evident as increased attenuation within the retroperitoneal fat, with encasement of one or both ureters. Hematomas, primary ureteral tumors, and polyps are also detectable. The diagnostic potential of CT is enhanced by the administration of contrast material, but this may limit its use in patients

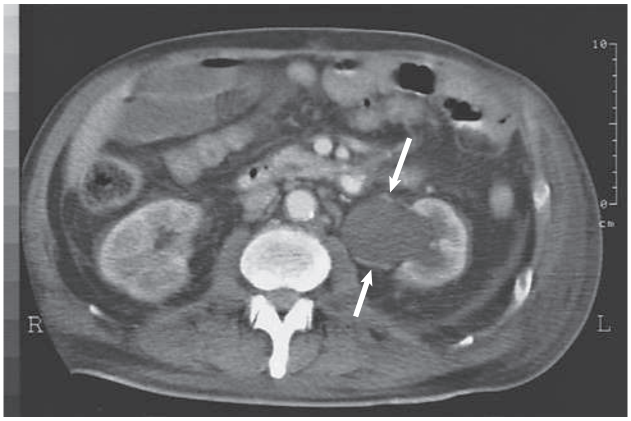


Fig. 58.9 **Computed tomography scan of the abdomen showing a grossly hydronephrotic kidney on the left (*arrows* mark dilated renal pelvis).** Dilated loops of small bowel are seen in the right hypochondrium. Sequential sections demonstrated that the ureter was dilated along its length and that there was a pelvic mass, which was responsible for both bowel and left ureteral obstruction. The mass was subsequently shown to be arising from a carcinoma of the colon.

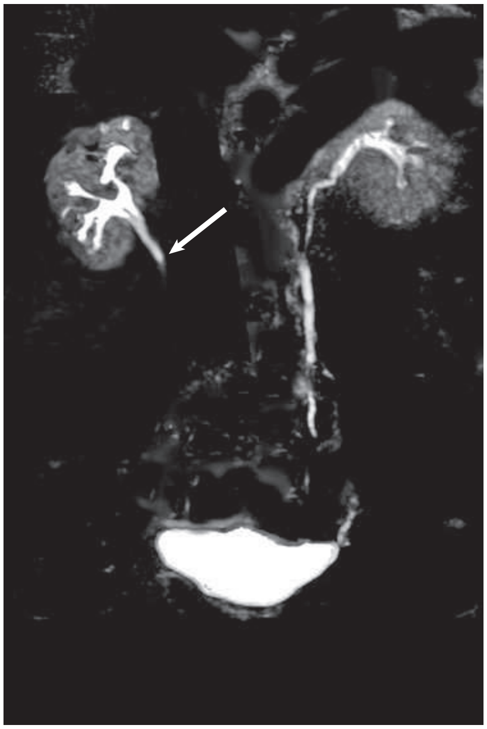


Fig. 58.10 **MR urography showing obstructive uropathy.** T2-weighted MR image showing a proximal right-sided ureteric ureteral obstruction with an associated mild hydronephrosis. The obstruction was secondary to a ureteral calculus.

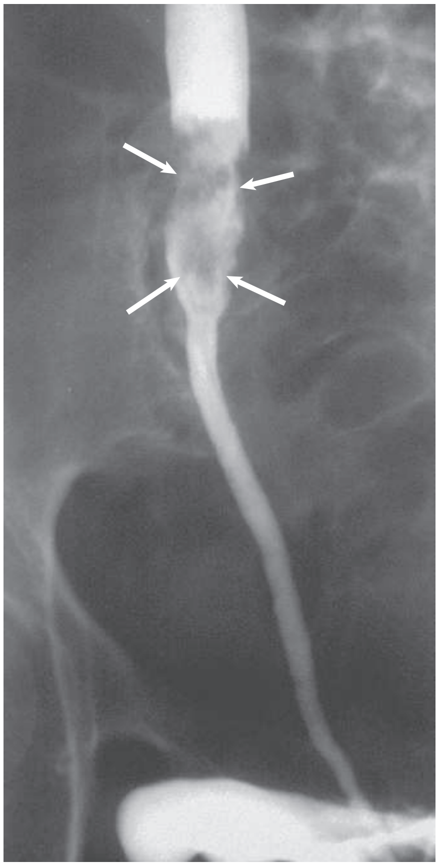


Fig. 58.11 **Ureteral obstruction by a tumor.** A retrograde pyelogram shows the tumor is within and obstructing the ureter *(arrows)*. Above the tumor, there is dilation of the ureter, but below it, the ureter is of a normal caliber.

with renal impairment. In addition, it involves exposure to ionizing radiation, especially if patients require multiple CT scans over time.

Magnetic Resonance Urography

MR urography (combined with KUB) can enable the diagnosis of ureteral obstruction caused by renal calculi with accuracy similar to that of spiral CT scanning but without exposure to contrast medium or ionizing radiation. The technique has less observer variability and is more accurate than CT in detecting indirect evidence of obstruction, such as perirenal fluid. MR urography can rapidly and accurately depict the morphologic features of dilated urinary tracts and provide information about the degree and level of obstruction[18] (Fig. 58.10). MR urography is a particularly attractive imaging modality for the evaluation of hydronephrosis in children because it provides both anatomic and functional data and can indicate whether the hydronephrosis is compensated (symmetric changes of signal intensity of the nephrogram) or decompensated.[19] Signs of decompensation (acute on chronic obstruction) include edema of the renal parenchyma, a delayed and increasingly dense nephrogram, a delayed calyceal transit time, and a more than 4% difference in the calculated differential renal function. MR urography is likely to be increasingly used in the future.

Retrograde Pyelography

Retrograde pyelography (Fig. 58.11; see also Fig. 58.2) usually requires a general anesthetic and cystoscopy but may be particularly useful to identify both the site and the cause of the obstruction because intervention (by stenting or dilatation) and biopsy of a suspected tumor (by ureteroscopy) are both possible. It is also helpful when nondilated urinary tract obstruction is suspected or when there is a history of allergic reactions to contrast material.

Diuresis Renography

A diuresis renogram using technetium-99m mercaptoacetyltriglycine (^{99m}Tc-MAG3), combined with intravenous furosemide administered 20 to 30 minutes after injection of the isotope (diuretic isotopic renography), can be used to distinguish between simple dilation of the

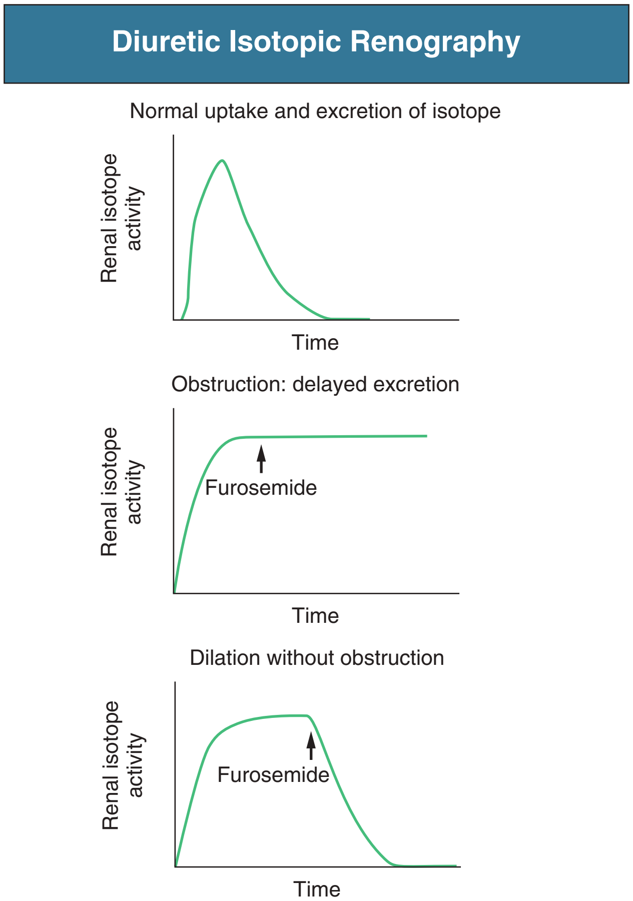


Fig. 58.12 Diuretic isotopic renography. Idealized tracings for normal, obstructed, and dilated kidneys without obstruction of the upper urinary tract. In obstruction, there is delayed excretion of ^{99m}Tc-MAG3 despite administration of furosemide. When there is dilation of the upper urinary tract without obstruction, the isotope is retained but is rapidly excreted after the administration of furosemide.

collecting system and true obstruction.[20] Normally, there is a rapid washout of the isotope from the kidney, and persistence of the isotope suggests a degree of obstruction (Fig. 58.12). Poor renal function significantly limits the usefulness of renography because the diuretic response to furosemide may be absent. Diuresis renography also may be used for follow-up of patients who have undergone surgical procedures to relieve obstruction, such as a pyeloplasty.

Pressure Flow Studies

A pressure flow study (Whitaker test) involves puncture of the collecting system with a fine-gauge needle to perfuse fluid (at 10 ml/min) with concurrent measurement of the differential pressure between the bladder and the collecting system; a pressure greater than 20 cm H_2O indicates obstruction. Although this test is rarely required, it may be informative in patients with potential upper tract obstruction when other, less invasive tests have generated equivocal results.[21]

Other Evaluations

Lower urinary tract obstruction may be evaluated by cystoscopy, which allows a visual inspection of the entire urethra and the bladder. Urodynamic studies (see Chapter 50, Fig. 50.14) can assess bladder outlet obstruction, measure the residual urine volume after voiding, and detect functional bladder abnormalities.

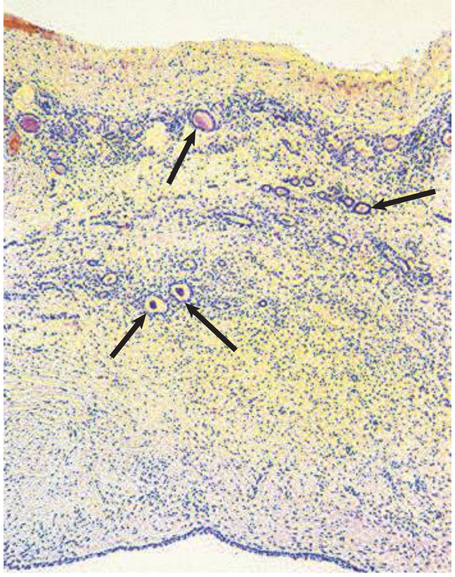


Fig. 58.13 Pathology of chronic ureteral obstruction. This is a section of the rim of renal tissue from the kidney shown in Fig. 58.7. The renal capsule is at the top, the urinary space at the bottom. The cortex is considerably thinned, and only a few atrophic tubules remain *(arrows)* within an interstitium comprising dense fibrous tissue and a mononuclear cell infiltrate *(blue staining nuclei).* No glomeruli can be seen. This demonstrates why there would be no prospect for any significant functional recovery in this kidney even after the relief of the obstruction.

DIFFERENTIAL DIAGNOSIS

Diagnostic uncertainty arises with nonobstructive dilation of the upper urinary tract, which may be seen with vesicoureteral reflux, diuretic administration, diabetes insipidus, congenital megacalyces, chronic pyelonephritis, and postobstructive atrophy. Diuresis renography or retrograde pyelography may be required to exclude obstruction.

NATURAL HISTORY

Obstructive uropathy is potentially curable but will result in progressive irreversible loss of nephrons and renal scarring if it is left untreated (Fig. 58.13). ESRD will result if both kidneys are affected or if there is only a solitary kidney. Outcome data for obstructive uropathy are limited, but the exact prognosis will depend on the pathologic process responsible for the obstruction, duration of the obstruction, and presence or absence of urosepsis. Relief of short-term obstruction (<1 to 2 weeks) usually results in an adequate return of renal function. With chronic progressive obstruction (>12 weeks), there is often irreversible and severe renal damage, and renal functional recovery may be limited even after relief of the obstruction. A single-center study identified 104 patients who presented with obstructive nephropathy.[22] The mean GFR at presentation and at 3, 12, and 36 months was 9, 28, 29, and 30 ml/min, respectively (patients on dialysis excluded), demonstrating significant but nonprogressive renal impairment after relief of obstruction. It is likely that the prognosis for renal functional recovery is better the earlier the obstruction is diagnosed and relieved.

TREATMENT

General Considerations

Treatment is dictated by the location of the obstruction, the underlying cause, and the degree of any renal impairment. If renal impairment is

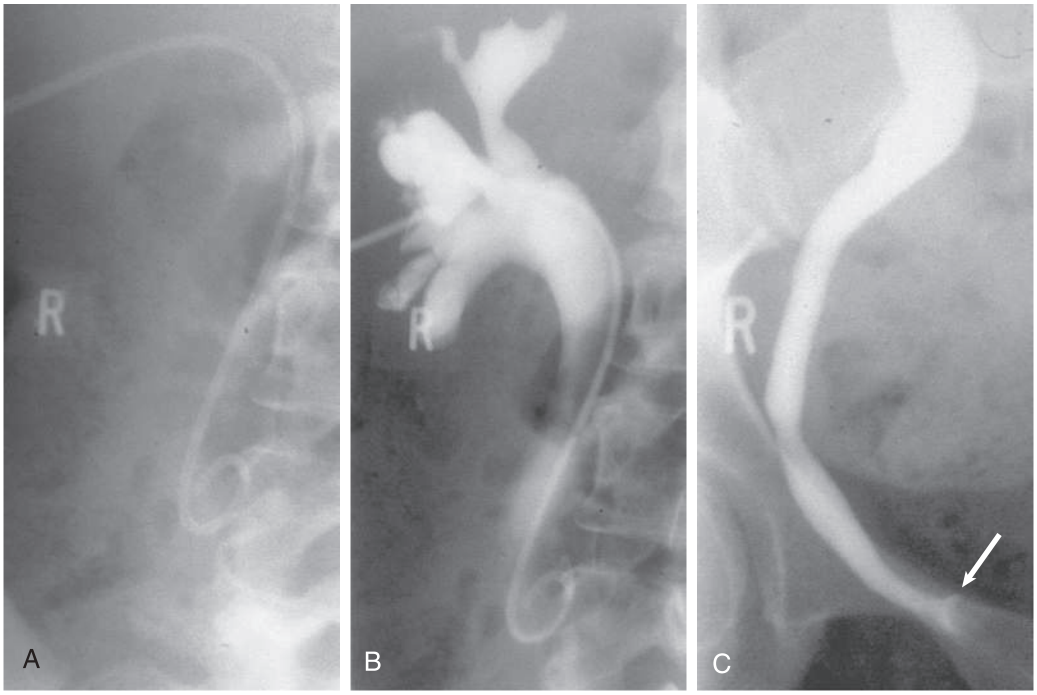


Fig. 58.14 Nephrostogram. A nephrostomy has been placed percutaneously into the dilated collecting system of the kidney under ultrasound control (A). After infusion of contrast material down the nephrostomy, the dilated pelvicalyceal system and upper ureter (B) and the lower ureter (C) are outlined. The ureter is dilated along its length but tapers abruptly at the vesicoureteral junction *(arrow).* In this case, the obstruction was caused by a radiolucent stone.

present, the treatment of obstruction requires close collaboration between nephrologists and urologists to reduce the risks associated with the metabolic and electrolyte consequences of renal failure and to optimize the chances for long-term recovery of renal function. For example, complete bilateral ureteral obstruction manifesting as AKI is a medical emergency and requires rapid intervention to salvage renal function. Prompt intervention to relieve the obstruction should result in a rapid improvement in renal function. Dialysis rarely should be required in patients with AKI secondary to obstruction except to make the patient fit for intervention, for example, by improving life-threatening hyperkalemia or severe fluid overload. The rapid relief of obstruction will limit permanent renal damage but renal function may not recover immediately if acute tubular injury has resulted from obstruction or any accompanying sepsis.

Some surgical aspects of the management of obstructive uropathy are discussed in Chapter 59. The site of obstruction frequently determines the approach. If the obstruction is distal to the bladder, a urethral catheter or, if this cannot be passed, a suprapubic cystostomy, will effectively decompress the kidneys. Placement of nephrostomy tubes or cystoscopy and passage of a retrograde ureteral stent will relieve upper urinary tract obstruction. Percutaneous nephrostomy (PCN) is generally the appropriate emergency treatment for upper urinary tract obstruction, especially in the setting of AKI. PCN can be achieved with local anesthetic and should allow rapid recovery of renal function in most patients (>70%), avoiding the need for dialysis. After relief of the obstruction by a nephrostomy, the exact site and nature of the obstructing lesion can be determined by an antegrade study infusing radiographic contrast material into the nephrostomy tube (nephrostogram), and time can be taken to plan definitive therapy (Fig. 58.14). Major complications of nephrostomy insertion (abscess, infection, and hematoma) occur in less than 5% of patients. If both kidneys are obstructed, the nephrostomy should initially be placed in the kidney with the most preserved renal parenchyma, although bilateral nephrostomies may be required to maximize the potential for the recovery of renal function. If infection occurs above a ureteral obstruction (pyonephrosis), drainage of the kidney by PCN can play an important therapeutic role together with appropriate antibiotics.

A nephrostomy can be used to gauge the potential for functional recovery in patients with chronic obstruction. Failure of renal recovery after several weeks of nephrostomy drainage strongly suggests irreversible structural damage and thus no likely benefit from undertaking a more definitive surgical correction of the obstructing lesion. Long-term nephrostomy or stenting may be used as a definitive therapy for patients who are unsuitable for major surgical intervention and those with incurable malignant disease, though patient selection is important in the latter[23] (see Chapter 59 for further discussion). Various types of stent are now available, and there is some evidence that metallic stents may provide more durable functional decompression in patients with malignant ureteric obstruction.[24]

Ureteral obstruction requiring intervention occurs in up to 3% of renal transplant recipients.[25] It can be treated by nephrostomy and ureteral stenting, percutaneous incision or balloon dilation of the stricture, or open surgical repair (see Chapter 103).

Specific Therapies

Calculi are the most common cause of ureteral obstruction, and their treatment includes relief of pain, elimination of obstruction, and treatment of infection (see Chapters 57 and 59). Ureteral obstruction by papillary tissue, blood clots, or a fungus ball is treated by procedures similar to those used for calculi. When obstruction is caused by neoplastic, inflammatory, or neurologic disease, there is unlikely to be spontaneous remission of the obstruction, and some form of urinary diversion, such as an ileal conduit, or long-term intermittent ureteral stenting should be considered. Some obstructing neoplastic lesions, such as lymphadenopathy from lymphoma, may respond to chemotherapy. Management of malignant urinary tract obstruction is discussed further in Chapter 59.

In idiopathic retroperitoneal fibrosis, ureterolysis (in which the ureters are surgically freed from their fibrous encasement) may be beneficial, especially if combined with corticosteroid therapy to prevent recurrence. A recent retrospective study demonstrated the effectiveness of ureteral stent insertion and corticosteroids in idiopathic retroperitoneal fibrosis[26]; retroperitoneal fibrosis complicating IgG4 disease may respond to corticosteroid treatment.[2] Although kidney obstruction per se results in renal inflammation involving multiple immune cells irrespective of the underlying cause, there are no published trials of therapies that target the immune system in this patient cohort. Although pharmacologic blockade of the renin-angiotensin system is not instituted in the acute setting, it is reasonable to employ angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors in patients with residual CKD.

Functionally significant PUJ obstruction should be corrected surgically; minimally invasive and robotic techniques have largely replaced the open (Anderson-Hynes) pyeloplasty. The laparoscopic approach results in significantly less morbidity and has good long-term outcomes that are comparable to those of the open procedure.[27] Balloon dilation of the abnormal segment of the ureter is also possible, but the recurrence rate is high. The severity of renal fibrosis and atrophy as assessed on intraoperative wedge renal biopsy in patients undergoing open PUJ surgery can be used to predict functional outcome.[28] There is increasing interest in the usefulness of urine proteomics to identify neonates with UPJ obstruction who require surgical intervention,[29] although a subsequent small study indicated that this approach was less specific and sensitive in older children.[30] Urinary biomarkers that show altered levels in children or adult patients with obstructive nephropathy include established well-studied AKI biomarkers (kidney injury molecule-1, neutrophil gelatinase–associated lipocalin, and liver-type fatty acid binding protein),[31] aquaporin-2, L1 cell adhesion molecule, and TGF-β,[32] as well as epidermal growth factor, monocyte chemotactic protein-1, and β_2-microglobulin.[33] Interestingly, a reduction in urinary epidermal growth factor is also seen in patients with CKD and is a predictor of CKD progression,[34] suggesting that urinary biomarkers may well facilitate the future stratification of patients with obstructive nephropathy and assist with predicting functional outcome after intervention.

Benign prostatic hypertrophy is the most common cause of lower urinary tract obstruction in men and may be mild and nonprogressive. A patient with minimal symptoms, no infection, and a normal upper urinary tract can continue with assessment until he and his physician agree that further treatment is desirable. Medical therapy with either α-adrenergic blockers (e.g., tamsulosin) or 5α-reductase inhibitors (e.g., finasteride) may be used in patients with moderate symptoms.[35] α-Blockers relax the smooth muscle of the bladder neck and prostate and decrease urethral pressure and outflow obstruction. 5α-Reductase inhibitors inhibit the conversion of testosterone to the active metabolite dihydrotestosterone and reduce prostatic hypertrophy. Combination therapy with these agents may be synergistic. Surgical intervention with transurethral resection of the prostate is generally required for failed medical treatment, debilitating symptoms, urinary retention, recurrent infection, or evidence of renal parenchymal damage. Holmium laser enucleation of the prostate is a less traumatic alternative to transurethral resection of the prostate with good short-term and long-term outcomes.[36]

Urethral strictures in men can be treated by dilation or direct-vision internal urethrotomy before definitive urethroplasty, although urethral stenting is evolving. The incidence of bladder neck and urethral obstruction in women is low and treatment rarely required. Suprapubic cystostomy may be necessary for bladder drainage in patients unable to void after injury to the urethra or in those who have an impassable urethral stricture.

When obstruction results from neuropathic bladder function, urodynamic studies are essential to guide therapy. The goals of therapy are to establish the bladder as a urine storage organ without causing renal parenchymal injury and provide a mechanism for bladder emptying acceptable to the patient. Patients may have either a flaccid atonic or an unstable hypertonic bladder. Ureteral reflux and parenchymal damage may develop in both cases, although it is more common in patients with a hypertonic bladder. Asking the patient to void at regular intervals may achieve satisfactory emptying of the bladder. Patients with an atonic bladder and significant residual urine retention associated with recurrent urosepsis need to undertake clean intermittent self-catheterization. The aim should be to catheterize four or five times per day to ensure the amount of urine drained from the bladder on each occasion is less than 400 ml. External sphincterotomy has been used in men with an atonic bladder and may relieve outlet obstruction and promote bladder emptying, but it may cause urinary incontinence and the need to wear an external collection device. In patients with a hypertonic bladder, improvement in the storage function of the bladder may be obtained with anticholinergic agents or intermittent detrusor injection with botulinum toxin. Occasionally, chronic clean intermittent self-catheterization is necessary.

Whenever possible, chronic indwelling catheters should be avoided in patients with a neurogenic bladder because they may lead to the formation of bladder stones, urosepsis, and urethral erosion, and they predispose to squamous cell carcinoma of the bladder. Patients who have chronic indwelling catheters for more than 5 years should have annual cystoscopic examinations. If deterioration in renal function occurs despite conservative measures or there is intractable incontinence or a small contracted bladder, an upper urinary tract diversion procedure such as an ileal conduit may be required.

Management of Postobstructive Diuresis

Marked polyuria (postobstructive diuresis) is frequently seen after the release of bilateral obstruction or obstruction of a single functioning kidney. Indeed, a diuresis of greater than 7 liters per day is associated with a good functional outcome.[37] Release of unilateral obstruction rarely results in a postobstructive diuresis despite the presence of tubular dysfunction and a concentrating defect. This is because of intrinsic differences in the tubular response to unilateral and bilateral obstruction and, more importantly, the salt and water retention and renal impairment that occurred in bilateral obstruction (not evident in unilateral obstruction because of the contralateral normal kidney). The resultant increase in natriuretic factors (including atrial natriuretic peptide) and substances able to promote an osmotic diuresis such as urea promote an appropriate postobstructive diuresis to excrete water and electrolytes that were retained during the period of obstruction. However, the postobstructive diuresis also may be inappropriate because of tubular dysfunction and, if not managed correctly, may result in severe volume depletion and electrolyte imbalance with continued renal dysfunction. Intravenous and oral fluid replacement is usually required, with careful and regular assessment of the fluid balance and serum electrolytes to tailor the fluid replacement regimen appropriately. Once the patient is deemed euvolemic, urine losses plus an allowance for insensible losses should be replaced. Urine volume should be measured regularly (hourly) to facilitate fluid administration, and serum electrolytes should be measured at least daily and as frequently as every 6 hours when there is a massive diuresis. Daily weighing of the patient is also helpful. Replacement fluid regimens should include sodium chloride and a source of bicarbonate and potassium. Calcium, phosphate, and magnesium replacement also may be necessary.

If fluid administration is overzealous, the kidney will not recover its concentrating ability, and a continued "driven" diuresis will result. It may then be necessary to decrease fluid replacement to levels below those of the urine output and observe the patient carefully for signs of volume depletion.

Future Prospects

Understanding the pathophysiologic changes that follow ureteral obstruction has allowed the development of rational interventional therapies to hasten the recovery of renal function and limit permanent renal damage. Although the best treatment option in humans remains prompt and effective relief of the obstruction, development and implementation of improved imaging modalities that provide more sophisticated anatomic and functional information (including intrarenal oxygen content[38]) and future advances in urine proteomics will undoubtedly refine patient management and increase the data available for making key clinical decisions, such as whether and when surgical intervention is required.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements are correct?
   - **A.** The presence of hydronephrosis does not always indicate significant obstruction.
   - **B.** Despite the effective relief of urinary tract obstruction, the majority of patients slowly progress to end-stage renal disease (ESRD).
   - **C.** Urinary tract obstruction is always associated with oliguria.
   - **D.** Patients with urinary tract obstruction typically exhibit microscopic hematuria on urinalysis.
   - **E.** Urinary tract obstruction is a risk factor for urinary infections.
2. Which of the following statements are correct?
   - **A.** The development of marked diuresis after relief of urinary tract obstruction is a poor prognostic indicator and is associated with the eventual development of end-stage renal disease.
   - **B.** Urinary tract obstruction may complicate neurologic disease.
   - **C.** Retroperitoneal disease may result in urinary tract obstruction.
   - **D.** Urinary tract obstruction leads to inflammation and scarring of the kidney.
   - **E.** Urinary tract obstruction may complicate immunoglobulin A (IgA) nephropathy.
3. Which of the following statements are correct?
   - **A.** Defective tubular function may persist after relief of urinary tract obstruction.
   - **B.** Urinary tract obstruction is associated with a reduction in the glomerular filtration rate but preservation of renal blood flow.
   - **C.** Non–contrast-enhanced spiral CT scanning is now established as the first-line imaging investigation in patients with suspected urinary tract obstruction.
   - **D.** A diuresis renogram accurately assesses kidney function but is unlikely to indicate the presence of obstruction.
   - **E.** Urinary tract obstruction may occur in the absence of hydronephrosis.

59

Urologic Issues for the Nephrologist

Raj P. Pal, James E. Dyer, J. Kilian Mellon

Close interaction between nephrologists and urologists is crucial to the optimal management of a number of common clinical problems. A proper understanding of urologic strategies helps the nephrologist ensure that patients with these problems are given clear information and are optimally managed. Areas in which such coordinated work is most important include the management of stone disease, the surgical approach to urinary tract obstruction, the investigation of hematuria, and the management of urinary tract malignant neoplasms.

ADVANCES IN MANAGEMENT OF KIDNEY STONES

The management of urinary tract stones has been transformed by the introduction of extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), and ureteroscopy. These advances mean that open stone surgery is now a final resort when other modalities have been exhausted or are contraindicated. Table 59.1 details the use of different treatment modalities over time since the introduction of newer techniques.[1] As familiarity with available techniques and technology develops, standardized treatment strategies will undoubtedly evolve, but the optimal treatment for certain patients with kidney stones remains controversial.

Improvements in Imaging

Unenhanced computed tomography (CT) scanning of the abdomen and pelvis has replaced intravenous urography (IVU) as the standard imaging modality for stone diagnosis (Fig. 59.1). CT is readily available, quicker to perform, offers increased sensitivity compared with IVU (99% vs. 70%), and avoids the need for intravenous contrast. An additional advantage is that CT can demonstrate radiolucent stones (mainly uric acid and xanthine stones) and detect concomitant lesions and/or alternative diagnoses. CT requires an increased radiation dose, but this is less of an issue with modern equipment and newer radiation protocols. Comparative doses are 2.5 mSv for IVU, 5 mSv for standard non–contrast-enhanced CT, and 2 mSv for low-dose non–contrast-enhanced CT.

Conservative (Nonsurgical) Management

Spontaneous stone passage can be expected in up to 80% of patients with stones smaller than 4 mm. Conversely, for stones with a diameter of more than 7 mm, the chance of spontaneous stone passage is very low. The location is also important; up to 70% of distal ureteral stones pass spontaneously, in contrast to only 45% of midureteral and 25% of proximal ureteral stones. Intervention is recommended when there is persistent pain (for more than 72 hours) despite adequate analgesia, persistent obstruction with risk for impaired renal function (e.g., with preexisting renal impairment or in a single kidney), bilateral obstruction, or associated urinary tract sepsis.

In the absence of an acute indication for surgical management, medical expulsive therapy (tamsulosin 400 μg once daily, nifedipine 30 mg once daily) had been thought to aid stone passage, particularly for distal ureteral stones. However, a recent large U.K. study demonstrated no significant benefit of this therapy, in contrast to earlier data from several systematic reviews of randomized trials.[2,3] Opinion is currently divided among urologists regarding medical expulsive therapy for ureteral stones.

Another conservative approach is chemolysis, because several stone types are in principle amenable to dissolution by oral medications or by direct instillation of chemical solutions. However, chemolysis is effective for only uric acid stones, which can be readily dissolved by alkalization of the urine, usually with oral potassium citrate, or with sodium bicarbonate solution instilled directly into the urinary tract via a percutaneous nephrostomy (PCN) tube.

Acute Surgical Intervention

The goals of acute surgical intervention are to relieve obstruction and, if feasible, remove the calculus. If the patient is well enough for general anesthesia, ureteroscopic stone destruction using laser lithotripsy can be attempted. Alternatively, a double-J stent (a ureteral stent with two coiled ends) can be inserted, which will relieve obstruction until definitive treatment is performed (Fig. 59.2). However, in the setting of uncontrolled urinary tract infection (UTI) resulting from an obstructing stone, PCN is the preferred option because it can be performed with local anesthesia and is less likely than endoscopic surgery to cause bacteremia (Fig. 59.3).

Elective Surgical Intervention

Extracorporeal Shock Wave Lithotripsy

During ESWL, acoustic shock wave energy is delivered to a stone under fluoroscopic or ultrasound guidance. Treatment sessions typically last about 30 minutes, during which 1500 to 2500 shock waves are delivered. Treatment is given to outpatients under analgesia or intravenous sedation and can be repeated at intervals of 10 to 14 days. Stones up to 20 mm in size can be treated effectively, and stone-free rates of 60% to 98% have been reported. However, ESWL is operator dependent, and outcome is influenced by the size, composition, and location of the stone and the type of lithotripter used. Cystine and calcium oxalate monohydrate stones are especially resistant. Targeting of the stone may be impossible in the presence of obesity and skeletal deformities

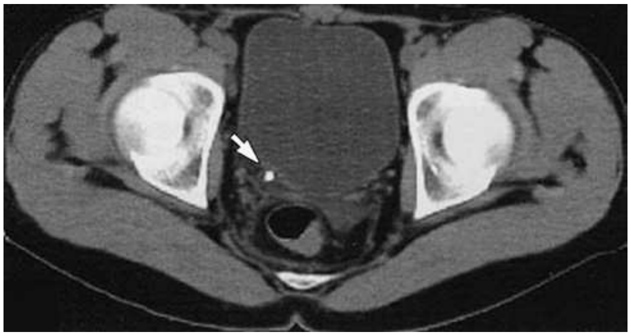

Fig. 59.1 Computed tomography (CT) scan demonstrating a ureteral calculus. Non–contrast-enhanced CT scan showing a calculus *(arrow)* at the right vesicoureteral junction.

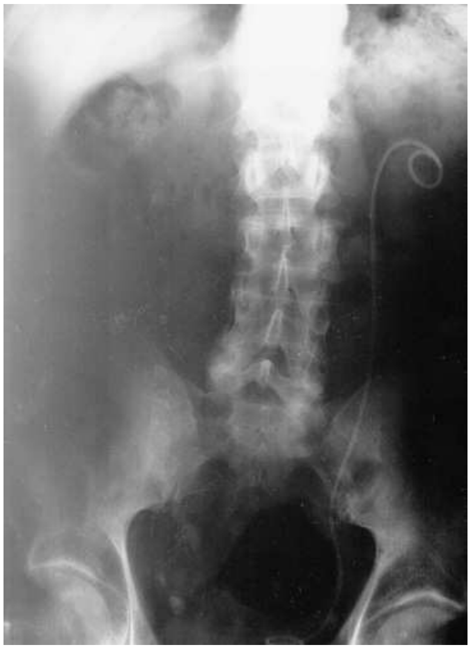

Fig. 59.2 Ureteral stenting. Plain radiograph showing a double-J ureteral stent in the left ureter. Note that the curled ends of the stent remain in the pelvis despite ureteral peristalsis.

TABLE 59.1 Changing Use of Techniques for Stone Removal

	1984	1990	1999
Location (%)			
Calyceal stones	35	43	46
Pelvic stones	42	20	13
Staghorn stones	8	3	1
Ureteral stones	15	34	40
Treatment Modality (%)			
ESWL	60	79	78
PCNL	20	5	2
Ureteroscopy	11	15	20
Open surgery	9	1	0.1

Data from reference 1.

ESWL, Extracorporeal shock wave lithotripsy; *PCNL,* percutaneous nephrolithotomy.

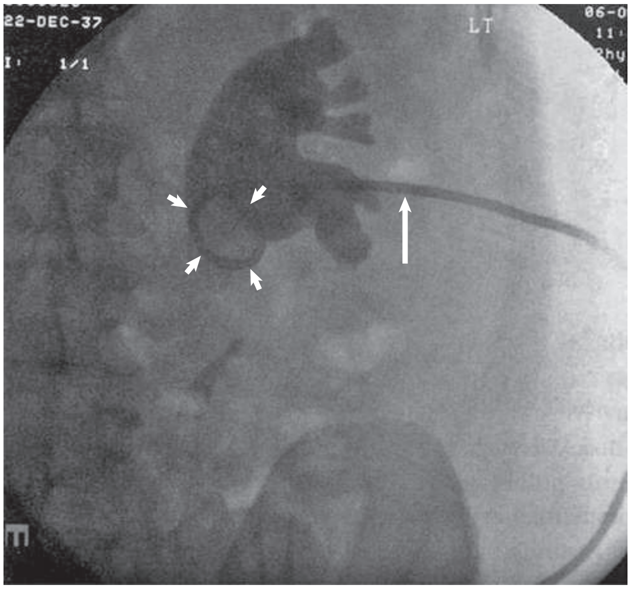

Fig. 59.3 Nephrostogram in ureteral obstruction caused by a stone. Contrast material is injected through a percutaneous nephrostomy tube placed in the lower pole calyx *(arrow).* The contrast material outlines a single large calculus *(arrowheads)* producing complete obstruction at the pelviureteral junction.

(increased skin-to-stone distance), and ESWL is contraindicated in patients with aortic or renal artery aneurysm, uncontrolled UTI, coagulation disorders, and pregnant women.

A double-J ureteral stent is sometimes placed endoscopically before ESWL treatment to prevent stone fragments from obstructing the distal ureter (*Steinstrasse,* literally "stone street"; Fig. 59.4). Other acute complications of ESWL include hemorrhage or hematoma, infection, and injury to adjacent organs. The risk for the later development of hypertension or renal impairment after ESWL remains controversial.

Percutaneous Nephrolithotomy

During PCNL, a tract through the renal parenchyma is created between the skin and the collecting system of the kidney. A metallic sheath within this tract is used as a working channel to remove stones. Preoperatively, CT imaging is used to localize calculi and neighboring organs (e.g., spleen, liver, large bowel, pleura, or lungs) and to plan access. The most frequently used access site is the dorsal calyx of the lower pole, and stone fragmentation is undertaken by ultrasound, pneumatic, or laser devices. With technologic advances, performing this procedure through smaller access sheaths (<18 Fr compared with standard 30-Fr sheaths) with fewer complications and equivalent stone clearance rates is becoming feasible.[5] The PCNL technique is modified for special circumstances, usually by altering the site of puncture (e.g., directly into a calyceal diverticulum) or, if there are ureteral stones, by using a higher placed puncture to permit antegrade ureteroscopy. The percutaneous puncture may be facilitated by the preliminary placement of a retrograde ureteral catheter to dilate and to opacify the collecting system, which is then punctured under fluoroscopy. After completion of PCNL, a self-retaining balloon nephrostomy tube is used to tamponade the tract and to provide further access if needed. Hemorrhage can complicate PCNL (from intrarenal or, rarely, intercostal arteries) and usually can be treated conservatively or by selective angiographic embolization. Other complications include sepsis; fluid overload (similar to transurethral resection syndrome); injury to spleen, pleura, or colon; and extravasation. PCNL usually results in minimal parenchymal injury, averaging only 0.15% of the total renal cortex.[6]

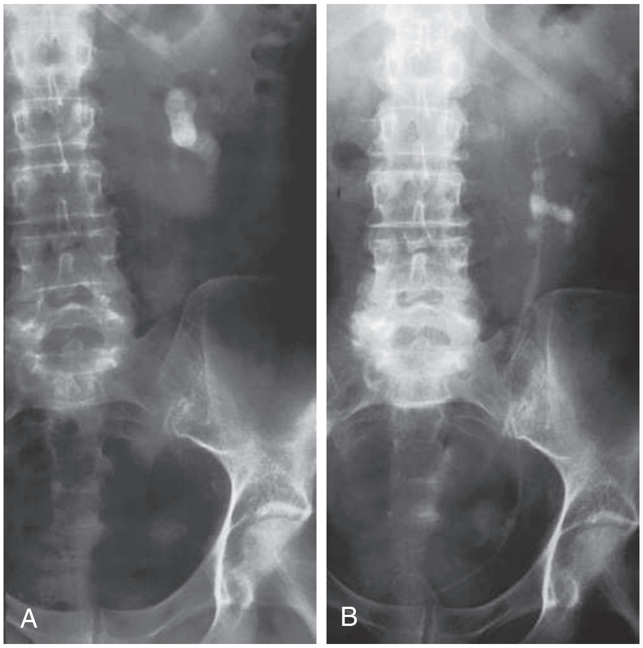

Fig. 59.4 **Extracorporeal shock wave lithotripsy (ESWL) complicated by Steinstrasse.** (A) Preoperative plain radiograph showing stones in the left renal pelvis. (B) After ESWL, note the disappearance of the pelvic stone, the string of stone fragments throughout the length of the ureter, and the double-J ureteral stent placed to facilitate their passage.

TABLE 59.2 Indications for Percutaneous Nephrolithotomy

Composition*	Struvite stones	Complete removal necessary to eliminate infection and minimize stone recurrence
	Calcium oxalate monohydrate stones	Difficult to pulverize by ESWL
	Cystine stones	Difficult to pulverize by ESWL
Stone position	Lower pole stones	Fragments less easily evacuated from dependent lower pole calyces, especially if collecting system dilated
Anatomic abnormalities	PUJ obstruction Calyceal diverticula	Prevent passage of fragments after ESWL
Patient characteristics	Morbid obesity Ureteral obstruction	Stone cannot be placed in focal point of ESWL machine

*Stone composition can be defined with certainty only by direct stone analysis, but advances in imaging may ultimately provide a means to accurately assess stone composition *in situ* before treatment, thus allowing the urologist to select the treatment most likely to be successful.

ESWL, Extracorporeal shock wave lithotripsy; *PCNL,* percutaneous nephrolithotomy; *PUJ,* pelviureteral junction.

ESWL is the first choice for stone intervention, except in those circumstances that may favor PCNL.

Indications for PCNL are shown in Table 59.2. These continue to evolve and are being challenged by developments in ureteroscopic techniques, which are allowing more upper ureteral and renal pelvic stones to be dealt with by a retrograde approach.

ESWL is the first-line treatment for more than 75% of stone patients. Table 59.2 shows circumstances in which ESWL is less effective and PCNL becomes the preferred approach or a combination of the two modalities is used. For lower pole stones in particular, ESWL may not provide optimal clearance because of problems with the drainage of residual fragments. A randomized controlled trial (RCT) has shown that for lower pole stones larger than 10 mm, PCNL has much better clearance rates than ESWL (92% vs. 23%).[4]

Open Stone Surgery

Open surgery still has a place in the treatment of stone disease. Approximately 2% of stone patients are now treated with open surgery, mainly when anatomic factors preclude the use of minimally invasive methods or when these techniques have failed. Other indications include complex stone burden and the presence of intrarenal anatomic abnormalities (e.g., pelviureteral junction [PUJ] obstruction). During surgery the renal pelvis as well as the parenchyma can be opened along avascular planes, and clamping of the renal vessels and hypothermia of the kidney may be needed. In selected patients a laparoscopic approach can be used for the treatment of stone disease.

Ureteroscopy

Continued advances in the design of endoscopes for ureteronephroscopy have rendered the entire urinary tract accessible to endoscopic examination and manipulation. Ureteroscopes may be semirigid or flexible, the latter allowing access to the renal pelvis and calyces. Stone fragmentation is achieved ideally by laser but also by ultrasound or pneumatic devices (lithoclast). Laser use is equally effective for all types of stones and has the additional advantages of a flexible fiber (allowing intrarenal stone fragmentation), low tissue penetration, and minimal stone displacement during use. Success rates for laser fragmentation of ureteral stones are approximately 80%. Fig. 59.5 highlights the increasing use of ureteroscopy in stone disease and also the increasing proportion of procedures in which a laser rather than ultrasound or a lithoclast is used to achieve stone fragmentation.

For lower pole renal stones, although flexible ureteroscopes can access the lower pole to facilitate treatment, the stone-free rate in comparative studies is similar to that of ESWL.[7,8] Furthermore, patients often prefer ESWL as the initial therapy compared with flexible ureteroscopy and lasertripsy. In the event of failed stone clearance after ureteroscopy, PCNL is commonly used next and is likely to remain an essential treatment for lower pole stones. Complications of ureteroscopy, particularly with use of graspers and baskets, include ureteral avulsion, perforation, extravasation, mucosal damage, hematuria, infection, and stricture. Advances in laser technology now enable stones to be reduced to dust-like particles, reducing the need for graspers and baskets and hence reducing complications.

Management of Staghorn Calculus

A staghorn calculus usually should be managed by intervention because reports of conservative therapy show a high rate of eventual nephrectomy (up to 50%) and an increase in associated morbidity (mainly renal failure) and mortality (up to 28%). Patient age and renal function heavily influence treatment decision making. The primary treatment option for staghorn calculi in a kidney with preserved renal function is PCNL. For a staghorn calculus in a nonfunctioning kidney, partial or total nephrectomy may be indicated. ESWL or ureteroscopic stone removal alone are rarely effective for large staghorn calculi, but can be used as an adjunct to PCNL to achieve total stone clearance. The advantage of a multimodal approach is the reduced need for additional renal

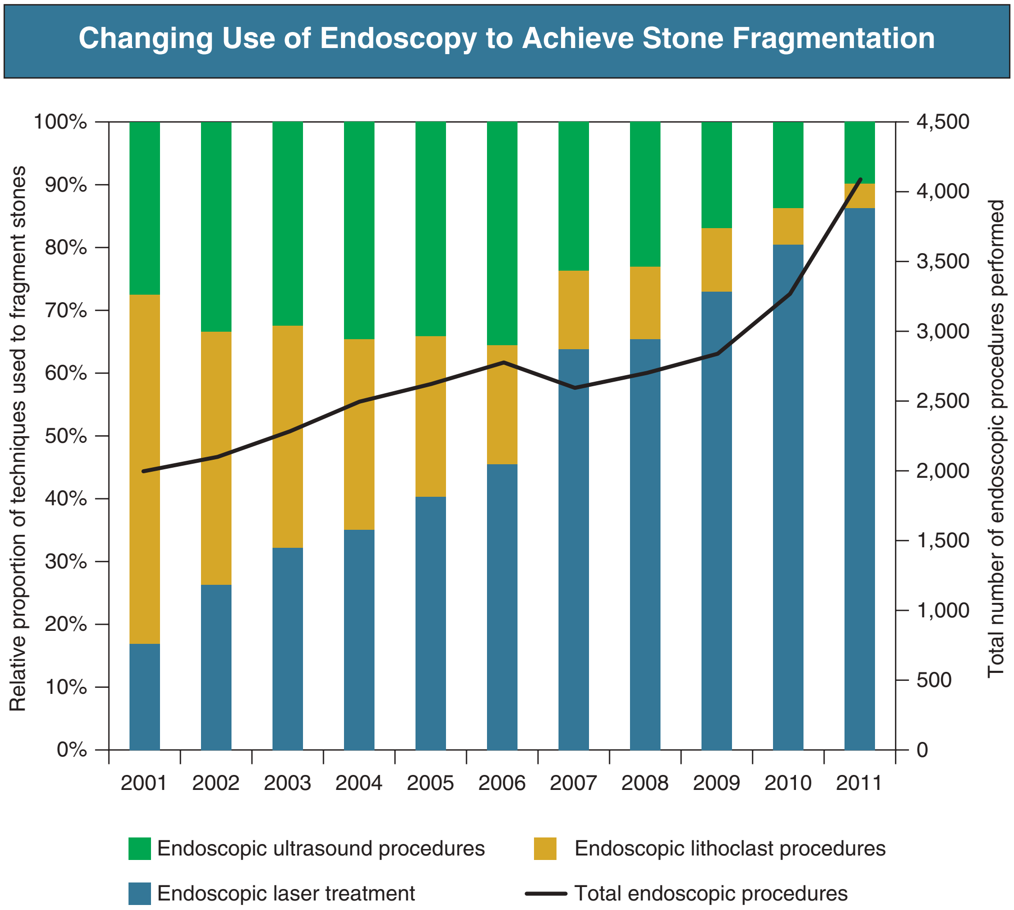

Fig. 59.5 **Changing use of endoscopy to achieve stone fragmentation.** Chart showing the increasing use of endoscopy in stone surgery in addition to the increasing proportion of cases using lasers to achieve stone fragmentation. (Data from UK Hospital Episode Statistics dataset. http://www.hscic.gov.uk/hes. Accessed June 9, 2012.)

access and secondary PCNL. Very rarely, open surgical removal of the stone may be indicated.

Stones in Transplanted Kidneys

The management of stone disease in a transplanted kidney is challenging because of the solitary kidney, the anatomic location within the pelvis, and the difficulty with retrograde access to the ureter and kidney. Early active intervention is indicated; prophylactic stenting, ureteroscopy, and PCNL are preferred to ESWL because stone targeting may not be possible. Open surgery may be needed in selected cases.

URINARY TRACT OBSTRUCTION

General Aspect

The causes of upper tract obstruction are listed in Chapter 58, Box 58.2, and a summary of the management of obstruction is given in Chapter 58, including Fig. 58.7. Upper tract obstruction caused by malignancy can be a result of direct tumor invasion or external compression by metastatic lymph node involvement or, rarely, true metastasis to the ureter. Some 70% of tumors causing ureteral obstruction are genitourinary (cervical, bladder, prostate) in origin; breast and gastrointestinal carcinomas and lymphoma constitute the majority of the remainder.[9] The presentation of a patient with obstruction may vary significantly, and hydronephrosis may develop progressively and insidiously and remain unrecognized until the patient develops anuria and uremia. Upper tract obstruction from malignancy rarely manifests with classic acute ureteral colic, which is typically seen with a benign cause such as a stone. Bladder outflow obstruction may be acute and dramatic or chronic with few or no symptoms. To aid in understanding of the immediate needs and longer term prognosis of these patients, the acute as well as the definitive management of the most common urologic diseases associated with obstruction and renal impairment are outlined.

Acute Management

Relief of obstruction is crucial to reverse renal impairment and preserve remaining renal function. In cases of bladder outflow obstruction, a urethral or suprapubic catheter is indicated; whereas in upper tract obstruction, a double-J ureteral stent is preferable, when possible. The most straightforward approach is endoscopic retrograde placement under fluoroscopy, with PCN reserved for patients in whom the procedure fails. Bilateral stents should be placed if technically possible. However, tumor infiltration can distort trigonal anatomy, making identification of ureteral orifices for double-J stent insertion impossible at the time of cystoscopy. Furthermore, it has been suggested that stents fail to relieve obstruction in 40% to 50% of cases of external ureteral compression. Thus these patients need to be closely monitored to ensure resolution of the obstruction. A new type of metallic, self-expanding stent, used alone or in conjunction with double-J stents, has had good results in maintaining ureteral patency and avoiding PCN in malignant ureteral obstruction.[10]

A stable patient with obstruction but without major signs of sepsis is a candidate for retrograde stent placement with use of general anesthesia. However, in a patient with sepsis, endoscopic manipulation can lead to bacteremia and septic shock. Furthermore, such patients may not be fit for general anesthesia, in which case the preferred initial approach is PCN, which can then be followed after an interval with antegrade ureteral stenting. The success rate of this combined approach is high (>90%).[11] In patients with bilateral ureteral obstruction, it is not always necessary to insert bilateral PCN tubes. Significant palliation and return to nearly normal renal function can be accomplished by drainage of the kidney with the better preserved parenchyma as determined by CT scan or ultrasound. Once they have been placed, PCN tubes or double-J stents need to be replaced every 3 to 6 months. If they are left for a longer period, they become increasingly brittle and encrusted and are liable to block or fracture under manipulation. Complications of ureteral stents include migration, obstruction with proteinaceous material, infection, fragmentation, and, rarely, erosion through the urinary tract.[12] As many as 70% of patients with stents report lower urinary tract symptoms, mainly urgency, frequency, and nocturia, as well as pain along the urinary tract.

Morbidity after stenting or PCN is similar.[13] The main problem with indwelling stents is the increased risk for recurrent obstruction (11% for stents vs. 1% for PCN). PCN may have an increased infection rate, and there may be psychological issues relating to the need for an external drainage bag.

Extraanatomic stents are an alternative for patients in whom conventional stent insertion has failed or for whom permanent nephrostomy drainage is unacceptable. An extraanatomic stent is placed by an initial percutaneous puncture and insertion of the upper end of a long (50-cm) double-J stent into the kidney. A subcutaneous tunnel is then created to bring the stent to the level of the iliac crest. Another tunnel is fashioned to bring the lower end of the stent out suprapubically, followed, finally, by suprapubic puncture of a full bladder and insertion of the lower end (Fig. 59.6).[14] Extraanatomic stents are usually changed at 6-month intervals, and preliminary experience confirms their value in maintaining ureteral patency and avoiding PCN. Because of the effectiveness of minimally invasive methods, open surgery today is rarely indicated in the acute setting.

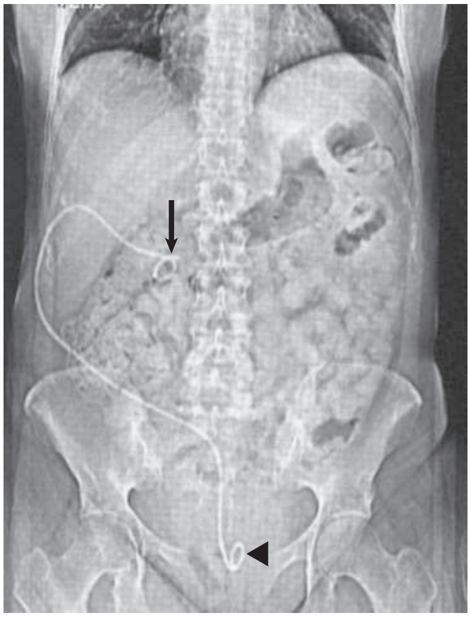

Fig. 59.6 Extraanatomic stenting for malignant ureteral obstruction. Plain radiograph showing placement of an extraanatomic stent for malignant obstruction of the right ureter. The upper end of the double-J stent has been placed in the right renal pelvis *(arrow)*. The stent then runs through a subcutaneous tunnel before the lower end enters the bladder *(arrowhead)*.

SPECIFIC TYPES OF OBSTRUCTION

Pelviureteral Junction Obstruction

Surgical management of PUJ obstruction is aimed at obliterating the redundant (aperistaltic) portion of the ureter, allowing normalization of drainage from the affected kidney. The need for treatment is heralded by the onset of pain, infection, calculus formation, decline in renal function, or proven impaired excretion on mercaptoacetyltriglycine (MAG3) renography with impending decline in renal function. The gold standard treatment is now laparoscopic or robotic pyeloplasty, although traditional open techniques are still used. Endoscopic (endopyelotomy) treatments are also performed in some centers. However, in treatment-naïve patients, endopyelotomy has inferior outcomes compared with pyeloplasty.[15,16]

Retroperitoneal Fibrosis

Retroperitoneal fibrosis can be treated medically or surgically. A causative factor should be excluded (see Chapter 58). There are reports of favorable outcomes after immunosuppression with high doses of corticosteroids or azathioprine. Alternatively, surgery, consisting of ureterolysis (freeing the ureters from the fibrotic plaques) and omentoplasty (transposition of the ureters into the peritoneal cavity in omental wraps), can have good long-term results.

Malignant Obstruction

For upper tract transitional cell carcinoma, acute obstruction is best treated by internal stenting. PCN is avoided because of the risk for tumor seeding. Upper tract transitional cell carcinoma is an aggressive tumor and necessitates prompt extirpative surgery.

Bladder cancer can lead to hydronephrosis by invading the ureteral orifices and intramural ureter. In the absence of metastatic disease, radical cystectomy is indicated, although temporary ureteral decompression may normalize renal function if neoadjuvant chemotherapy is planned. In selected cases, bladder preservation strategies combining systemic chemotherapy and radiotherapy can offer long-term control of the disease.

Prostate cancer causes obstruction by occluding the urethra or invading the ureteral orifices. Hormonal treatment can shrink prostatic tissue and malignant deposits and offer long-term remission of symptoms. Limited resection of the prostate may sometimes be indicated.

The decision to offer ureteral decompression for upper tract obstruction caused by cancer is not straightforward and requires input not only from the urologist but also from colleagues in radiation and medical oncology and the palliative care team. There must also be careful discussion of the options with the patient and family.

Ureteral decompression is justified when radiotherapy and systemic chemotherapy remain therapeutic options after improvement in renal function but also may be justified for palliation of pain or ongoing renal tract sepsis.

A review of patients undergoing PCN for obstructive uropathy secondary to pelvic malignancy identified a subset with very poor survival in whom ureteral decompression is usually not justified (Table 59.3).[17] Patients with gastric or pancreatic cancer survive a median of only 1.4 months after ureteral decompression.[18] In another report, the average survival of patients with advanced malignant neoplasms undergoing endourologic diversion was only 5 months, half of which time was spent in the hospital.[19]

TABLE 59.3 Percutaneous Nephrostomy for Malignant Obstructive Uropathy

	Median Survival (wk)	5-yr Survival Rate (%)
Group I: Primary untreated malignancy	27	10
Group II: Recurrent malignancy with further treatment	20	20
Group III: Recurrent malignancy with no further treatment	6.5	None survived longer than 1 yr
Group IV: Benign disease as a result of previous treatment	Not stated	64
Overall	26	22

Outcome in 77 patients undergoing percutaneous nephrostomy for obstructive uropathy secondary to pelvic malignant disease.
Data from reference 12.

Benign Ureteral Strictures

These can be secondary to stone disease, iatrogenic, or caused by various benign diseases. The treatment of choice is endoscopic balloon dilation or ureterotomy. Open surgical repair or major reconstructive surgery may be needed in cases of recurrent strictures.

Bladder Outflow Obstruction

Bladder outflow obstruction in men is most frequently caused by either benign or malignant prostatic enlargement. Common presentations of both conditions include the onset of lower urinary tract symptoms and acute (painful) or chronic (painless) retention of urine.

Chronic retention can be considered as the maintenance of voiding with incomplete bladder emptying. It is further classified into low- and high-pressure chronic retention. Low-pressure chronic retention occurs in the absence of upper tract compromise, whereas high-pressure chronic retention is associated with hydronephrosis and kidney injury.

In acute retention, low-pressure chronic retention, and lower urinary tract symptoms caused by bladder outflow obstruction, treatment with 5α-reductase inhibitors (finasteride, dutasteride) or α-adrenergic receptor blockers (tamsulosin, alfuzosin) is usually indicated before surgery is offered.[20] Given the risk for worsening renal failure if medical therapy fails, it is not a safe management option in high-pressure chronic retention. Surgical management is reserved for patients who either derive no benefit from or are not willing to pursue medical therapy, those with acute and low-pressure chronic retention, and those with high-pressure chronic retention. Before surgery, evaluation of likelihood of success is essential. Patients with very high postvoid residual volumes of urine (>1 liter) are less likely to benefit from surgery because of the chronicity of their symptoms and consequent detrusor muscle weakness. These patients are often treated best with intermittent clean self-catheterization or a permanent urethral or suprapubic catheter.

The number of surgical management options available for bladder outflow obstruction is continually increasing. Although transurethral resection of the prostate (TURP) has been the gold standard procedure for decades, the development of laser technology is challenging this. Holmium laser enucleation of the prostate (HoLEP) and vaporization of prostatic tissue (Green light laser) are being increasingly performed in specialist centers with superior results with respect to reduced patient stay, bleeding, and duration of postoperative catheterization. Unlike standard TURP, laser prostatectomy also can be routinely performed safely in patients with large gland size (>100 cc) and on anticoagulation therapy. A recently published 7-year follow-up study comparing TURP with HoLEP reported no significant difference in quality of life, maximum urinary flow, incontinence, or erectile dysfunction, with a reduced need for reoperation in the HoLEP arm of the study.[21]

TABLE 59.4 Outcome of Evaluation in a Hematuria Clinic: Percentage of cases investigated

Diagnoses Found	All	Microscopic Hematuria	Macroscopic Hematuria
No diagnosis	59	69	53
Renal cancer	0.6	0.3	0.9
Upper tract transitional cell carcinoma	0.1	0.1	0.1
Bladder cancer	12	5	19
Prostate cancer	0.4	0.2	0.6
Stone disease	4	4	3
Urinary tract infection	13	13	13
Renal parenchymal disease	10	9	10
Likelihood of Finding Malignancy			
Male, age >40 yr		8	24
Male, age <40 yr		2	7
Female, age >40 yr		5	19
Female, age <40 yr		0	0

Data from reference 17.

Neurologic Diseases of the Lower Urinary Tract

Diseases of the central or peripheral nervous system can manifest with bladder underactivity or detrusor-sphincter dyssynergia and lead to bilateral hydroureternephrosis. Diabetes mellitus also can produce a flaccid denervated bladder through destruction of the peripheral nerves and can cause chronic retention and renal failure. Of diabetics who develop peripheral neuropathy, 75% to 100% will develop some neurogenic lower urinary tract dysfunction. The treatment of choice is generally intermittent clean self-catheterization, with a limited role for surgery.

INVESTIGATION OF HEMATURIA

Macroscopic hematuria is perhaps the most important symptom in urologic practice, and apart from being alarming to the patient, it can be the first presenting sign of an underlying malignant urologic condition (most often a transitional cell tumor of the bladder). Studies show that 15% to 22% of patients with visible hematuria have an underlying genitourinary tract malignant neoplasm.

Patients with visible hematuria must be distinguished from those who have been found to have microhematuria (microscopic or dipstick), in whom the risk for malignant change is significantly lower (2% to 11%).

The outcome of full evaluation of a large group of patients attending a hematuria clinic is shown in Table 59.4.[22] In addition to a small but important group of patients in whom malignant disease was identified, there was a significant pickup rate of parenchymal renal disease (~10%) presenting with both visible and nonvisible hematuria. It is also important to note the sizable proportion of patients in whom a definitive diagnosis could not be reached.

Evaluation of Visible Hematuria

All adults with a single episode of visible hematuria require full urologic evaluation, including renal imaging and cystoscopy. The only exception to this rule occurs when an adult younger than 40 years gives a history characteristic of glomerular hematuria, such as is typically seen in immunoglobulin A (IgA) nephropathy, in which dark brown hematuria lasting 24 to 48 hours coincides with intercurrent mucosal infection, usually of the upper respiratory tract. This hematuria may be painless, or there may be bilateral loin ache. These young adults should be referred first for nephrologic assessment.

Evaluation of Microhematuria

Perhaps the greatest degree of overlap in practice between urologists and nephrologists occurs in the initial assessment of patients with microhematuria. Concurrent UTI will cause microhematuria and should be treated before further evaluation. Furthermore, features such as menstruation, vigorous exercise, viral illness, and trauma can themselves account for microhematuria. In the presence of a transient or treatable underlying cause other than UTI, repeat urinalysis should be performed 2 days later. Further urinalysis should be deferred until 6 weeks after treatment of confirmed UTI. If microhematuria resolves, no further investigation is required.

In 2012 the American Urological Association, after extensive systematic review of the literature, produced their guidance on the assessment and management of asymptomatic microscopic (nonvisible) hematuria (AMH).

These guidelines defined AMH by the presence of three or more red blood cells (RBCs) per high-power field on microscopic examination of one properly collected, noncontaminated urine sample. In addition to the benign causes listed, pyuria and bacteriuria also should be excluded with either dipstick or microscopy.

The most notable departure from previous guidance is the recommendation of urologic investigation after one episode of AMH, rather than waiting for two of three positive samples as previously suggested. There are currently no direct comparative studies identifying diagnostic yields in patients with one or more than one episode of AMH. Indirect comparison, however, reveals a diagnostic yield of urinary tract malignancy of 1.8% and 3.6% in patients with one or more than one episode of AMH, respectively.[23] Dipstick-positive hematuria may still herald significant disease in the absence of RBCs on microscopy because RBCs may lyse in alkaline or hypotonic urine before reaching the laboratory for analysis.[24]

Complete evaluation of microhematuria includes a history and physical examination, laboratory analysis, and radiologic imaging of the upper urinary tract, followed by cystoscopy (Fig. 59.7). In women, urethral and vaginal examinations should be performed to exclude local causes of microhematuria. In uncircumcised men, the foreskin should be retracted to expose the glans penis, if possible. If phimosis is present, a catheter specimen of urine may be required. An assessment of renal function should be made (serum creatinine, estimated glomerular filtration rate [eGFR]) because intrinsic renal disease may have implications for consequent imaging and treatment. The remaining laboratory investigations are guided by specific findings of the history, physical examination, and urinalysis. Multiphase CT urography, which allows evaluation of renal parenchyma and also the collecting system, has been shown to have the highest sensitivity and specificity for imaging the upper tracts. If CT urography is unavailable, then IVU and ultrasound combined with plain abdominal radiography are alternative imaging strategies. Cystoscopy is now advocated in all patients with AMH who are older than 35 years and those under the age of 35 years with risk factors for urologic malignancy or clinical suspicion of malignancy (Box 59.1). The use of adjuncts to AMH workup such as urine cytologic examination and other urine biomarkers is no longer advocated.

BOX 59.1 Common Risk Factors for Urinary Tract Malignancy in Patients With Microhematuria

- Male gender
- Age (>35 years)
- Past or current smoking
- Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines)
- Analgesic abuse
- History of visible hematuria
- History of urologic disorder or disease
- History of irritative voiding symptoms
- History of pelvic irradiation
- History of chronic urinary tract infection
- History of exposure to known carcinogenic agents or chemotherapy such as alkylating agents
- History of chronic indwelling foreign body

Significant proteinuria (>0.3 g/24 h), RBC casts, predominance of dysmorphic RBCs in the urine, or renal impairment should prompt referral to a nephrologist and evaluation for parenchymal renal disease. When present, RBC casts are virtually pathognomonic of glomerular bleeding, but they are often absent in low-grade glomerular disease. Accurate determination of RBC morphology requires inverted phase contrast microscopy. In general, glomerular bleeding is associated with more than 80% dysmorphic RBCs, and lower urinary tract bleeding is associated with more than 80% normal RBCs.[25] This assessment is operator dependent. (Urine microscopy is further discussed in Chapter 4). An alternative is to assess urinary RBC size by Coulter counter analysis because dysmorphic RBCs are smaller than normal RBCs, but this method is not useful when RBC numbers in the urine are small. Even in the absence of features of glomerular bleeding, many patients with isolated microhematuria have glomerular disease, most commonly IgA nephropathy or thin basement membrane nephropathy.[26] Because there is a low risk for progressive renal disease, renal biopsy in this setting is not usually recommended. Nevertheless, one study showed that microhematuria unexplained by urologic evaluation carries a twofold risk for eventual development of ESRD,[27] so these patients should be observed for the development of hypertension, renal impairment, or proteinuria.

Cyclophosphamide

Past treatment with cyclophosphamide increases the risk for bladder cancer up to ninefold, probably in a dose- and duration-dependent manner. Tumors have been reported 6 to 13 years after cyclophosphamide exposure and are often of high grade. Hematuria is also common after cyclophosphamide in the absence of cancer. If full evaluation does not identify a cause of hematuria, there is no agreed surveillance protocol; it is not clear whether routine follow-up by cystoscopy and urine cytology is valuable, although a high index of suspicion should be maintained.

INVESTIGATION AND MANAGEMENT OF A RENAL MASS

The incidence of renal cell carcinoma (RCC) has more than doubled in the last 30 years, now accounting for 3% of all cancers. It is the third

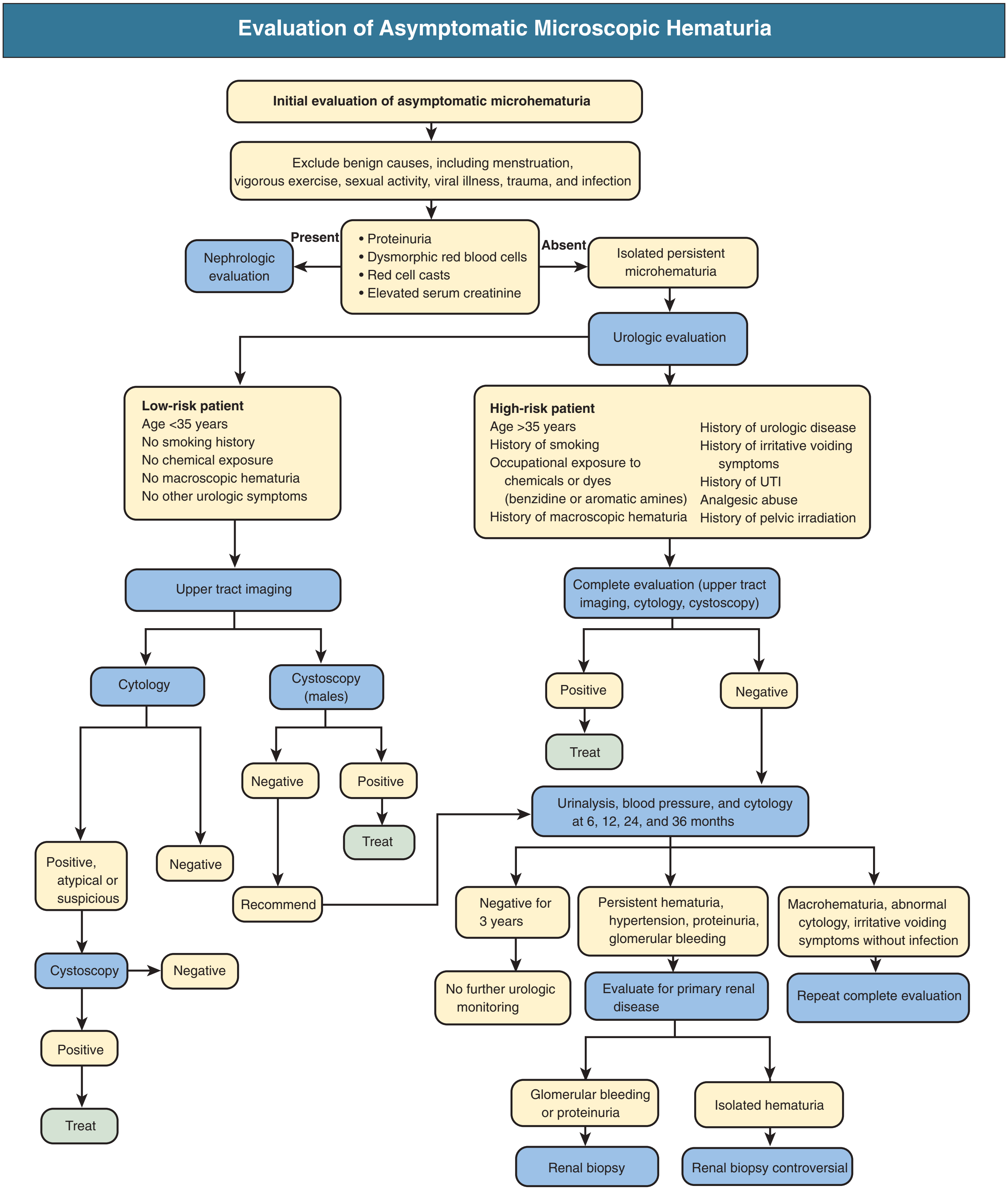
Evaluation of Asymptomatic Microscopic Hematuria
Initial evaluation of asymptomatic microhematuria
Exclude benign causes, including menstruation, vigorous exercise, sexual activity, viral illness, trauma, and infection
Present
• Proteinuria
• Dysmorphic red blood cells
• Red cell casts
• Elevated serum creatinine
Absent
Nephrologic evaluation
Isolated persistent microhematuria
Urologic evaluation
Low-risk patient
Age <35 years
No smoking history
No chemical exposure
No macroscopic hematuria
No other urologic symptoms
High-risk patient
Age >35 years
History of smoking
Occupational exposure to chemicals or dyes (benzidine or aromatic amines)
History of macroscopic hematuria
History of urologic disease
History of irritative voiding symptoms
History of UTI
Analgesic abuse
History of pelvic irradiation
Upper tract imaging
Complete evaluation (upper tract imaging, cytology, cystoscopy)
Cytology
Cystoscopy (males)
Positive
Negative
Treat
Negative
Positive
Treat
Urinalysis, blood pressure, and cytology at 6, 12, 24, and 36 months
Positive, atypical or suspicious
Negative
Recommend
Negative for 3 years
Persistent hematuria, hypertension, proteinuria, glomerular bleeding
Macrohematuria, abnormal cytology, irritative voiding symptoms without infection
Cystoscopy
Negative
No further urologic monitoring
Evaluate for primary renal disease
Repeat complete evaluation
Positive
Glomerular bleeding or proteinuria
Isolated hematuria
Treat
Renal biopsy
Renal biopsy controversial

Fig. 59.7 Evaluation of asymptomatic microscopic hematuria. *UTI,* Urinary tract infection.

TABLE 59.5 **Bosniak Classification and Management of Cystic Renal Masses***

Bosniak Class	Features on Imaging	Comment	Management
Class I: Simple benign cyst	Round or oval Uniform density <20 HU Unilocular No perceptible wall No contrast enhancement	Majority of asymptomatic cystic lesions	No further intervention required
Class II: Benign cyst	One or two nonenhancing septa Calcifications in the wall or septum Hyperdense lesions (50-90 HU, resulting from the presence of blood, protein, or colloid) <3 cm No contrast enhancement		No further intervention required
Class II F: Probable benign cyst	Multiple hairline septa "Perceived" enhancement Nodular calcification Hyperdense lesions >3 cm	"Perceived" enhancement resulting from contrast within capillaries of septa	Surveillance with CT scans every 6-12 months
Class III: Indeterminate cystic lesions	One or more of the following: Thick, irregular borders Irregular calcifications Thickened or enhancing septa Multilocular form Uniform wall thickening Small nonenhancing nodules	About 40% are neoplastic Magnetic resonance imaging may improve characterization	Surgical exploration
Class IV: Presumed malignant cystic masses	Appear malignant Heterogeneous cysts Shaggy, thickened walls or enhancing nodules	Appearances result from necrosis and liquefaction of a solid tumor or a tumor growing in the wall	Surgical exploration

Data from reference 25.
Approach to renal mass found incidentally by ultrasound or CT scanning.
*All patients with symptomatic renal masses should be referred for urologic assessment.
HU, Hounsfield units.

most common tumor of the urinary tract but the most lethal. The apparent increased incidence is partly attributed to the widespread use of cross-sectional and ultrasound imaging; more than 50% of new cases are incidental findings on CT, magnetic resonance imaging (MRI), or ultrasound.

The primary goal in investigating a renal mass is to diagnose or exclude malignancy. Ultrasound has been reported to be 79% sensitive for the detection of renal parenchymal masses but does not detect lesions smaller than 5 mm. Contrast enhancement with ultrasound also can identify malignancy and improve sensitivity. However, CT scanning before and after contrast administration is the most common modality used to characterize renal masses. MRI, especially with T2-weighted images and diffusion weight imaging, may be superior to CT in the correct characterization of benign lesions,[28] but distinguishing an RCC from a benign lesion (i.e., oncocytoma, fat-free angiomyolipoma) is occasionally not feasible radiologically. Choice of imaging techniques and their interpretation are discussed further in Chapter 5.

Because of the limitations of radiologic evaluation, percutaneous biopsy of a renal mass is increasingly used to obtain a histologic diagnosis before treatment. Up to 30% of small renal masses (<3 cm) are nonmalignant. Traditional fears regarding tumor seeding after percutaneous biopsy are not supported by recent studies. Biopsy of a renal mass is now recommended for diagnostic uncertainty, despite imaging, before systemic therapy for metastatic RCC and in renal tumors managed with surveillance or ablative modalities.[29] Many clinicians also perform biopsy before embarking on surgery in high-risk or elderly surgical candidates, those who will require technically challenging surgery, and patients with small renal masses. In a recent systematic review evaluating 57 studies investigating over 5000 patients, percutaneous biopsy was shown to have a high diagnostic yield, sensitivity (>98%), and specificity (>98%) for renal cancers, with a low associated complication rate.[30]

The management of mixed cystic and solid masses is more problematic. Table 59.5 shows the Bosniak classification of cystic renal masses.[31] This classification, based on CT appearances, provides the basis for management according to risk for malignancy. The evaluation of multiple cystic lesions in the kidney is discussed further in Chapter 45.

Tumor size is important; in a large retrospective study of 2935 patients with surgically treated solid renal tumors, 46% of lesions smaller than 1 cm were benign compared with 22% and 10% of tumors 1 to 2 cm and 4 to 5 cm, respectively. Furthermore, only 2.3% of cancers smaller than 1 cm were of high grade, whereas for tumors larger than 7 cm, the percentage was 58%.[32] Surveillance studies of small renal tumors have shown a median growth rate of 0.28 cm per year; about 30% of these lesions will not increase in size.

Traditionally, radical nephrectomy was the gold standard treatment for localized renal cancers. However, nephron-sparing surgery (NSS) is now recommended in all tumors smaller than 7 cm where technically feasible.[29] Comparison of these two approaches for T1a (<4 cm) and T1b (4 to 7 cm) lesions has shown equivalent tumor clearance and a reduction in long-term renal complications with partial nephrectomy.[33] Radical nephrectomy therefore should be reserved for larger renal cancers (≥T2), those technically not amenable to partial nephrectomy and in patients unlikely to benefit from NSS.[29]

The last two decades have also seen a shift from open to minimally invasive surgery. Laparoscopic radical nephrectomy and robotic assisted partial nephrectomy (particularly for small exophytic tumors) have

TABLE 59.6 Evidence-Based Recommendations for Targeted Therapy in Metastatic Renal Cell Carcinoma

RCC Type	Prognosis Risk Group	First Line	Second Line After VEGF Therapy	Third Line
Clear cell	Favorable, intermediate	Sunitinib Pazopanib Bevacizumab + interferon-α	*Based on OS:* Nivolumab *Based on PFS:* Cabozantinib Axitinib Sorafenib Everolimus	*After VEGF therapy:* Nivolumab Cabozantinib Everolimus *After VEGF and mTOR therapy:* Sorafenib *After VEGF and nivolumab:* Cabozantinib Axitinib Everolimus
Clear cell	Poor	Temsirolimus	Any targeted agent	
Non–clear cell	Any	Sunitinib Everolimus Temsirolimus	Any targeted agent	

Based on 2016 European Association of Urology Guidelines for renal cell carcinoma.
Data adapted from reference 29.
mTOR, Mammalian target of rapamycin complex, *OS,* overall survival; *PFS,* progression-free survival; *VEGF,* vascular endothelial growth factor.

now superseded open approaches for these techniques in most large centers. Minimally invasive treatment modalities give equivalent long-term cancer control, while reducing perioperative blood loss, postoperative analgesic requirement, and hospitalization.

Cryosurgery and radiofrequency ablation via laparoscopic or percutaneous approaches have emerged as treatment options for small localized renal cancers. There is currently no consensus on the maximum size of lesions amenable to these techniques, but they are usually reserved for tumors smaller than 4 cm. Such treatments offer the advantages of NSS, especially in patients with high surgical risk. Case series evaluating these modalities individually have reported promising results. However, there are no data from RCTs on either modality and nonrandomized studies have not shown any significant oncologic or survival benefit when comparing these modalities to partial nephrectomy, although several studies have reported reduced efficacy in terms of local recurrence, metastatic progression, and survival.[34-36] Further disadvantages of both techniques include absence of histologic confirmation of complete tissue destruction and potential for more difficult salvage surgery for local recurrence.

Adjunctive Therapy for Renal Cancer

The 5-year survival for patients diagnosed with localized RCC is approximately 80% to 90%. However, in the United States up to 20% of patients with RCC present with metastasis. The 5-year survival falls to 60% and 10% in the presence of regional and distant metastasis, respectively. Metastatic RCC is resistant to commonly used chemotherapeutic agents, and cytokine therapy with either interleukin (IL)-2 or interferon-α (IFN-α) was standard treatment for metastatic RCC in the United States and Europe until 2005. Although more effective than traditional chemotherapy, it produced only modest response rates with significant toxicity.[37] Identification of the molecular pathways implicated in the etiology of RCC has led to the development of targeted tyrosine kinase inhibitors and monoclonal antibodies directed against the vascular endothelial growth factor (VEGF) pathway (sorafenib, sunitinib, bevacizumab, pazopanib, axitinib, cabozantinib) and mammalian target of rapamycin (mTOR) (temsirolimus, everolimus). In randomized studies, many of these agents, when compared with standard existing therapy, have improved both progression-free and overall survival when used as first- or second-line therapy.[38-43] The European Association of Urology has made recommendations on the sequence in which these agents should be used (Table 59.6).[29] Nephrologic aspects of cancer therapy are further discussed in Chapter 65.

Natural History of Renal Impairment After Surgical Treatment of Renal Cancer

Normal renal function is usually preserved in the long term after donor transplant nephrectomy. Donors are highly selected to minimize comorbidities and generally are younger than patients treated for renal tumors. However, emerging long-term evidence suggests those undergoing donor nephrectomy do have increased long-term cardiovascular complications and reduced survival.[44] Similarly, after surgery for renal cancer, when the residual functioning renal tissue is reduced, there is significant risk for late sequelae, including proteinuria, glomerulosclerosis, and progressive renal failure resulting in increased cardiovascular complications and reduced survival. These risks are thought to be greater when radical rather than partial nephrectomy is performed. A recent systematic review of 21 nonrandomized comparative studies (11,204 patients) evaluating partial nephrectomy versus radical nephrectomy demonstrated superiority for NSS.[45] Partial nephrectomy was associated with greater perioperative blood loss and postoperative complications, affirming that it is a more challenging procedure. However, NSS was associated with a lower long-term decline in eGFR and reduced risk for chronic kidney disease. NSS also provided a more favorable cancer-specific survival. The one RCT to compare partial nephrectomy versus radical nephrectomy also has demonstrated that fewer patients undergoing NSS develop chronic kidney disease (eGFR <60), but overall survival and cancer outcomes are similar with either modality.[33]

Renal Cell Carcinoma in von Hippel–Lindau Disease

von Hippel–Lindau disease (VHL) is a rare autosomal dominant condition with a predisposition to the development of RCC. The genetics, clinical manifestations, and general management of VHL are discussed further in Chapter 45. The incidence of RCC in patients with VHL is about 45%. On histologic examination, the tumors are of the clear cell type, often multifocal and bilateral, and can be solid or cystic. The mean age at diagnosis is 39 years, and there is a 30% to 35% risk for tumor progression, metastasis, and death.

Longitudinal imaging studies have described the natural history of VHL renal lesions. In one study multifocal lesions were frequent[46] (on average, eight per patient), of which 74% were classified as simple cysts, 8% as complex cysts with solid components, and 18% as solid masses. The solid components of VHL lesions almost always contain RCC. During a mean 2.4-year follow-up, most cysts remained the same size (71%) or enlarged (20%), and 9% became smaller. On the contrary, 95% of solid masses increased in size. Although it is generally thought that the cysts are premalignant, the transformation of a simple cyst to a solid lesion was observed in only two patients. Patients with VHL require multidisciplinary management. Surgical intervention is not used for tumors smaller than 3 cm because metastasis is rare below this threshold. In addition, bilateral nephrectomy should be avoided, if possible, because of the substantial morbidity associated with renal replacement therapy. The standard of care for these patients is partial nephrectomy, and a 10-year survival rate of 81% has been reported.

The results of NSS for VHL appear less satisfactory than for sporadic RCC because of a high risk for local tumor recurrence. Repeated surgery may be needed for new or growing lesions, and for this reason the use of minimally invasive methods is being investigated. Repeated ablation of tumors with radiofrequency and cryotherapy is possible with minimal morbidity; however, the long-term effectiveness of these methods has not yet been established.

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SELF-ASSESSMENT QUESTIONS

1. A 50-year-old man presents with right-sided ureteral colic and on subsequent investigation is found to have a 4-mm distal ureteral calculus with no hydronephrosis. He has a normal estimated glomerular filtration rate (eGFR). In the absence of ongoing pain or sepsis, what is the most appropriate management option?
   A. Acute endoscopic lasertripsy
   B. Decompression with ureteric stenting
   C. Trial of medical expulsive therapy
   D. Discharge from care of urologist
   E. Percutaneous nephrostomy
2. A 70-year-old man is seen in an outpatient clinic with a 2-month history of intermittent hematuria. He takes warfarin for atrial fibrillation but is otherwise healthy. His eGFR is in the normal range. What urologic investigations does he require?
   A. Clotting screen to exclude overanticoagulation as the sole cause of his hematuria
   B. Clotting screen; proceed to urologic workup only if international normalized ratio (INR) is within therapeutic range
   C. Clotting screen, flexible cystoscopy, and computed tomography (CT) urogram
   D. Clotting screen, renal function tests, flexible cystoscopy, and CT urogram
3. A 60-year-old man with diabetic nephropathy is referred with a 3-cm lower pole renal lesion suspicious for malignancy on routine ultrasound scan. These findings are confirmed on CT scan. Despite his comorbidity he is deemed fit for surgery. What is the most appropriate procedure to consider?
   A. Open radical nephrectomy to achieve maximum oncologic benefit
   B. Laparoscopic cryosurgery
   C. Laparoscopic partial nephrectomy
   D. Laparoscopic radiofrequency ablation

60

Acute Interstitial Nephritis

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DEFINITION

Acute interstitial nephritis (AIN) is an acute, often reversible disease characterized by inflammatory infiltrates within the interstitium. AIN is a relatively rare cause of acute kidney injury (AKI), but it should not be overlooked because it usually requires specific therapeutic interventions.

PATHOGENESIS

Most studies suggest that AIN is an immunologically induced hypersensitivity reaction to an antigen that is classically a drug or an infectious agent. Evidence for a hypersensitivity reaction in drug-induced AIN includes the following: it occurs only in a small percentage of individuals; it is not dose dependent; it is often associated with extrarenal manifestations of hypersensitivity; it recurs after accidental reexposure to the same drug or to a closely related one; and it is sometimes associated with evidence of delayed-type hypersensitivity reaction (renal granulomas). Similarly, AIN secondary to infections can be differentiated from pyelonephritis by the relative absence of neutrophils in the interstitial infiltrates and the failure to isolate the infective agent from the renal parenchyma, again suggesting an immunologic basis to the disease.

Experimental models of AIN have identified three major types of antigens that induce AIN.[1] Antigens may be tubular basement membrane (TBM) components (e.g., the glycoproteins 3M-1 and TIN-Ag/TIN1), secreted tubular proteins (e.g., uromodulin), or nonrenal proteins (e.g., from immune complexes).

Although human AIN may be secondary to an immune reaction directed against a renal antigen, most cases of AIN are probably induced by extrarenal antigens, being produced in particular by drugs or infectious agents. These antigens may induce AIN by a variety of mechanisms, including binding to kidney structures ("planted antigen"); acting as haptens that modify the immunogenicity of native renal proteins; mimicking renal antigens, resulting in a cross-reactive immune reaction; and precipitating within the interstitium as circulating immune complexes.

Experimental models have identified both cell-mediated immunity and antibody-mediated immunity in the pathogenesis of AIN (Fig. 60.1). In humans, most forms of AIN are not associated with antibody deposition, which suggests that cell-mediated immunity plays a major role. This hypothesis is reinforced by the fact that interstitial infiltrates usually contain numerous T cells and these infiltrates sometimes form granulomas. Nevertheless, deposition of anti-TBM antibodies or of immune complexes can be observed occasionally in renal biopsy specimens, and antibody-mediated immunity may play a role in the pathogenesis of the disease in these cases.

Formation of immune complexes within the interstitium, or interstitial infiltration with T cells, will result in an inflammatory reaction. This reaction is triggered by many events, including activation of the complement cascade by antibodies and release of inflammatory cytokines by T lymphocytes and phagocytes (see Fig. 60.1). Although the interstitial inflammatory reaction may resolve without sequelae, it sometimes induces interstitial fibroblast proliferation and extracellular matrix synthesis, leading to interstitial fibrosis and chronic kidney disease (CKD). Cytokines such as transforming growth factor-β appear to play a key role in the latter process.

EPIDEMIOLOGY

AIN is a relatively uncommon cause of AKI, although its incidence may be increasing.[2] It accounts for 2% to 3% of all renal biopsies, 10% to 15% or biopsies performed for unexplained AKI, and up to 25% of those performed for drug-induced AKI.[2] Of kidney biopsies done in children with AKI, 3% to 7% show AIN.[3]

Before antibiotics were available, AIN was most commonly associated with infections such as scarlet fever and diphtheria. Drug-induced AIN now appears to account for about 70% to 90% of all cases.

DRUG-INDUCED ACUTE INTERSTITIAL NEPHRITIS

Clinical Manifestations

In the 1960s and 1970s, most cases of drug-induced AIN were caused by methicillin, and the clinical manifestations of methicillin-induced AIN were considered the prototypical presentation of AIN. Since then, many other drugs have been implicated in the induction of AIN (Box 60.1), of which antimicrobial agents (in particular, β-lactam antibiotics, sulfonamides, fluoroquinolones, and rifampin), nonsteroidal antiinflammatory drugs (NSAIDs) (especially fenoprofen), and proton pump inhibitors (PPIs) have been most commonly involved.[4,5] In a large case series of biopsy-proven AIN, drug-induced AIN was due to antibiotics in 49% of cases, NSAIDs in 11%, and PPIs in 14%.[4] Other antiulcer agents, diuretics, phenindione, phenytoin, allopurinol, highly active antiretroviral therapy (HAART), and anticancer agents such as tyrosine kinase inhibitors, pemetrexed, and ifosfamide also have been reported

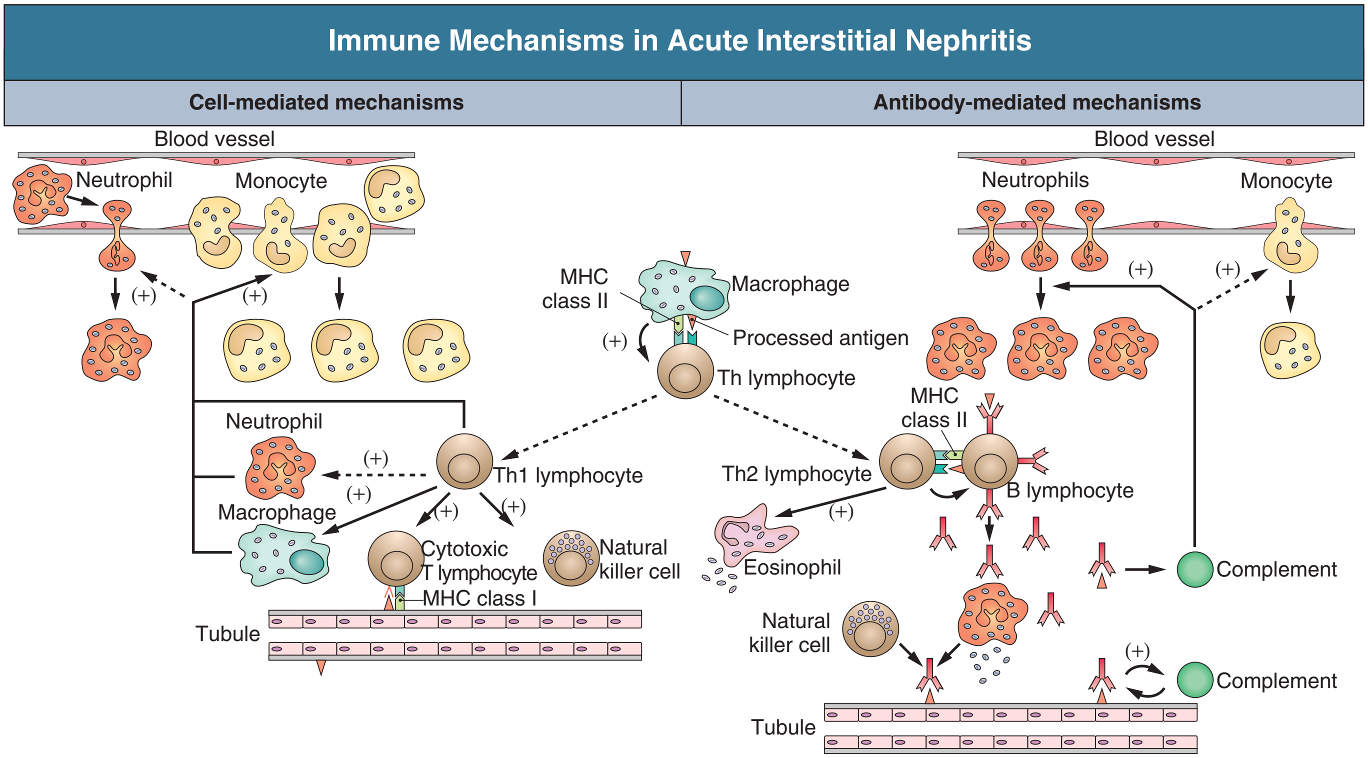
Immune Mechanisms in Acute Interstitial Nephritis
Cell-mediated mechanisms
Antibody-mediated mechanisms
Blood vessel
Neutrophil
Monocyte
(+)
(+)
MHC class II
Macrophage
Processed antigen
(+)
Th lymphocyte
Neutrophil
(+)
(+)
Th1 lymphocyte
Macrophage
(+)
(+)
Cytotoxic T lymphocyte
Natural killer cell
MHC class I
Tubule
Blood vessel
Neutrophils
Monocyte
(+)
(+)
MHC class II
Th2 lymphocyte
(+)
B lymphocyte
Eosinophil
Complement
Natural killer cell
(+)
Complement
Tubule

Fig. 60.1 Immune mechanisms that can be involved in acute interstitial nephritis. Both cell-mediated and antibody-mediated mechanisms occur. The cell-mediated mechanism is primarily associated with macrophages and T cells. The antibody-mediated mechanism is frequently associated with neutrophil or eosinophil infiltration as well as with local complement activation. *MHC,* Major histocompatibility complex.

to cause AIN.[6,7] In addition, AIN is one of the immune-related adverse events that can be caused by immune checkpoint inhibitors (e.g., PD-1, PD-L1, and CTLA-4 inhibitors), and more than 20 cases have been published.[8,9] Most other drugs only rarely have been linked with AIN (see Box 60.1). AIN also has been reported after snake or wasp envenomation, and the pathogenic mechanism is likely to be similar to that in drug-induced AIN.

The clinical characteristics of drug-induced AIN are now recognized as much more varied and nonspecific than the spectrum seen in classic methicillin-induced AIN (Fig. 60.2).[2,10,11]

Renal Manifestations

Symptoms of AIN usually develop a few days to a few weeks after the inciting drug is started, although cases have occurred months after initial exposure to the drug. In particular, AIN induced by NSAIDs or PPIs is often diagnosed several months after treatment initiation, and a similar delay has been reported with immune checkpoint inhibitors. The typical presentation is sudden impairment in renal function, associated with mild proteinuria (<1 g/day) and abnormal urinalysis, in a patient with flank pain, normal blood pressure, and no edema. However, the clinical presentation is often incomplete (see Fig. 60.2), and AIN should be considered in any patient with unexplained AKI.[2,10,11] Renal dysfunction may be mild or severe, and dialysis is required in about one third of patients. Hematuria and pyuria are present in a little more than half of the patients, and although leukocyte casts are common, hematuria is almost never associated with red blood cell casts. Flank pain (reflecting distention of the renal capsule) is observed in about one third of the patients and can be the main complaint on hospital admission. Some patients have low fractional sodium excretion.

Standard imaging procedures show kidneys normal in size or slightly enlarged. Ultrasound usually discloses an increased cortical echogenicity (comparable to or higher than that of the liver).

Extrarenal Manifestations

Extrarenal symptoms consistent with a hypersensitivity reaction are occasionally observed, including low-grade fever, maculopapular rash (Fig. 60.3), mild arthralgias, and eosinophilia. However, each of these symptoms is typically present in fewer than half of the patients (see Fig. 60.2), and these symptoms are all present together in less than 10% of patients.[2,10,11] With some drugs, other manifestations of hypersensitivity, such as hemolysis or hepatitis, can be present. Serum immunoglobulin E (IgE) levels also may be elevated.

The association of AKI with clinical signs suggestive of hypersensitivity or eosinophilia should lead to consideration of AIN. However, signs of hypersensitivity can be observed in patients with AKI not related to AIN, including patients with drug-induced acute tubular necrosis.

Specific Drug Associations

The clinical and biological manifestations of AIN may have some specificity, depending on the drug involved.

As outlined earlier, methicillin-induced AIN was characterized by a high frequency of abnormal urinalysis and extrarenal symptoms and by well-preserved renal function. Renal failure has been reported in only about 50% of patients (see Fig. 60.2).[10]

More than 200 cases of rifampin-induced AKI have been reported.[12] Prior exposure is common; most cases have been observed either after readministration of rifampin or several months after intermittent administration of the drug has begun. Renal failure is usually associated

BOX 60.1 Drugs Responsible for Acute Interstitial Nephritis

Antimicrobial Agents

Penicillins

Amoxicillin
Ampicillin*
Aztreonam
Carbenicillin
Cloxacillin
Flucloxacillin
Methicillin*
Mezlocillin
Nafcillin
Oxacillin*
Benzylpenicillin*
Piperacillin

Cephalosporins

Cefaclor
Cefazolin
Cefotaxime
Cefotetan
Cefoxitin
Ceftriaxone
Cephalexin
Cephaloridine
Cephalothin
Cephradine

Quinolones

Ciprofloxacin*
Levofloxacin*
Moxifloxacin
Norfloxacin

Others

Acyclovir
Azithromycin
Clarithromycin
Colistin
Cotrimoxazole*
Erythromycin*
Ethambutol
Flurithromycin
Foscarnet
Gentamicin
Indinavir
Interferon
Isoniazid
Lincomycin
Linezolid
Minocycline
Nitrofurantoin*
Piromidic acid
Polymyxin B*
Quinine
Rifampin* (rifampicin*)
Spiramycin*
Sulfonamides*
Teicoplanin
Telithromycin
Tetracycline
Vancomycin*

NSAIDs Including Salicylates

Salicylates and Derivatives

Aspirin (acetyl salicylic acid)
Diflunisal*

Propionic Acid Derivatives

Benoxaprofen
Fenbufen
Fenoprofen*
Flurbiprofen
Ibuprofen*
Ketoprofen
Naproxen

Acetic Acid Derivatives

Indometacin* (indomethacin*)
Alclofenac
Diclofenac
Fenclofenac
Sulindac
Zomepirac

Enolic Acid Derivatives

Meloxicam
Piroxicam*

Fenamic Acid Derivatives

Mefenamic acid

Coxibs

Celecoxib
Rofecoxib

Others

Azapropazone
Mesalamine (mesalazine, 5-ASA)
Phenazone
Phenylbutazone
Sulfasalazine
Tolmetin

Antalgics

Aminopyrine
Antipyrine

Anticonvulsants

Carbamazepine*
Diazepam
Lamotrigine*
Levetiracetam
Phenobarbital (phenobarbitone)
Phenytoin*
Valproic acid (valproate sodium)

Diuretics

Chlorthalidone
Etacrynic acid (ethacrynic acid)
Furosemide* (frusemide*)
Hydrochlorothiazide*
Indapamide
Triamterene*

Antiulcer Agents

Histamine-2 Receptor Antagonists

Cimetidine*
Famotidine
Ranitidine

Proton Pump Inhibitors

Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole

Immune Checkpoint Inhibitors

Ipilimumab*
Nivolumab
Pembrolizumab

Other Anticancer Agents

Adriamycin
Bevacizumab
Bortezomib
Carboplatin
Cytosine arabinoside
Gemcitabine
Ifosfamide
Interleukin-2
Lenalidomide
Methotrexate
Pemetrexed
Sorafenib
Sunitinib

Others

Allopurinol*
α-Methyl dopa
Amlodipine
Azathioprine
Betanidine (bethanidine)*
Bismuth salts
Captopril*
Carbimazole
Cetirizine
Chlorpropamide*
Clofibrate
Clozapine
Cyclosporine
Deferasirox
Diltiazem
D-Penicillamine
Etanercept
Exenatide
Fenofibrate*
Fluindione
Gold salts
Griseofulvin
Interferon
Isotretinoid
Liraglutide
Nifedipine*
Phenindione*
Phenothiazine
Phenylpropanolamine
Probenecid
Propranolol
Propylthiouracil
Sirolimus
Streptokinase
Sulfinpyrazone
Warfarin
Zopiclone
Nonsteroidal antiinflammatory drugs.

*Drugs that can cause granulomatous AIN.
Drugs most commonly involved are in bold.

with the sudden onset of fever, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), and myalgias. It also may be associated with hemolysis, thrombocytopenia, and, less frequently, hepatitis. Renal biopsy typically discloses tubular injury in addition to interstitial inflammatory infiltrates. Although circulating antirifampin antibodies are usually found in these patients, immunofluorescence staining of renal biopsy specimens for immunoglobulin and complement has been negative in most cases, suggesting that cell-mediated immunity plays a key role in the induction of the nephritis. In a few cases, AIN developed after continuous treatment with rifampin for 1 to 10 weeks. It

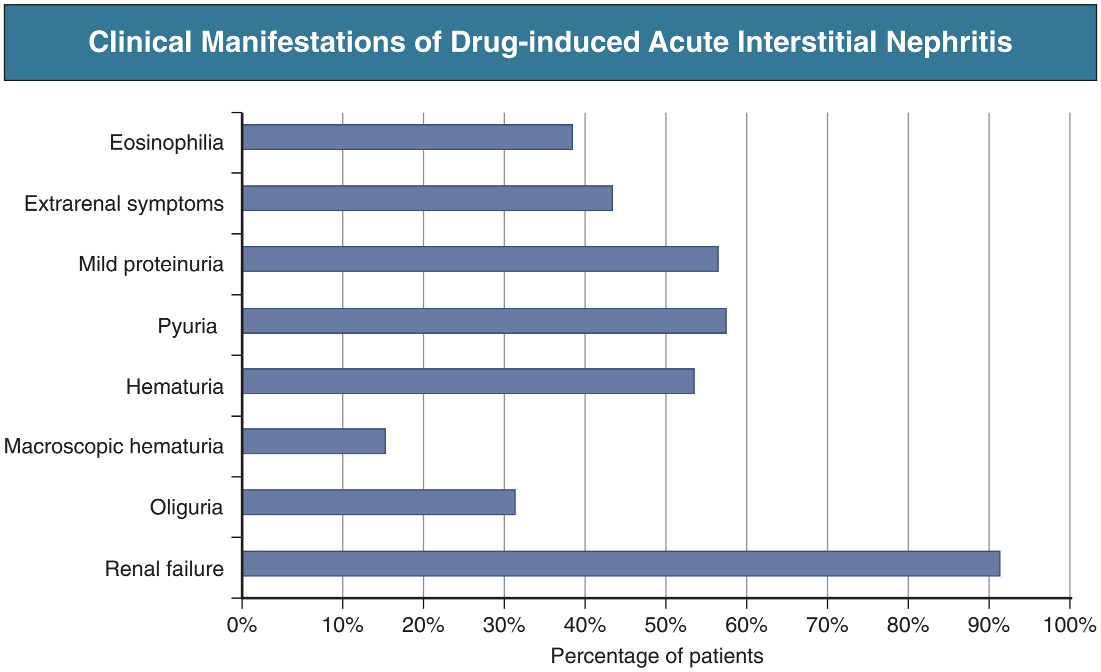

Fig. 60.2 Clinical manifestations of drug-induced acute interstitial nephritis (AIN). Data were pooled from different case reports, including more than 200 patients with drug-induced AIN. Patients with AIN associated with methicillin therapy or with a nephrotic syndrome are not included.

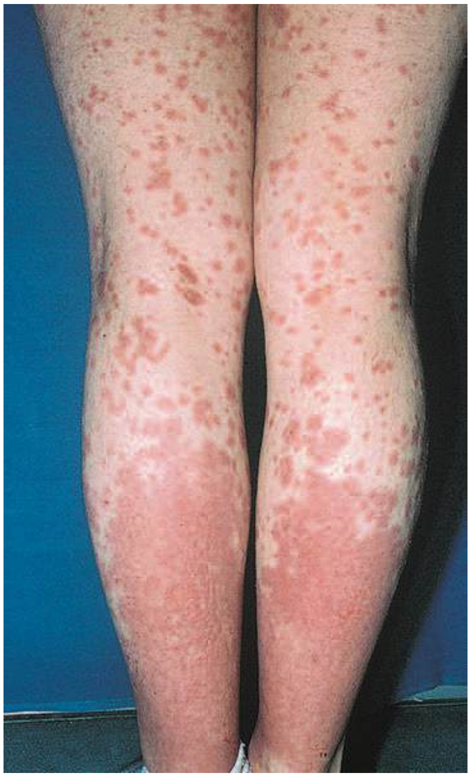

Fig. 60.3 Maculopapular rash in a patient with drug-induced acute interstitial nephritis (AIN). Such cutaneous lesions occur in about 40% of patients with drug-induced AIN, but they can also be seen in patients with drug-induced acute tubular necrosis.

was almost never associated with extrarenal symptoms or antirifampin antibodies, and renal biopsy specimens showed severe interstitial infiltrates but few tubular lesions.

Phenindione-induced AIN is generally associated with the development of hepatitis, which can be fatal.

Allopurinol-induced AIN appears to occur more often in patients with CKD and is usually seen in association with rash and liver dysfunction and sometimes with full manifestations of Stevens-Johnson syndrome.[13] This severe allergic reaction is primarily observed in patients with the human leukocyte antigen B58 genotype.

AIN caused by NSAIDs is associated with nephrotic syndrome in about three fourths of cases. This usually occurs in patients older than 50 years, and although it has been observed with all NSAIDs, including COX-2–selective inhibitors, half of the cases have been reported with fenoprofen. Most occurrences develop after the patient has taken NSAIDs for some months (6 months on average), but AIN can occur within days or after more than a year. With the exception of the heavy proteinuria and associated edema, the presentation of these patients is similar to that of patients with other forms of drug-induced AIN (Fig. 60.4). The main difference is that extrarenal symptoms are present in only about 10% of patients. Renal disease caused by NSAIDs must be differentiated from other NSAID-induced nephropathies, including hemodynamically mediated AKI, papillary necrosis, and NSAID-induced membranous nephropathy. Drugs other than NSAIDs can rarely induce AIN associated with the nephrotic syndrome; a few cases have been reported after administration of ampicillin, rifampin, lithium, interferon, phenytoin, pamidronate, and D-penicillamine.

PPIs, such as omeprazole or pantoprazole, are increasingly recognized as a cause of AIN, with over 100 cases reported. Symptoms are often nonspecific, although approximately 10 percent of subjects present with fever, chills, and anorexia. Consistent with the fact that drug-induced AIN can lead to permanent kidney damage, large observational studies have shown that the use of PPIs is associated with an increased risk for development or progression of CKD, and development of AIN is viewed as being the likely underlying mechanism.[18]

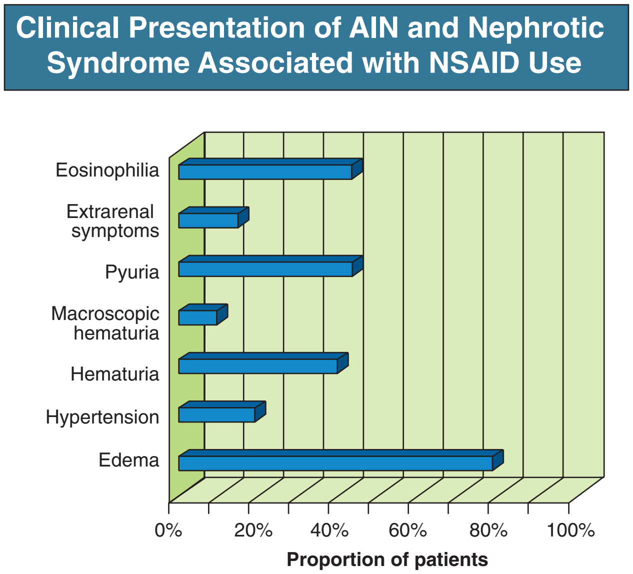

Fig. 60.4 Clinical presentation of acute interstitial nephritis (AIN) and nephrotic syndrome associated with nonsteroidal antiinflammatory drug (NSAID) use. Data were pooled from different case reports including more than 60 patients.

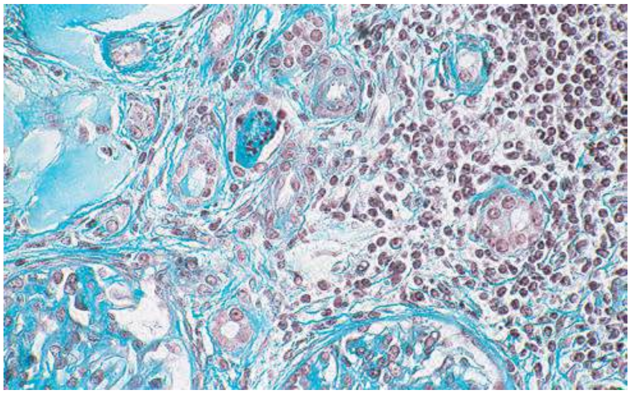

Fig. 60.5 Drug-induced acute interstitial nephritis. On light microscopy, the characteristic feature is interstitial infiltration with mononuclear cells, with normal glomeruli. It is usually associated with interstitial edema and tubular lesions. (Courtesy Dr. B. Mougenot, Paris VI University, Paris.)

Pathology

The hallmark of AIN is the presence of inflammatory infiltrates within the interstitium (Fig. 60.5). These infiltrative lesions are often patchy, predominating in the deep cortex and outer medulla, but they can be diffuse in severe cases. They are composed mostly of T cells and monocytes-macrophages, but plasma cells, eosinophils, and a few neutrophilic granulocytes also may be present. The relative number of $CD4^+$ T cells and $CD8^+$ T cells is variable from one patient to another. In some cases, T lymphocytes infiltrate across the TBM and between tubular cells, mainly in distal tubules, and the resulting lesion is referred to as *tubulitis*.

In some cases of drug-induced AIN, renal biopsy shows interstitial granulomas (Fig. 60.6). These granulomas are usually sparse and nonnecrotic, with few giant cells, and are associated with nongranulomatous interstitial infiltrates. Granulomas are also found in AIN related to infection (Table 60.1), sarcoidosis, Sjögren syndrome, and Wegener granulomatosis.

Interstitial infiltrates are always associated with an interstitial edema, which is responsible for separating the tubules (see Fig. 60.5). They can

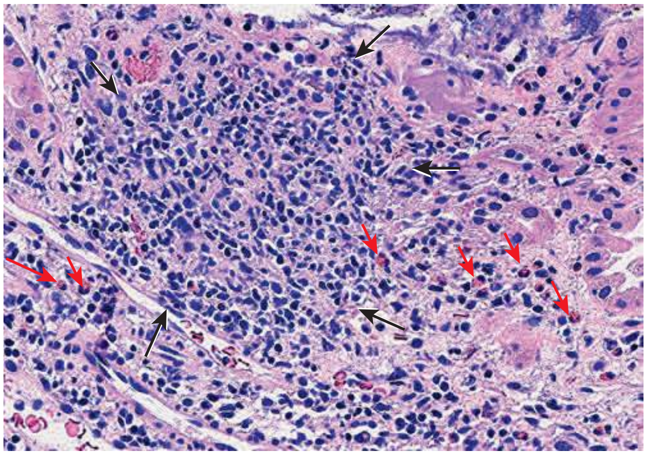

Fig. 60.6 Drug-induced granulomatous acute interstitial nephritis (AIN). The patient was taking omeprazole over the counter and presented with fever, chills, malaise, and cough. Workup showed a serum creatinine of 4.5 mg/dl (400 µmol/L) and 15.5-cm enlarged kidneys that were pushing up on the diaphragm, causing the cough. Biopsy shows AIN with eosinophils *(red arrows)*, lymphocytes, and early granuloma formation (demarcated by *black arrows*). (Courtesy R. J. Johnson, University of Colorado, Denver, Colo.)

TABLE 60.1 Infections That Can Be Associated With Acute Interstitial Nephritis

Bacteria	Viruses	Parasites	Others
Brucella spp.	Adenovirus	*Toxoplasma* spp.*	*Chlamydia* spp.
Campylobacter jejuni	Cytomegalovirus	*Leishmania donovani*	*Mycoplasma* spp.
Corynebacterium diphtheriae	Epstein-Barr virus*		
Escherichia coli	Hantavirus		
Legionella spp.	Hepatitis A virus		
Leptospira spp.	Hepatitis B virus		
*Mycobacterium tuberculosis**	Herpes simplex virus		
Salmonella spp.*	Human immunodeficiency virus		
Staphylococcus spp.	Measles virus		
Streptococcus spp.	Polyomavirus		
Yersinia pseudotuberculosis	Rickettsia		

*Infections that can induce granulomatous AIN.

also be associated with focal tubular lesions, which range from mild cellular alterations to extensive necrosis of epithelial cells, and are sometimes associated with a disruption of the TBM. These tubular lesions usually predominate where the inflammatory infiltrates are most extensive.

Tubulointerstitial lesions are not associated with vascular or glomerular lesions. Even in AIN associated with a nephrotic syndrome, glomeruli appear normal on light microscopy; glomerular lesions are similar to those seen in minimal change disease (see Chapter 17).

In most patients with AIN, renal biopsy specimens do not show immune deposits, and both immunofluorescence and electron microscopy are negative. Nevertheless, staining of the tubular or capsular basement membrane for IgG or complement may occasionally be seen by immunofluorescence; the staining pattern is either granular or linear (Fig. 60.7). Linear fixation of IgG along the TBM indicates the presence of antibodies directed against membrane antigens or against drug metabolites bound to the TBM, and circulating anti-TBM antibodies have been detected in some cases. These linear deposits are seen mostly in patients taking NSAIDs, phenytoin, or allopurinol.

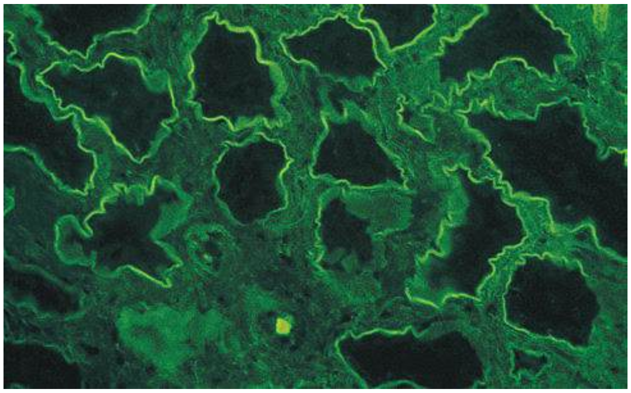

Fig. 60.7 Linear deposits of IgG in drug-induced acute interstitial nephritis. Deposits along the tubular basement membrane (TBM) are shown on immunofluorescence microscopy. These antibodies recognize either a component of the TBM or a drug metabolite bound to the TBM. (Courtesy Dr. B. Mougenot, Paris VI University, Paris.)

Diagnosis

The most accurate way to diagnose AIN is by renal biopsy. However, both eosinophiluria and gallium scanning have been suggested as helpful in making the diagnosis.

Eosinophils can be detected in urine and, although eosinophiluria is frequently used to corroborate the diagnosis of drug-induced AIN, review of published series shows that this test has rather poor sensitivity and a low positive predictive value, even when only patients with AKI are considered. In the largest and most recent series, only 36% (26 of 73) of patients with drug-induced AIN had eosinophiluria, and 28% (20 of 69) of patients with acute tubular necrosis also had eosinophiluria (Fig. 60.8).[14] In addition, eosinophiluria has been reported in patients with diseases such as proliferative or crescentic glomerulonephritis (GN), atheroembolic renal disease, urinary tract infection, urinary schistosomiasis, and even prerenal AKI.[15] Thus eosinophiluria as a screening test for AIN should be abandoned. Firm diagnosis requires renal biopsy and/or a clinical response on withdrawal of the drug of concern.

An increased renal uptake of gallium-67 (^{67}Ga) has been reported in AIN.[16] Analysis of available series shows that in 53 patients with AIN, 83% had an abnormal renal scan (maximum after 48 hours), whereas it was normal in 17 of 18 patients with acute tubular necrosis. However, these studies were small and retrospective, and ^{67}Ga renal scanning is not specific for AIN and may be abnormal in patients with pyelonephritis, cancer, or glomerular diseases. Therefore we do not recommend use of gallium scanning as a diagnostic tool.

Because the clinical presentation of AIN may be polymorphic and because noninvasive diagnostic procedures have important limitations, renal biopsy is often essential for the diagnosis of AIN. Several studies have shown that prebiopsy diagnosis may be incorrect in a substantial number of patients.

Identification of the Causative Drug

Identification of the causative drug is relatively easy when AIN occurs in a patient taking only one drug. However, patients are often taking more than one drug capable of inducing AIN. Two biological tests have been used, primarily in research laboratories, to help identify the

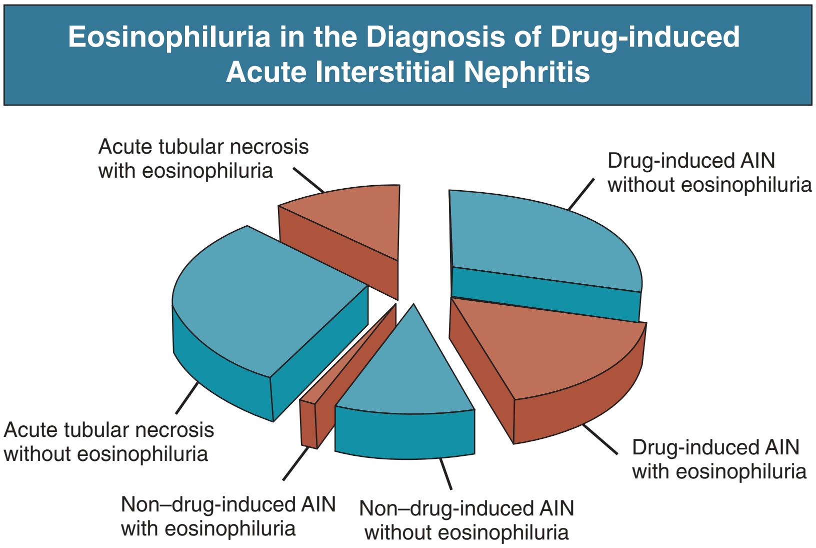

Fig. 60.8 Eosinophiluria in the diagnosis of drug-induced acute interstitial nephritis (AIN). Data from a recent and large retrospective series confirm that eosinophiluria (defined by the presence of 1% or more eosinophils in urine) lacks sensitivity and specificity for the diagnosis of drug-induced AIN in patients with AKI. (From reference 14.)

causative drug: the lymphocyte stimulation test and the identification of circulating antidrug antibodies.

Identification of circulating antidrug antibodies has been used mostly for patients thought to have AIN induced by rifampin. Antirifampin antibodies are present in most patients with rifampin-induced AIN, but, unfortunately, they have also been detected in patients taking rifampin and having no adverse reaction to the drug, so this test has limited diagnostic value.

The lymphocyte stimulation test has been used since the 1960s to identify a sensitizing drug. It is based on the measurement of lymphocyte proliferation in the presence of different drugs; a high proliferative index reflects a sensitization of T lymphocytes against the drug. However, this test lacks specificity and we do not recommend using it.

Natural History

Drug-induced AIN was long considered benign, with complete recovery of renal function if the inciting agent was removed. However, recent studies show that the course of AIN is not always benign and serum creatinine does not return to baseline in about 40% to 50% of patients.[4,10,17] Even in those with renal recovery, an increase in serum creatinine can persist for several weeks. Unfortunately, there are few known prognostic predictors. The severity of renal failure does not appear to be linked with the prognosis.[4,10] It has been suggested that the presence on renal biopsy of diffuse neutrophil- or macrophage-rich infiltrates, interstitial granulomas, or tubular atrophy is associated with a poor prognosis, but this has not been consistently found in all series. The best prognostic predictors may actually be the duration of AKI and the severity of interstitial fibrosis.

Treatment

In addition to removal of the inciting agent, which is essential and should be done as soon as possible, corticosteroids have been used to treat AIN. Most commonly, patients received high-dose oral corticosteroids sometimes associated with pulses of intravenous methylprednisolone. Analysis of series comparing patients who did or did not receive corticosteroids does not allow firm conclusions about the effect of corticosteroid therapy on long-term renal function because all the series were small, uncontrolled, and retrospective. However, some authors advocate an early and systematic use of a short course of corticosteroids[11,17] because of the possibility that this will hasten the recovery of renal function. In different series, corticosteroids rapidly induced a reduction in serum creatinine in patients whose renal function did not improve within about 1 week after discontinuation of the inciting agent. It is interesting to note that in patients with NSAID-induced AIN, corticosteroids do not seem to modify the course of the nephrotic syndrome.

On the basis of anecdotal case reports, some authors have advocated use of mycophenolate mofetil in patients resistant to corticosteroids.[19]

We recommend administration of a short course of prednis(ol)one in patients who are dialysis dependent or whose renal function fails to improve within 1 week after discontinuation of the inciting drug and rapidly return to baseline values, provided the diagnosis of AIN has been confirmed by renal biopsy. We initiate the treatment with a dose of prednisone of 1 mg/kg/day and not higher than 60 mg/day, and after 1 to 2 weeks, we progressively taper the dose so that the total duration of treatment is 4 to 6 weeks.

ACUTE INTERSTITIAL NEPHRITIS SECONDARY TO INFECTIOUS DISEASES

Infections were once the most common cause of AIN, but the frequency of AIN induced by an infection has dramatically decreased with the widespread use of antibiotics. Nevertheless, the diagnosis of infectious AIN should not be overlooked, and AIN occurring in patients treated with antibiotics should not always be attributed to the drug.

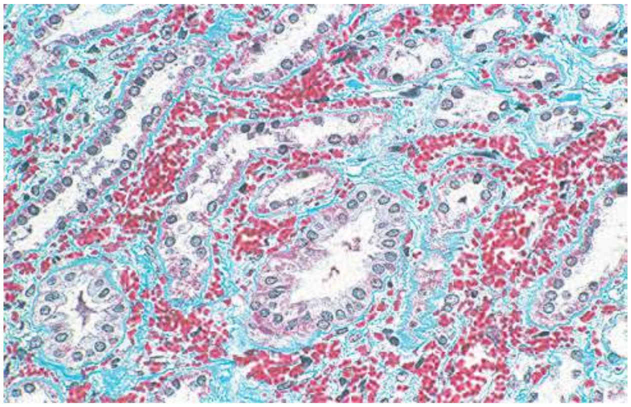

Fig. 60.9 Acute interstitial nephritis secondary to Hantavirus infection. Vascular congestion and foci of medullary hemorrhage are suggestive of the diagnosis. (Courtesy Dr. B. Mougenot, Paris VI University, Paris.)

Infectious agents can cause renal parenchymal inflammation by direct infection, resulting in acute pyelonephritis (see Chapter 51). However, many infectious agents may induce an immunologically mediated AIN in the absence of direct invasion (see Table 60.1). In this case, the clinical presentation depends mostly on the underlying infection. On histologic examination, lesions are identical to those described for drug-induced AIN, and they also can occasionally result in granulomas (see Table 60.1). Infection-associated AIN usually resolves with the treatment of the underlying infection, and corticosteroid therapy is not recommended.

An important cause of infection-associated AIN is hantavirus.[20] Hantavirus infections occur worldwide and are responsible for a disease that has been known as *hemorrhagic fever with renal syndrome*, epidemic hemorrhagic fever, and nephropathia epidemica. Rodents are the main reservoir of the virus, and humans are most probably infected by the airborne route. Besides fever, fatigue, and muscle aches, which are observed in all patients, extrarenal symptoms often include headache, lightheadedness, abdominal pain, nausea and vomiting, and thrombocytopenia; the last can be responsible for hemorrhagic complications. AKI is almost always associated with proteinuria, sometimes in the nephrotic range, and with hematuria. When a kidney biopsy is performed, it discloses not only interstitial inflammatory infiltrates, which predominate in the medulla, but also vascular congestion and interstitial bleeding (Fig. 60.9). In about 50% of patients, immunofluorescence studies show granular immune deposits along the TBM and within glomeruli. Serum creatinine concentration usually starts to decrease after a few days, and a complete recovery of renal function is the rule. Nevertheless, in the more severe cases, recovery can be complicated by the occurrence of hemorrhagic complications or severe shock. The diagnosis is based on serologic test results, which become positive early (within weeks) in the course of the disease.

Tubulointerstitial lesions are common in HIV-positive patients who undergo a renal biopsy for AKI. Interstitial infiltrates are often associated with glomerular lesions, but they can be isolated. These forms of AIN have been observed in both White and Black patients, and they might be related not only to drugs and opportunistic infections but also to the HIV infection itself.[21,22]

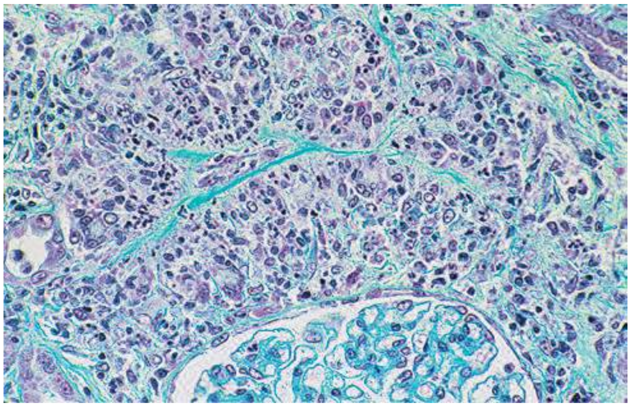

Fig. 60.10 Granulomatous acute interstitial nephritis in a patient with sarcoidosis. (Courtesy Dr. B. Mougenot, Paris VI University, Paris.)

ACUTE INTERSTITIAL NEPHRITIS ASSOCIATED WITH SYSTEMIC DISEASES

Sarcoidosis

In sarcoidosis, renal impairment usually occurs as a complication of hypercalciuria and hypercalcemia, but granulomatous AIN associated with sarcoidosis also has been reported (Fig. 60.10).[23,24] The presentation is usually that of AKI, which can be isolated or associated with mild proteinuria and sterile leukocyturia. It is associated with extrarenal symptoms of sarcoidosis in about 90% of patients, most frequently with lymphadenopathy and lung, eye, or liver involvement. Nevertheless, only slightly more than half of the patients have hilar lymphadenopathy or pulmonary interstitial fibrosis at the time of diagnosis.[24] Treatment with high-dose corticosteroids quickly improves renal function, but most patients do not recover completely. The starting dose should be prednis(ol)one 1 mg/kg/day and not higher than 60 mg/day, and corticosteroid therapy should be tapered slowly and not withdrawn before at least 1 year to prevent relapses. Whereas some authors advocate long-term maintenance therapy with low-dose corticosteroids, we usually stop corticosteroids after 2 to 3 years. Because of the risk for late relapse, these patients should be observed for a prolonged time.

Sjögren Syndrome

Clinically significant interstitial nephritis is rare in Sjögren syndrome and usually results in chronic tubular dysfunction.[25,26] Some patients may present with severe symptomatic hypokalemia with distal renal tubular acidosis. Rarely, Sjögren syndrome presents with AKI due to AIN, which is often responsive to treatment with high-dose corticosteroids.

Systemic Lupus Erythematosus

About two thirds of renal biopsy samples in patients with systemic lupus show some tubulointerstitial involvement, but significant tubulointerstitial injury in the setting of minimal glomerular abnormalities is rare, with only about 10 cases reported in the literature.[27] In these cases, renal biopsy shows typical features of AIN on light microscopy and immunofluorescence staining always discloses immune deposits along the TBM, usually with a granular pattern. Renal function improves after high-dose corticosteroids, and additional immunosuppressive drugs are not usually required. However, azathioprine has been used as a corticosteroid-sparing agent.

Immunoglobulin G4–Related Disease

IgG4-related disease is a newly recognized systemic autoimmune disease that predominantly affects males older than 50 years of age (see Chapter 62). In the kidney, it is most commonly responsible for AIN characterized by the presence of interstitial infiltrates rich in IgG4-positive plasma cells and immune deposits along the TBM.[28,29] This interstitial nephritis can be associated with membranous nephropathy, with renal inflammatory masses visible on imaging or with ureteral obstruction. It usually responds very rapidly to treatment with corticosteroids.

Other Systemic Diseases

Among patients with cryoglobulinemia and AKI, a few exhibit significant interstitial inflammatory infiltrates associated with granular immune deposits in the interstitium and along the TBM. This AIN is usually associated with characteristic glomerular lesions and, rarely, lesions of the arterioles, and treatment is the same as for cryoglobulinemia-induced GN (see Chapter 21).

Most renal lesions associated with small-vessel vasculitis consist of both extracapillary GN and tubulointerstitial nephritis (see Chapter 25). Nevertheless, a few patients with AIN and minimal glomerular lesions have been described.

ACUTE INTERSTITIAL NEPHRITIS ASSOCIATED WITH MALIGNANT NEOPLASMS

Infiltration of renal parenchyma by malignant cells is common in patients with leukemia or lymphoma. Most of the time, this infiltration is clinically silent (or causes enlarged kidneys), but a few patients with AKI have been described.[30] Chemotherapy or radiotherapy may rapidly improve renal function in these patients, but before these treatments are started, it is important to exclude more common causes of AKI associated with neoplastic diseases (see Chapter 65).

IDIOPATHIC ACUTE INTERSTITIAL NEPHRITIS

More than 50 cases of idiopathic AIN with anterior uveitis have been reported (TINU syndrome).[31] This syndrome is found most commonly in girls of pubertal age but also can occur in pubertal boys and in adults. Initial symptoms may be ocular, with ocular pain and visual impairment, or pseudoviral, with fever, myalgia, and asthenia. AIN is responsible for AKI, ranging from mild to severe, that may be associated with abnormal urinalysis. Renal biopsy shows diffuse interstitial inflammatory infiltrates, almost always without granulomas and without immune deposits. In children, renal prognosis is excellent, and serum creatinine usually returns to baseline values within a few weeks, with or without corticosteroid therapy. In adults the renal prognosis seems to be less favorable, and corticosteroid therapy might be useful in preventing evolution to chronic renal impairment. Uveitis, which can occur at any time in respect to AIN, is usually responsive to topical corticosteroids, but it may relapse without any recurrence of AIN.

Cases of idiopathic AIN without uveitis have been reported. Immunofluorescence studies of renal biopsy specimens can show linear deposits of IgG along the TBM, granular deposits of IgG along the TBM, or no immune deposits, suggesting this entity is heterogeneous. The treatment of patients with idiopathic AIN is still controversial. Patients who receive corticosteroids usually show a dramatic improvement of renal function, but others have recovered normal renal function without any treatment.

ACUTE INTERSTITIAL NEPHRITIS IN RENAL TRANSPLANTS

Acute rejection is by far the most common cause of AIN in renal allograft recipients (see Chapter 104). Nevertheless, AIN can be induced by drugs or infections. Cases of drug-induced AIN have been reported even in the first weeks after transplantation, when immunosuppression is maximal.[32] Among patients with infectious AIN, the frequency of polyomavirus (BK)-induced AIN appears to be increasing, and it should be suspected in patients with acute deterioration of renal function and so-called decoy cells in urine (see Chapter 105).[33]

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SELF-ASSESSMENT QUESTIONS

1. A 65-year-old man presents with unexplained acute kidney injury (AKI). A kidney biopsy shows the presence of diffuse inflammatory infiltrates within the interstitium, leading to the conclusion that the AKI is a result of acute interstitial nephritis (AIN). He has a recent history of treatment with a nonsteroidal antiinflammatory drug (NSAID) and a proton pump inhibitor (PPI) for osteoarthritis. Which *one* of the following statements is correct?
   A. Both nonsteroidal antiinflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) are among the classes of drugs most commonly responsible for AIN.
   B. Only very few cases of AIN have been attributed to treatment with a PPI, and the AIN was most likely induced by treatment with an NSAID.
   C. Only very few cases of AIN have been attributed to treatment with an NSAID, and the AIN was most likely induced by treatment with a PPI.
   D. Only very few cases of AIN have been attributed to treatment with a PPI or an NSAID, and the AIN is unlikely to have been induced by treatment with an NSAID or a PPI.
2. A 75-year-old woman presents with AKI associated with mild proteinuria (albumin-to-creatinine ratio 500 mg/g), microscopic hematuria, and pyuria. This AKI developed while she was being treated with a fluoroquinolone, and her treating physician suspects that the AKI was caused by AIN induced by the fluoroquinolone. Which *one* of the following statements is correct?
   A. The patient should be tested for eosinophiluria. If less than 1% of urinary white blood cells are eosinophils, the diagnosis of AIN can almost certainly be ruled out.
   B. The patient should undergo a renal gallium scan. If there is no renal uptake, the diagnosis of AIN can almost certainly be ruled out.
   C. The presence of an elevated ratio of albumin to creatinine is sufficient to rule out the diagnosis of drug-induced AIN in a patient who previously did not have albuminuria and who has not been treated with an NSAID.
   D. A renal biopsy is the only test that can be performed to reliably rule out or confirm the diagnosis of AIN.
3. A 30-year-old woman develops AKI while being treated with penicillin. A renal biopsy shows diffuse interstitial infiltrates, confirming the diagnosis of AIN. Her serum creatinine has been stable at 3.0 mg/dl for the last 5 days. Which *one* of the following statements is correct?
   A. The prognosis for drug-induced AIN is excellent, and full recovery should be expected within 6 weeks after removal of the inciting agent.
   B. The prognosis for drug-induced AIN is excellent in patients who do not have granulomas on renal biopsy, and full recovery should be expected.
   C. The prognosis for drug-induced AIN is excellent in patients who do not require dialysis, and full recovery should be expected if serum creatinine does not continue to rise.
   D. The course of drug-induced AIN is not always benign, and it leads to chronic kidney disease in at least 40% of cases.

61

Primary Vesicoureteral Reflux and Reflux Nephropathy

Ranjiv Mathews, Tej K. Mattoo

DEFINITION

Vesicoureteral reflux (VUR) is a congenital or acquired abnormality in which there is retrograde flow of urine from the bladder to the kidneys. VUR may be primary (congenital) and can be associated with various syndromes, or secondary, such as from increased bladder pressure resulting from obstructive uropathy or neurogenic bladder. This chapter discusses primary VUR.

VUR may be suggested by fetal ultrasound in pregnancy (in which intermittent renal pelvic dilation is observed) or after urinary tract infection (UTI) in childhood. Prenatal renal injury in the form of dysplasia has been noted with high-grade VUR. The presence of VUR increases the risk for postnatal upper UTI, and the two together can cause renal injury leading to scarring of the kidney termed *reflux nephropathy* (RN). RN may manifest as hypertension, preeclampsia, chronic kidney disease (CKD), and even end-stage renal disease (ESRD). Some patients present with proteinuria as a result of secondary focal segmental glomerulosclerosis (FSGS).

Traditional management includes prompt treatment of UTI and long-term antimicrobial prophylaxis until the resolution of VUR. Surgical correction of the VUR may be recommended in those with high-grade VUR who have recurrent UTI in spite of antimicrobial prophylaxis or who are noncompliant with medical management. Debate persists as to whether surgery is superior to medical management; most studies have concluded that long-term outcomes are similar.

CLASSIFICATION

VUR is classified by radiologic evaluation on voiding cystourethrography (VCU) into five grades as defined by the International Reflux Study in Children (Fig. 61.1 and Table 61.1).[1] Grade I is reflux into the ureter; grade II is reflux into the renal pelvis without any dilation of the calyces; grade III is reflux to the renal pelvis with mild dilation of the renal pelvis; grade IV is reflux to the renal pelvis with greater dilation of the renal pelvis; and grade V is reflux to the renal pelvis with ureteral and pelvic dilation. An example of grade V reflux is shown in Fig. 61.2.

Grading of VUR is used to predict the outcomes of children with VUR. Because VUR may resolve spontaneously, grading is used to standardize management strategies as well as compare clinical outcomes between institutions. Although it is widely used, the classification system is not perfect; differences between grade III and grade IV are not always obvious. The degree of reflux may be modified by how aggressively the bladder is filled during VCU. Ureteral dilation also may be present without calyceal dilation, leading to difficulties with grading.

EPIDEMIOLOGY

VUR is often first suggested by dilation of the fetal kidney during ultrasound examination. VUR is suspected when the fetal renal pelvis is more than 5 mm in anteroposterior diameter; a diameter of more than 10 mm is suggestive of high-grade VUR. In neonates who had evidence of fetal dilation, as many as 13% to 22% will have VUR on VCU. Indeed, it is estimated that 1% to 2% of neonates have VUR, with a higher frequency in boys and premature infants.[2] The incidence of renal dysplasia is also greater in male infants with VUR.[3] Most cases of grades I to III VUR will spontaneously resolve within the patient's first year of life, whereas grades IV and V are more likely to persist. Spontaneous resolution of VUR is greater in male infants, even for those with higher grades of VUR (grades IV and V).

VUR is also diagnosed in 30% to 40% of children presenting with UTI, predominantly in girls. VUR is both less common and less severe in African American children.[4,5] Only about one third as many African American as White girls with UTI have VUR, and no significant differences in age or mode of presentation exist between the two races.

RN is responsible for 5% to 10% of ESRD in pediatric and adult patients.[6,7] In the Chronic Kidney Disease in Children (CKiD) study, among children with estimated glomerular filtration rate (eGFR) of 30 to 90 ml/min/1.73 m^2, RN was the underlying cause for CKD in 14.8% of the patients.

ETIOLOGY AND PATHOGENESIS

Primary VUR is a congenital anomaly of the ureterovesical junction caused by shortening of the intravesical submucosal length of the ureter, leading to an incompetent valve (Fig. 61.3). The formation of the ureteral bud from the mesonephric duct signals the initial development of the metanephric kidney, the final stage of renal development. The ureteral bud interacts with the mesenchyme to give rise to the metanephric kidney. As the mesonephric duct is gradually absorbed into the enlarging urogenital sinus (the precursor of the developing bladder), the location of the ureteral bud plays a role in the eventual location of the ureteral meatus within the bladder. If the ureteral bud reaches the urogenital sinus too early because of the absorption pattern of the mesonephric duct, it is eventually located more laterally and proximally in the bladder. This location is associated with the development of reflux because there is reduction in the intravesical submucosal length of the ureter.

The ureterovesical junction is designed to prevent free reflux of urine from the bladder to the kidney. The ureters pass into the bladder

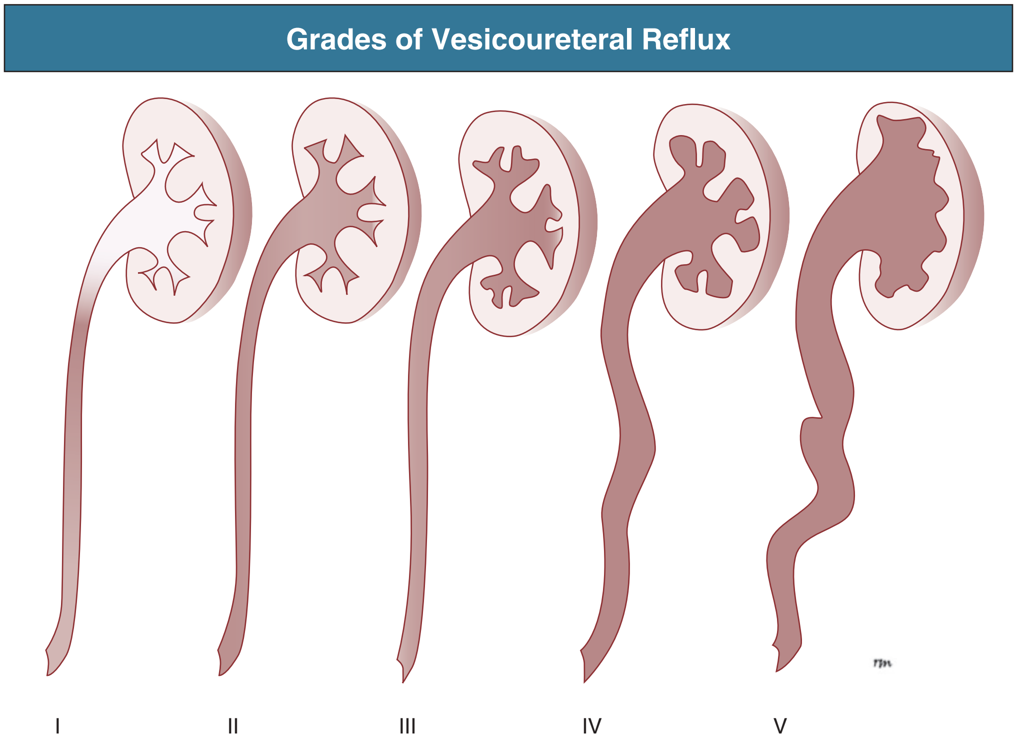

Fig. 61.1 Grades of vesicoureteral reflux.

TABLE 61.1 Classification of Vesicoureteral Reflux

Grade	Degree of VUR
I	Ureter only
II	Reflux into ureter, pelvis, and calyces with no dilation and with normal calyceal fornices
III	Mild or moderate dilation and/or tortuosity of the ureter and mild or moderate dilation of the pelvis; no or slight blunting of the fornices
IV	Moderate dilation and/or tortuosity of the ureter and moderate dilation of the pelvis and calyces; complete obliteration of the pelvis and calyces; complete obliteration of the sharp angles of the fornices but maintenance of the papillary impressions in the majority of the calyces (see Fig. 63.7C)
V	Gross dilation and tortuosity of the ureter, pelvis, and calyces; the papillary impressions are no longer visible in the majority of calyces (see Fig. 63.2)

Classification of vesicoureteral reflux according to the international reflux study in children.

VUR, Vesicoureteral reflux.

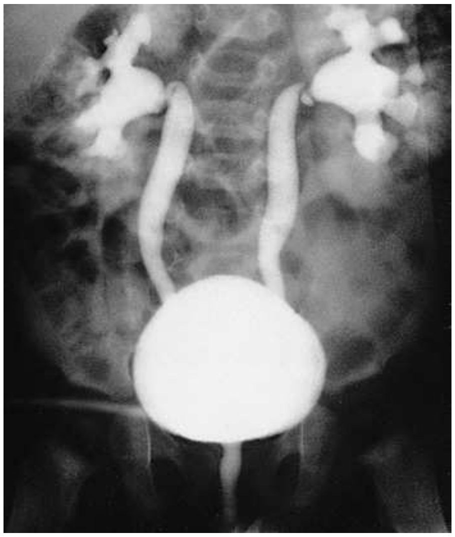

Fig. 61.2 **Gross vesicoureteral reflux (VUR) and intrarenal reflux.** A voiding cystourethrogram shows grade V VUR with intrarenal reflux into several renal lobes in an infant.

through the detrusor in an oblique path. The distal end of the ureter is located submucosally within the bladder. The length of the submucosal ureter is critical in the prevention of VUR. The muscles of the ureter extend into the trigone of the bladder and mesh with the fibers from the opposite ureter. This intermingling of fibers helps anchor the ureters into the trigone of the bladder. The distal submucosal segment is compressed against the muscular bladder wall with bladder filling, acting as an additional mechanism to prevent reflux. Because urine is propelled antegrade down the ureter, the tone of the ureter and the meatus in the bladder also help prevent reflux.

Multiple genes are involved in the development of VUR. *PAX2* (necessary for ureteral budding in mice), glial-derived neurotrophic factor *(GDNF)*, angiotensin II type 2 receptor, and uroplakin 3 (which is a component of tight junctions in uroepithelial cells) have been implicated in the development of VUR in mice; however, their role in human VUR remains controversial.[8,9] Neither autonomic innervation nor histology of the ureterovesical junction differs between patients with VUR and controls.[10]

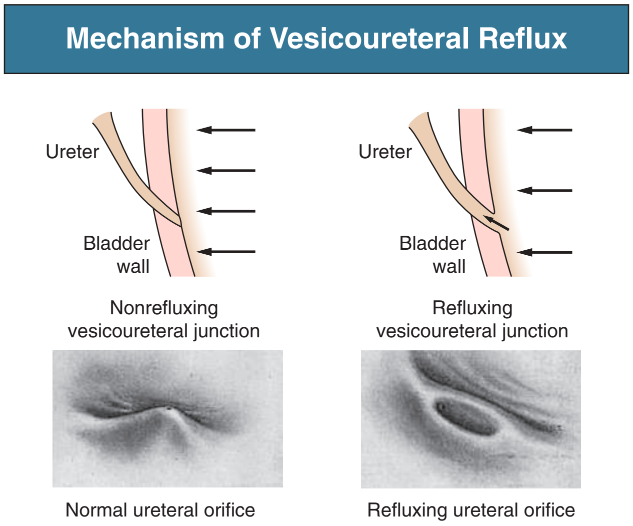
Mechanism of Vesicoureteral Reflux
Ureter
Bladder wall
Nonrefluxing vesicoureteral junction
Ureter
Bladder wall
Refluxing vesicoureteral junction
Normal ureteral orifice
Refluxing ureteral orifice

Fig. 61.3 **Pathogenesis of vesicoureteral reflux (VUR).** Competent *(left)* and incompetent *(right)* vesicoureteral junctions and ureteral orifices.

TABLE 61.2 Types of Renal Damage Associated With Vesicoureteral Reflux

	Congenital	Acquired
Time of occurrence	Often prenatal	Postnatal, sometimes in adulthood
Previous urinary infection	Not usually	Usually
Gender	Usually boys	Usually girls (particularly after infancy)
Grade of VUR	Usually grades IV and V	Grades IV and V less common
Renal scarring	Often present	Present in minority*
Associated bladder dysfunction	Hypercontractile bladder common	Less commonly, high-capacity bladder with incomplete voiding

Modified from reference 11, with permission.

*Depends on unilateral versus bilateral involvement and the severity of renal involvement.

Reflux Nephropathy

RN is thought to result from one of two processes (Table 61.2).[11] Prenatal renal injury has been postulated to be secondary to the "water-hammer" effect of high-grade reflux and occurs in the absence of infection. This typically causes renal dysplasia. This form of renal scarring, which is also called *congenital RN*, is more commonly noted in infants with high-grade VUR, with a greater predominance of males. The second mechanism for development of renal injury is the combination of VUR and repeated UTI (so-called acquired RN). In these children, who are more commonly female, the combination of upper tract infection and reflux leads to renal inflammation and permanent scarring. Scarring tends to be more commonly located at the upper and lower poles of the kidney because of the anatomy of the renal papillae in these regions.

The risk for renal damage is greatest in presence of high-grade VUR.[12] The recently concluded Randomized Intervention for Vesicoureteral Reflux (RIVUR) trial also documented that the risk for new renal scarring is higher in relatively older children and not in younger children as reported in the literature previously.[12] One possible explanation for previously reported higher incidence of renal scarring in younger children could be a lower threshold for diagnosing and investigating younger children with UTI compared with the older children.

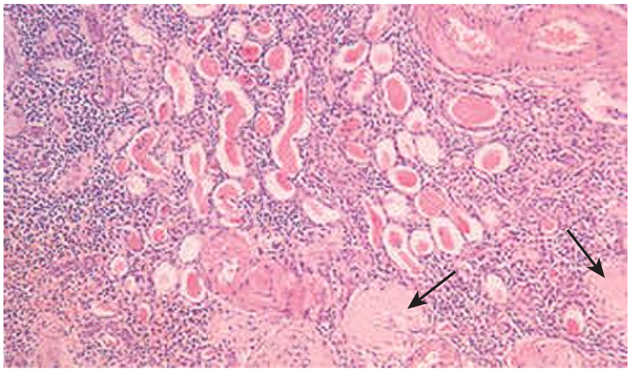

Fig. 61.4 **Histologic changes in reflux nephropathy.** Sclerosed glomeruli *(arrows),* chronic inflammatory cell infiltration, and atrophic tubules with eosinophilic casts are present. (Hematoxylin-eosin; original magnification ×40.)

RN is diagnosed by using technetium-99m (^{99m}Tc)-labeled dimercaptosuccinic acid (DMSA) renal scanning that demonstrates defects in the renal outline.[13] As noted previously, high-grade prenatal reflux can lead to renal injury in the absence of infection. Unfortunately, renal scarring secondary to UTI is indistinguishable by DMSA renal scan from that caused by prenatal renal dysplasia. In addition, renal injury can be noted after febrile UTI in the absence of identified VUR. Renal scarring as shown by ^{99m}Tc DMSA scan correlates more closely with the severity of VUR than with a history of UTI.[14]

PATHOLOGY

The process of renal scarring may take several years; in one study, the mean time from discovery of VUR to the appearance of a renal scar was 6.1 years.[15] Injury is seen more at the renal poles and is associated with clubbed calyces with medullary and cortical damage. The injury results from the local inflammatory response that may persist with chronic inflammation, tubular injury, local fibroblast activation, and interstitial collagen deposition (Fig. 61.4).[16] The loss of nephrons is associated with hyperfiltration and hypertension that result in proteinuria and progressive loss of renal function. This also can lead to the development of FSGS (Fig. 61.5).

CLINICAL MANIFESTATIONS

Presentation of Vesicoureteral Reflux

The three most common presentations are during follow-up for antenatal hydronephrosis, after a diagnosis of UTI, and on screening of siblings of a patient with VUR (Box 61.1).

Reflux Identified Secondary to Antenatal Hydronephrosis

Diagnosis of VUR may be suspected in utero with unilateral or bilateral hydronephrosis and confirmed at birth with VCU. There is a higher incidence of male infants diagnosed with VUR after identification of antenatal hydronephrosis.[17] Spontaneous resolution of the VUR occurs more commonly in boys with lower grades and unilateral reflux; infection rates are also lower in this cohort.[18] Female infants are more likely to have lower grades of VUR and are also less likely to develop renal

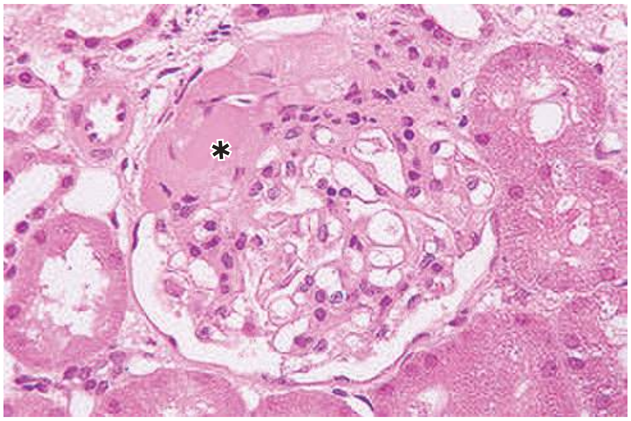

Fig. 61.5 **Focal segmental glomerulosclerosis (FSGS) in reflux nephropathy.** Light microscopy of a glomerulus from a patient with reflux nephropathy shows FSGS with the scarred area marked by an asterisk (*). (Hematoxylin-eosin; original magnification ×400.)

BOX 61.1 Clinical Presentations of Vesicoureteral Reflux

- Complicated urinary tract infection: Usually acute pyelonephritis in infants and children
- Asymptomatic
  - Detected by fetal ultrasound
  - Detected in the workup of members of an affected family
  - Detected in pregnant women with urinary tract infection
  - Detected during workup of kidney stones in children
  - Detected during assessment of other urologic congenital abnormalities

damage compared with newborn boys. Reflux in newborn boys may be a result of elevated bladder pressures secondary to posterior urethral valves or dyssynergia of the urethral sphincter; the latter improves with time, leading to higher potential for spontaneous resolution of even higher grades of VUR.[19,20]

Reflux Identified After a Urinary Tract Infection

VUR is most commonly found after UTI, particularly in a young child. The prevalence of VUR is higher in younger patients and decreases with age (Table 61.3). In neonates and toddlers, UTI may manifest as failure to thrive as opposed to typical symptoms of dysuria and frequency. VUR is more common in patients with complicated or upper tract UTI. Because VUR may potentiate the effect of UTI in children, the recommendations for evaluation of UTI have included ultrasound and VCU after resolution of the first UTI in both boys and girls. Indeed, neither the National Institute for Health and Care Excellence (NICE) nor the American Academy of Pediatrics (AAP) recommend routine voiding cystourethrogram (VCUG) in children with first febrile UTI.[21] The recent AAP guidelines suggested limiting the use of VCU to children identified as having complex UTIs or abnormalities on ultrasound. Our recommendations are therefore to begin with an ultrasound of the kidneys and bladder and performing a VCUG particularly if the ultrasound is abnormal (Fig. 61.6).

Most children diagnosed with VUR after a UTI are younger than 7 years. UTI in these patients may be associated with modifiable host factors, such as bladder and bowel dysfunction (BBD) in children. BBD is typically identified in toilet-trained children with urinary urgency, frequency, and/or incontinence in conjunction with constipation and is felt to be secondary to long-standing urine holding patterns. BBD is associated with development of UTIs that may be potentiated by the presence of VUR. For example, toilet-trained children with VUR identified after a UTI have a 43% incidence of dysfunctional voiding.[22]

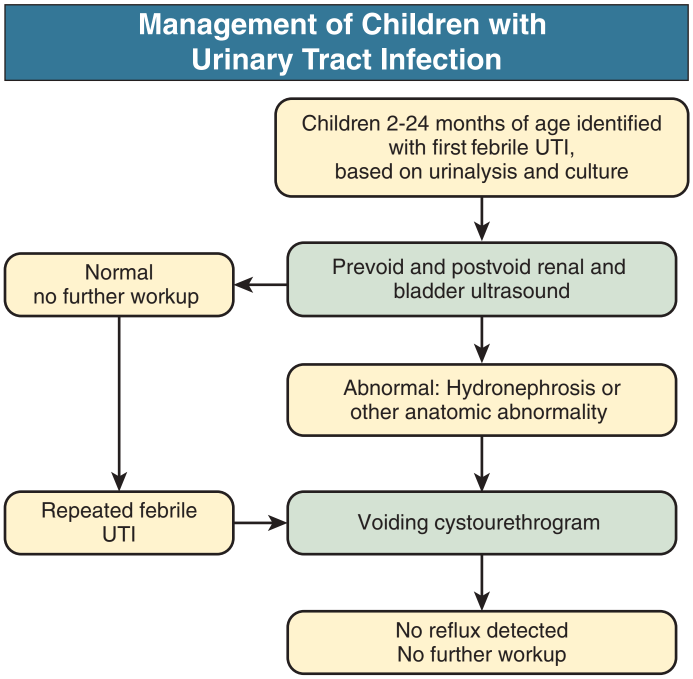
Management of Children with Urinary Tract Infection
Children 2-24 months of age identified with first febrile UTI, based on urinalysis and culture
Prevoid and postvoid renal and bladder ultrasound
Normal no further workup
Abnormal: Hydronephrosis or other anatomic abnormality
Repeated febrile UTI
Voiding cystourethrogram
No reflux detected No further workup

Fig. 61.6 American Academy of Pediatrics algorithm for evaluation of young children with diagnosed urinary tract infection (UTI).

TABLE 61.3 Prevalence of Vesicoureteral Reflux in Patients With Urinary Tract Infection, According to Age

Age	Percentage With VUR
2-3 days	57
3-6 days	51
2-6 months	60
7-12 months	35
1-4 years	50
5-9 years	35
10-14 years	14
14 years	10
Adult	5

VUR, Vesicoureteral reflux.

Vesicoureteral Reflux in a Sibling

Approximately one third of siblings of an index patient with VUR also have VUR.[23] There is a slightly higher incidence of VUR in female siblings of female index patients; 75% of children with VUR identified by evaluating siblings are asymptomatic. The incidence of renal damage is also lower in the siblings diagnosed with reflux compared with the index patient with VUR.[24] For example, UTI with progression of scar was noted in only 5% of siblings with VUR observed for 3 to 7 years, and most of those with grades I and II VUR had spontaneous resolution.[24] The more “benign” course of sibling reflux compared with reflux identified after a UTI has led many to suggest limiting the testing of siblings. At this time, we recommend evaluating younger siblings (younger than 2 years) of index children with VUR using ultrasound to identify renal abnormalities and reserve testing in older siblings to those who present with a UTI or other symptoms.

Presentation of Vesicoureteral Reflux in Women During Pregnancy

VUR also may first manifest in women during pregnancy, when it can be associated with asymptomatic bacteriuria or symptomatic UTI, hypertension, preeclampsia, low-birth-weight babies, or miscarriage. VUR is present in approximately 5% of women with UTI in pregnancy and 4% to 5% of women with preeclampsia. VUR can be distinguished from the normal ureteral dilation that occurs in pregnancy, which preferentially affects the midportion of the ureter, and lack of involvement of the renal parenchyma.

Other Presentations

An increased risk for renal calculi has been reported in children with VUR. Recurrent infections with urease-splitting organisms can lead to staghorn calculi. VUR or RN also may be discovered in adults after recurrent lower or upper UTI; indeed, about 5% of sexually active women with UTI have VUR.

Reflux Nephropathy

Renal scarring can occur in patients with VUR and can be seen in those with or without proven UTI. This scarring is called RN.[25,26] Young children are particularly at risk for renal scarring. Renal scarring is more common with febrile UTI in children, and in those younger than 5 years, as many as 75% develop acute pyelonephritis and renal scarring. Renal cortical defects (by DMSA scanning) are present in 45% of children with febrile UTI and VUR compared with 24% with UTI without VUR.[26] In a large prospective study of a population-based cohort of 1221 children aged 0 to 15 years with symptomatic UTI, scarring during initial evaluation was even higher, occurring in 86% of the boys and 30% of the girls. Girls had significantly more recurrences of febrile UTIs and acquired renal scarring than boys.[27]

The clinical manifestations of RN are varied and may include complicated UTI, hypertension, proteinuria, and various manifestations of CKD (Box 61.2).

Hypertension

Hypertension occurs in 10% to 30% of children and young adults with RN,[27,28] and according to one study, hypertension may take 8 years to develop from the time of diagnosis.[15] The exact cause of hypertension resulting from renal scarring is not known, but it is thought to be caused by impaired sodium excretion resulting from the renal injury and loss of renal function. Hypertension is relatively uncommon in children with VUR, with an estimated probability of 2%, 6%, and 15% at 10, 15, and 21 years of age, respectively. However, hypertension increases in proportion to the degree of renal injury.[29] Renal scarring (noted by DMSA scans) was reported in 20% of newly diagnosed hypertension in children and adolescents.

BOX 61.2 Clinical Presentations of Reflux Nephropathy

- Complicated urinary infection: Usually acute pyelonephritis in infants and children
- Hypertension: May be accelerated
- During pregnancy: Urinary infection, hypertension, preeclampsia
- Proteinuria
- Chronic renal impairment
- Urinary calculi
- Asymptomatic
    - Detected in the workup of members of an affected family
    - Detected by fetal ultrasound
    - Detected during assessment of other urologic congenital abnormalities

Proteinuria

Patients also may present with mild to moderate or (rarely) nephrotic-range proteinuria. Severe or nephrotic proteinuria may suggest a histologic diagnosis of secondary FSGS, which can be confirmed by renal biopsy if kidney size is normal and diagnosis is uncertain (see Fig. 61.5).[30] Proteinuria is commonly associated with hypertension and renal dysfunction. CKD progression often occurs gradually over 5 to 10 years.

End-Stage Renal Disease

According to the North American Pediatric Renal Transplant Cooperative Study annual report of 2008, 3.5% of the 6491 children on dialysis had RN, which makes it the fourth most common cause of ESRD in children after FSGS; renal aplasia, hypoplasia, or dysplasia; and obstructive uropathy.[31,32] The number of children with RN who present with ESRD as adults is not clear. According to one study of 123 adults with VUR diagnosed in childhood, the eGFR in those with nondilating VUR averaged 75 ml/1.73 m^2 and that in the dilating group was 72 ml/1.73 m^2; four patients (9%) in the nondilating group and 13 (17%) in the dilating group had an eGFR below 60 ml/1.73 m^2.[31]

Diagnosis of Vesicoureteral Reflux and Reflux Nephropathy

An algorithm for diagnosis of VUR after the discovery of UTI as recommended by AAP, is shown in Fig. 61.6. However, this is not followed universally by all practitioners, partly because of other published guidelines and recent evidence on the usefulness of antimicrobial prophylaxis in VUR as reported by the RIVUR study.[33] An example of the various tests in a child with UTI and VUR is shown in Fig. 61.7.

Renal Ultrasound

Ultrasound is the initial modality for the evaluation of postnatal hydronephrosis and UTI in children. Ultrasound is also used in siblings of children with VUR to determine whether renal dilation suggestive of high-grade reflux is present. Whereas ultrasound can suggest the possibility of high-grade VUR, it is less sensitive for diagnosis of acute pyelonephritis. In patients with acute pyelonephritis, abnormalities compatible with the diagnosis were reported in 20% to 69% by ultrasound compared with 40% to 92% by DMSA scintigraphy.[34] Nonetheless, ultrasound may be useful in detection of renal abscess and abnormalities of the perinephric space. Renal ultrasound is not diagnostic for VUR and is not a sensitive method for diagnosis of renal scars.

Voiding Cystourethrography

Voiding cystourethrography (VCU) is the primary diagnostic modality for identification of VUR. It requires catheterization. The grading of VUR is based on radiographic appearance by VCU (see Fig. 61.1). In children with UTI, VCU should be performed as soon as the child has completed antibiotic therapy.

The results of VCU can be affected by size, type, and position of the catheter; rate of bladder filling; height of the column of contrast media; state of hydration of the patient; and volume, temperature, and concentration of the contrast medium.

Nuclear cystography has been used to reduce the radiation exposure for children during follow-up of VUR. Nuclear cystography, although more sensitive, does not permit specific grading of VUR or reveal other anatomic defects, such as ureterocele and diverticulum. Therefore it is typically not the primary study performed for identification of VUR,

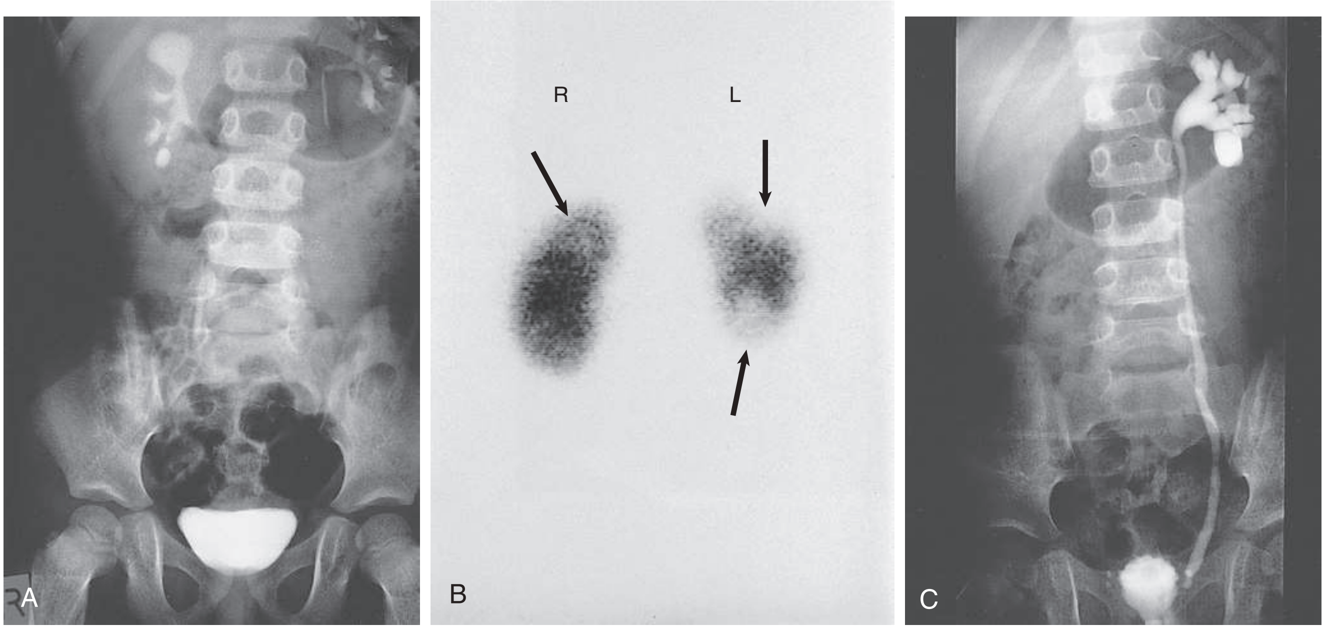

Fig. 61.7 Investigation of reflux nephropathy. Investigation of a 3-year-old child with urinary tract infection. (A) Intravenous urogram showing calyceal diverticulum in the upper pole of the right kidney and renal scarring in the upper pole and, probably, the lower pole of the left kidney. (B) DMSA scintigraphy (posterior view) demonstrating upper and lower pole scarring *(arrows)* in the left kidney and scarring of the right upper kidney in association with the calyceal diverticulum *(arrowhead)*. (C) Voiding cystourethrogram showing grade IV vesicoureteral reflux on the left.

but it is useful in determining improvement or resolution of reflux during follow-up or after surgical correction.

DMSA Renal Scintigraphy

DMSA scintigraphy is currently the gold standard for diagnosis of acute pyelonephritis and renal scarring with a high rate of sensitivity. Single-photon emission computed tomography (SPECT) DMSA scintigraphy is superior to planar imaging for detection of renal cortical damage.[35-37] The sensitivity of DMSA scintigraphy in experimentally induced acute pyelonephritis in a pig model was reported to be 92% when correlated with histologic findings.[37] By use of standardized criteria for its interpretation, high levels of intraobserver and interobserver agreement were reported.[38]

An abnormal DMSA scan during a febrile UTI allows the identification of children with renal inflammation who are at risk for development of renal scars. For acute pyelonephritis, DMSA scintigraphy can be performed within 2 to 4 weeks after the onset of UTI symptoms, but is not encouraged because it usually does not change clinical management. Some have suggested the use of DMSA scanning as an initial modality to identify children with abnormalities that may suggest the need for evaluation for VUR. DMSA scintigraphy to identify renal scarring should be performed 6 months after acute infection to allow reversible lesions to resolve.[39,40]

Dysplasia secondary to congenital reflux will appear similar to renal scarring after postnatal infections. In a child presenting with VUR, obtaining a baseline DMSA renal scan allows identification of renal dysplasia and scarring, which can then be observed over time.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) can be used for the diagnosis of renal scars because it discriminates swelling from scarring, both of which would be interpreted by DMSA scintigraphy as renal scarring. MRI may diagnose other coexisting conditions, such as nephrolithiasis,[40,41] which is not diagnosed by DMSA scintigraphy. Newer imaging methods that show promise in diagnosis of renal scarring include dynamic contrast-enhanced MRI and MRI using a gadolinium-enhanced short tau inversion recovery (STIR) sequence. However, routine use of MRI is less practical because of limited availability, especially for infants, need for prolonged sedation, and high cost. Gadolinium is also contraindicated in the presence of significant renal impairment (glomerular filtration rate <30 ml/min/1.73 m^2).

Proteinuria as a Marker for Reflux Nephropathy

Proteinuria predicts CKD progression due to RN.[42] Persistent albuminuria is helpful in diagnosis of glomerular damage at a very early stage.[43] Albuminuria increases with increasing severity of VUR and renal scarring.[44] In children with bilateral VUR with renal scarring and normal creatinine clearance, mild albuminuria was detected in 54% of the cases.[45] Evaluation for albuminuria offers the possibility of early intervention, such as the use of angiotensin-converting enzyme (ACE) inhibitors, aimed at retarding CKD progression. Proteinuria, when it is severe, is usually associated with FSGS.

NATURAL HISTORY OF VESICOURETERAL REFLUX AND REFLUX NEPHROPATHY

Primary VUR, especially grades I to III, generally improves with time, likely the result of growth and lengthening of the submucosal segment of the ureter. Spontaneous resolution of VUR is more common with non-White race, lower grades of reflux, absence of renal damage, and lack of voiding dysfunction. Resolution of VUR occurs more slowly in children with bilateral VUR in most but not all studies. In one study of children younger than 5 years with grades I to III VUR, the resolution rate of left unilateral VUR was better than for right VUR.[46] In another study, the mean time until spontaneous resolution in Black children was 15 months versus 21 months in White children.[47]

TABLE 61.4 **American Urologic Association Guidelines for Management of Vesicoureteral Reflux**

Grade of VUR	I	II	III	IV	V
<1 yr without UTI	Consider CAP	Consider CAP	CAP	CAP	CAP
<1 yr with UTI	CAP	CAP	CAP	CAP	CAP
>1 yr without BBD or UTI	Consider CAP	Consider CAP	Consider CAP	Possible surgery	Possible surgery
>1 yr without BBD *and* UTI	CAP/possible surgery	CAP/possible surgery	CAP/possible surgery	CAP/possible surgery	CAP/possible surgery
>1 yr with BBD *and* without UTI	Treat BBD/CAP	Treat BBD/CAP	Treat BBD/CAP / possible surgery when BBD improved	Treat BBD/CAP/ possible surgery when BBD improved	Treat BBD/CAP/ possible surgery when BBD improved
>1 yr with BBD *and* UTI	Treat BBD/CAP/ change CAP	Treat BBD/CAP/ change CAP	Treat BBD/CAP/change CAP/possible surgery when BBD improved	Treat BBD/CAP/change CAP/possible surgery when BBD improved	Treat BBD/CAP/change CAP/possible surgery when BBD improved

Modified from American Urological Association. Vesicoureteral reflux. Available at www.auanet.org/education/guidelines/vesicoureteral-reflux-a.cfm.

BBD, Bladder/bowel dysfunction; *CAP,* continuous antibiotic prophylaxis; *possible surgery,* injectable materials or reimplantation for lower grades and reimplantation for higher grades.

Increasing age at presentation and bilateral VUR decrease the probability of resolution, and bilateral grade IV or grade V VUR has a particularly low potential for spontaneous resolution.[48]

The natural history of VUR in adults has been reported in few studies. In one study of adults (mean age of 24 years) with gross VUR diagnosed in infancy, proteinuria and CKD were present in 3 of the 13 patients with unilateral RN and 2 of the 4 patients with bilateral RN.[49] In another study of 127 adults (mean age of 41 years) with VUR diagnosed during childhood, 35% had unilateral renal scarring, 24% had bilateral renal scarring, 24% had albuminuria, and 11% had hypertension. Of the patients with bilateral renal scars, 83% had reduced GFR.[50] An increased frequency of UTI and abnormal voiding patterns has been noted in adults with VUR. UTIs may be more common in adults who have had surgical management of VUR.

TREATMENT

The management of VUR has been based on the premise that VUR predisposes to the development of recurrent UTI and renal parenchymal injury, but also has the potential for spontaneous resolution. Various treatment strategies have been used with the ultimate objective of preventing renal injury. The two main treatment modalities are long-term antimicrobial prophylaxis and surgical correction. Surgical correction of VUR was common until antimicrobial prophylaxis for childhood UTI was introduced in 1975.[51] Many subsequent studies have reported no significant differences in outcome with medical management of VUR versus surgical treatment in the prevention of renal injury. For example, in the International Reflux Study in Children ($n = 306$ patients), no significant difference in outcome was found between medical and surgical management in terms of the development of new renal lesions or the progression of established renal scars, although there was a lower incidence of pyelonephritis in the surgical arm.[52] Long-term follow-up of this cohort for a period of 5 years in the European arm of the study also indicated no difference in outcomes.[53]

The 2010 American Urological Association guidelines reviewed seven treatment modalities used to manage VUR in children: intermittent antibiotic therapy; bladder training; continuous antibiotic prophylaxis; antibiotic prophylaxis and bladder training; antibiotic prophylaxis, anticholinergics, and bladder training; open surgical repair; and endoscopic repair. The key outcome measures were resolution of VUR, risk for pyelonephritis and scarring, and complications of medical versus surgical management. The study panel's recommendations are shown in Table 61.4. Antibiotic prophylaxis is recommended for all grades of VUR in children younger than 1 year because of a very high rate of spontaneous resolution. For children 1 to 5 years old, the study panel recommended antibiotic prophylaxis for all grades of VUR, with surgical options in grades III to V if VUR is bilateral or renal scarring is present. For children older than 6 years, the study panel recommended antibiotic prophylaxis for grades I and II (unilateral or bilateral) and unilateral grades III and IV, with surgical options if renal scarring is present, and surgical repair for bilateral grades III and IV and unilateral or bilateral grade V with or without scarring because the VUR has the lowest possibility of spontaneous resolution.[48]

Medical Management

Medical management involves long-term antimicrobial prophylaxis, appropriate management of BBD, if present, and follow-up renal imaging to assess the resolution of VUR and the potential development of renal injury. The antimicrobial agents most appropriate for prophylaxis include trimethoprim-sulfamethoxazole, trimethoprim alone, nitrofurantoin, and cephalexin. Follow-up of patients with VUR and UTI requires rapid evaluation (within 72 hours of the onset of fever) to allow early detection and prompt treatment of UTI. The timing of follow-up VCU is not well defined, but studies have suggested time intervals of 12 to 24 months. The treatment of bladder and bowel dysfunction may include the use of laxatives and timed frequent voiding every 2 to 3 hours. Pelvic floor exercises, behavioral modification, or anticholinergic medication may be required. A combined conservative medical and computer game–assisted pelvic floor muscle retraining decreases the incidence of breakthrough UTI and facilitate VUR resolution in children with BBD and VUR. Treatment of constipation by dietary measures, behavioral therapy, and laxatives helps reduce UTI recurrence and resolve enuresis and uninhibited bladder contractions.

Antibiotic Prophylaxis Versus Surveillance Only

Some studies challenge the benefit of long-term antimicrobial prophylaxis in the prevention of renal injury in patients with VUR. Concerns have been raised regarding the potential risks for long-term antibiotic use, including the possibility of development of resistance or allergy.

In the last few years, six prospective randomized trials evaluated the role of antimicrobial prophylaxis in the prevention of recurrent UTI and renal scarring in children. Altogether 1435 patients were randomized,

TABLE 61.5 **Surgical Techniques for Vesicoureteral Reflux**

Technique	Success Rates (%)	Pros	Cons
Open reimplantation	95	High success rates Limited requirement for follow-up VCU Reduction in hospital stays	Surgical incision Hospitalization required Catheters needed during postoperative management Need for pain control
Endoscopic injection Dextranomer and hyaluronidase (Deflux)	70-80	Reasonable success rates Outpatient management Minimal pain	Expensive Lower success rates Need for repeated procedures Need for follow-up VCU
Laparoscopic or robotic reimplantation	70-90	Reasonable success rates Small incisions Less discomfort	Lower success rates Requires hospitalization Need for follow-up VCU Long procedure Expensive equipment Significant surgical learning curve

VCU, Voiding cystourethrography.

including 961 (67%) female patients. Four studies[14,54-56] reported no benefit with antimicrobial prophylaxis in children with or without VUR. One study[57] reported a decrease of 6 percentage points (95% confidence interval [CI] 1-13) in the number of UTIs with prophylaxis compared with placebo. The Swedish reflux trial[57-59] demonstrated that the rate of UTI recurrence in girls was higher than in boys, and that this rate can be decreased with antibiotic prophylaxis and endoscopic procedure. None of the five studies showed any difference in the rate of renal scarring with or without prophylaxis.

The results of the recently concluded RIVUR trial, which randomized 600 children with VUR to prophylaxis or surveillance, demonstrated a 50% reduction in the incidence of recurrent UTIs with the use of daily prophylaxis. The impact on renal scarring was difficult to determine because few children enrolled in the study had scarring at entry and fewer still developed scarring over the short 24-month follow-up.

None of these studies showed any difference in the rate of renal scarring with or without prophylaxis. This stems from the fact that none of these studies were designed with renal scarring as the primary study end-point and the duration of follow-up was not long enough.

Hypertension and Proteinuria

Appropriate management of hypertension and proteinuria includes the use of ACE inhibitors or angiotensin receptor blockers (ARBs) as in other renal diseases (see Chapter 80). Combinations of ACE inhibitors and ARBs may provide additional lowering of proteinuria.[60] However, it is not known whether this antiproteinuric effect slows the progression of the renal disease. Historically, some patients also occasionally had their scarred kidney removed to help control hypertension, provided the contralateral kidney was healthy. However, this is exceptionally rare these days because of the availability of many potent antihypertensive agents.

Surgical Management

Surgical management of VUR is now reserved for patients in whom medical management with antimicrobial prophylaxis has failed to prevent UTIs. Current indications for surgical management of VUR are recurrent infections despite compliance with a prophylactic antibiotic regimen, worsening of renal scars, as judged by DMSA scanning, and failure to comply with prophylaxis. The recent introduction of minimally invasive surgery for VUR management has made some clinicians reconsider surgical correction as a potential first-line therapy. Immediate correction could potentially offset the need for antibiotic prophylaxis in children. Although most surgical techniques have high success rates for the correction of reflux and have been shown to reduce the risk of pyelonephritis, lower UTIs have been shown to occur in almost 20% of children that have had successful surgical management and no definitive impact on prevention of renal scarring.[61] A review of surgical techniques is presented in Table 61.5.

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SELF-ASSESSMENT QUESTIONS

1. Which *one* of the following is correct about urinary tract infections (UTIs) in pediatric patients?
   - **A.** They are more common in younger children.
   - **B.** Girls are at a higher risk than boys.
   - **C.** Vesicoureteral reflux (VUR) increases the risk for UTI.
   - **D.** Constipation increases the risk for UTI.
   - **E.** All of the above.
2. Which of the following imaging modalities is commonly used for the diagnosis of vesicoureteral reflux?
   - **A.** Ultrasound
   - **B.** Voiding cystourethrogram
   - **C.** DMSA renal scan
   - **D.** Magnetic resonance imaging
   - **E.** Computed tomography scan
3. Complications of reflux nephropathy include:
   - **A.** Hypertension
   - **B.** Proteinuria
   - **C.** Progressive renal failure
   - **D.** Pregnancy-related complications
   - **E.** All of the above

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Chronic Interstitial Nephritis

Tetsuhiro Tanaka, Masaomi Nangaku

DEFINITION

Chronic interstitial nephritis is a histologic entity characterized by progressive scarring of the tubulointerstitium, with tubular atrophy, macrophage and lymphocytic infiltration, and interstitial fibrosis. Because the degree of tubular damage accompanying interstitial nephritis is variable, the term *tubulointerstitial nephritis* is used interchangeably with *interstitial nephritis. Tubulitis* refers to infiltration of the tubular epithelium by leukocytes, usually lymphocytes.

There are many primary as well as secondary causes of chronic interstitial nephritis (Box 62.1). Tubulointerstitial injury is clinically important because it is a better predictor than the degree of glomerular injury of present and future renal function. Although any glomerular disease can injure the tubulointerstitium secondarily through mechanisms involving the direct effects of proteinuria and ischemia, in this chapter we discuss only primary chronic interstitial nephritis.

PATHOGENESIS

The tubulointerstitium can be injured by toxins (e.g., heavy metals), drugs (e.g., analgesics), crystals (e.g., calcium phosphate, uric acid), infections, obstruction, immunologic mechanisms, and ischemia. Regardless of the initiating mechanism, however, the tubulointerstitial response shows little variation. Tubular injury results in the release of chemotactic substances and the expression of leukocyte adhesion molecules that attract inflammatory cells into the interstitium. Tubular cells express human leukocyte antigens, serve as antigen-presenting cells, and secrete complement components and vasoactive mediators, all of which may further stimulate or attract macrophages and T cells. Growth factors released by tubular cells and macrophages, such as platelet-derived growth factor and transforming growth factor β, may stimulate fibroblast proliferation and activation, leading to matrix accumulation.[1] The source of fibroblasts in renal interstitial fibrosis remains controversial but may include an intrinsic fibroblast (perivascular Gli1-positive progenitors) population, migration of circulating fibrocytes from perivascular areas, and phenotypic transition of pericytes into fibroblasts.[2] Over time, a loss of peritubular capillaries and decreased oxygen diffusion caused by expansion of the interstitium render the kidney hypoxic, and progressive apoptosis leads to local hypocellularity and fibrosis.[2] Renal function can become severely decreased, and renal replacement therapy may be required.

EPIDEMIOLOGY

Whereas chronic interstitial nephritis occurs with progressive renal disease of all causes, primary chronic interstitial nephritis is not a common cause of end-stage renal disease (ESRD); reports range from 42% in Scotland to 3% to 4% in China and the United States.[3-5] This variability in incidence may relate to differences in how diagnoses are made, exposure to causal factors, and treatment modalities such as the choice of antibiotics and the indication for pain killers.

In several regions of the world, marked increases in the incidence of chronic interstitial nephritis have been reported. These include Sri Lanka, some coastal areas of Central America, and the Balkan region in Europe (see Chapters 63 and 76).

PATHOLOGY

The pathologic features of chronic interstitial nephritis are nonspecific. They include tubular cell atrophy or dilation; interstitial fibrosis that is composed of interstitial (types I and II) collagens; and mononuclear cell infiltration with macrophages, T cells, and occasionally other cell types (neutrophils, eosinophils, and plasma cells). Tubular lumina vary in diameter but may show marked dilation, with homogeneous casts producing a thyroid-like appearance, hence the term *thyroidization.*

Some forms of chronic interstitial nephritis are associated with granulomatous lesions. Whereas a noncaseating granulomatous pattern is typical of sarcoidosis, interstitial granulomatous reactions also occur in response to infection of the kidney by mycobacteria (Fig. 62.1), fungi, or bacteria; certain drugs (including rifampin, sulfonamides, proton pump inhibitors [PPIs], and narcotics); and oxalate or uric acid crystal deposition.[6] Interstitial granulomatous reactions have been noted in renal malacoplakia (Chapter 51), granulomatosis with polyangitis (Wegener granulomatosis), heroin abuse, and after jejunoileal bypass surgery. The etiology for granulomatous interstitial nephritis remains obscure in 10% of cases.

CLINICAL MANIFESTATIONS

The impaired renal function is often insidious, and the early manifestations of the disease are those of tubular dysfunction, which may go undetected (Box 62.2).[7] Diagnosis is often made incidentally on routine laboratory screening or during evaluation of hypertension, in association with reduced glomerular filtration rate (GFR). Proteinuria is commonly less than 1 g/day. Urinalysis may show only occasional white blood cells and, rarely, white blood cell casts. Hematuria is uncommon. Anemia may occur relatively early because of dysfunction or loss of renal erythropoietin-producing cells in the interstitium.

The tubular dysfunction is often generalized, but some conditions may manifest with proximal tubular defects, including aminoaciduria, phosphaturia, proximal renal tubular acidosis (RTA), or, rarely, complete Fanconi syndrome (see Chapter 48). Distal tubular defects can

BOX 62.1 Major Causes of Chronic Interstitial Nephritis*

Diseases in Which the Kidneys Are Macroscopically Normal

- Drugs and toxins (e.g., aristolochic acid, lithium, cyclosporine, tacrolimus, indinavir, cisplatin, proton pump inhibitors)
- Metabolic (hyperuricemia, hypokalemia, hypercalcemia, hyperoxaluria, cystinosis)
- Heavy metals (lead, cadmium, arsenic, mercury, gold, uranium)
- Radiation
- Balkan nephropathy
- Mesoamerican nephropathy
- Immune-mediated conditions (systemic lupus erythematosus, Sjögren syndrome, sarcoidosis, granulomatosis with polyangitis [Wegener granulomatosis], other vasculitides)
- Vascular diseases (atherosclerotic kidney disease) (see Chapter 41)
  - Transplantation (chronic transplant rejection)
  - Hematologic disturbances (multiple myeloma, light-chain deposition disease, lymphoma, sickle cell disease, paroxysmal nocturnal hemoglobinuria) (see Chapters 49 and 64)
  - Progressive glomerular disease of all causes (glomerulonephritides, diabetes, hypertension)
  - Idiopathic

Diseases in Which the Kidneys Are Macroscopically Abnormal

- Analgesic nephropathy
- Chronic obstruction (see Chapters 58)
- Hereditary (nephronophthisis, medullary cystic kidney disease, familial juvenile hyperuricemic nephropathy, autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease)
- Infection (chronic pyelonephritis, malacoplakia, xanthogranulomatous pyelonephritis; see Chapter 51)

*Kidneys of any clinical entity can be shrunken at end stage. Some diseases categorized as macroscopically normal can in later stages result in macroscopically abnormal kidneys. For example, kidneys of sickle cell nephropathy are macroscopically normal unless papillary necrosis is present.

BOX 62.2 Functional Manifestations of Chronic Interstitial Nephritis

- Deterioration of glomerular filtration rate with insidious onset
- Tubular proteinuria mainly composed of low molecular weight protein (generally <1 g/day)
- Inactive urinary sediment
- Anemia of chronic kidney disease at a relatively early stage
- Proximal tubular dysfunction (aminoaciduria, phosphaturia, proximal renal tubular acidosis, Fanconi syndrome)
- Distal tubular dysfunction (type IV renal tubular acidosis)
- Medullary dysfunction (concentrating defects)
- Salt-wasting syndrome
- Salt-sensitive hypertension

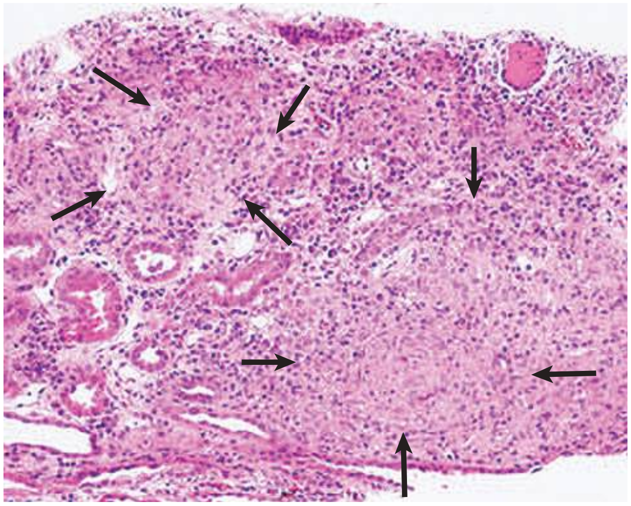

Fig. 62.1 Renal tuberculosis. Noncaseating granulomas with epithelioid cells in miliary tuberculosis (*arrows* show the peripheries of the granulomas). Although the typical pathologic change is granuloma with caseous necrosis with Langerhans-type giant cells, these atypical granulomas can be observed in tuberculosis and should be differentiated from sarcoidosis. (Hematoxylin-eosin [HE] stain.) (Courtesy Dr. Noriko Uesugi, Ibaraki, Japan.)

be associated with distal RTA (type 1 or type 4) (see Chapter 12). Concentrating defects (increased urinary frequency and nocturia) can be a sign of medullary dysfunction and may be severe enough to result in nephrogenic diabetes insipidus. Some patients develop a salt-wasting syndrome. Others, particularly with microvascular disease, may have a relative inability to excrete salt with resultant salt-sensitive hypertension.[8]

Clues to the causes of tubulointerstitial nephritis by history and physical examination are shown in Table 62.1.[9]

TREATMENT

Treatment includes identification and elimination of any exogenous agents (drugs, heavy metals), metabolic causes (hypercalcemia), or conditions (obstruction, infection) potentially causing the chronic interstitial lesion. In addition to classic drugs and toxins, a growing list of medications (e.g., PPIs) is now being linked to the risk for developing chronic kidney disease (CKD), which emphasizes a need to consider the risk and benefit of any drug carefully, particularly in patients with progressive course. Specific treatments may be required for an underlying cause of chronic interstitial nephritis, such as corticosteroids for sarcoidosis. General measures include control of blood pressure. Most clinicians favor the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which reduce glomerular and systemic pressures, decrease proteinuria, and increase renal blood flow. However, the role of ACE inhibitors and ARBs is less clear when blood pressure is normal or when there are excessive solute losses (such as salt-wasting). Specific therapies for each clinical entity are discussed later.

DRUG-INDUCED CHRONIC INTERSTITIAL NEPHRITIS

Several drugs and herbs can cause chronic interstitial nephritis. Cyclosporine- and tacrolimus-induced nephropathy are discussed in Chapter 101; aristolochic acid as a cause of aristolochic acid–associated nephropathy (formerly known as *Chinese herbs nephropathy*) is discussed in Chapter 76.

TABLE 62.1 **Clues to Causes of Tubulointerstitial Nephritis by History and Physical Examination**

Feature	Symptom, Sign, or Historical Clue	Potential Diagnosis
Occupational history	Exposure to heavy metals (e.g., batteries, alloys)	Lead or cadmium nephropathy
Alcohol	History of moonshine ingestion	Lead nephropathy
Social history	Country of origin	Balkan nephropathy
Past history	Systemic lupus erythematosus	Disease-associated chronic interstitial nephritis
	Sjögren syndrome	
	Sarcoidosis	
	Inflammatory bowel disease	
	Autoimmune pancreatitis	
	Chronic pain syndrome	Analgesic nephropathy
	Gouty attack	Lead nephropathy
Medication	Prescribed	Drug-induced chronic interstitial nephritis
	Over-the-counter (NSAIDs, PPIs)	Analgesic nephropathy
	Herbal	Aristolochic acid–associated nephropathy
	Indinavir	Crystal nephropathy
Physical examination	Dry eyes	Sjögren syndrome
	Uveitis	TINU syndrome
Laboratory examination	Hyperuricemia	Chronic uric acid nephropathy
	Hypokalemia	Hypokalemic nephropathy
	Hypercalcemia	Hypercalcemic nephropathy
	High serum IgG4 levels	IgG4-related sclerosing disease
Radiologic examination	Decreased volume, bumpy contours, and papillary calcification on CT	Analgesic nephropathy
	Microcysts on MRI or ultrasound	Lithium nephropathy
	Nephrocalcinosis on CT	Hypercalcemic nephropathy

Modified from reference 10.

CT, Computed tomography; *IgG,* immunoglobulin G; *MRI,* magnetic resonance imaging; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PPIs,* proton pump inhibitors; *TINU,* tubulointerstitial nephritis and uveitis.

Lithium Nephropathy

Definition and Epidemiology

Lithium is commonly used in the treatment of bipolar disorder. Complications of lithium treatment include nephrogenic diabetes insipidus, acute lithium intoxication, and chronic lithium nephrotoxicity. A meta-analysis of the data of 14 studies involving 1172 patients receiving chronic lithium therapy showed that the prevalence of reduced GFR was 15%.[10]

Pathogenesis

Diabetes insipidus results from accumulation of lithium in the collecting tubular cells after entry into these cells through sodium channels in the luminal membrane. Lithium blocks vasopressin-induced reabsorption by inhibiting adenylate cyclase activity, and hence cyclic adenosine monophosphate production, and also by decreasing the apical membrane expression of aquaporin 2, the collecting tubule water channel. Chronic lithium-induced interstitial nephritis may occur, possibly because of inositol depletion and inhibition of cell proliferation.

Pathology

Biopsies show focal chronic interstitial nephritis with interstitial fibrosis, tubular atrophy, and glomerulosclerosis. Whereas similar histologic changes have been reported in psychiatric patients without a history of lithium therapy, patients with lithium exposure often show microcystic changes in the distal tubule; interstitial inflammation and vascular changes are relatively minor. The degree of interstitial fibrosis is related to the duration of administration and cumulative dose.

Clinical Manifestations

Lithium-associated diabetes insipidus. The most common presentation of lithium-induced nephrotoxicity is nephrogenic diabetes insipidus, characterized by resistance to vasopressin, polyuria, and polydipsia. Impaired renal concentrating ability is found in about 50% of patients, and polyuria resulting from nephrogenic diabetes insipidus occurs in about 20% of patients chronically treated with lithium.

Lithium is also rarely a cause of hypercalcemia, which could potentially exaggerate the tubular concentrating defect and contribute to the development of chronic interstitial nephritis in lithium-treated patients. Nephrogenic diabetes insipidus in lithium treatment may be associated with distal RTA, although this partial functional defect is virtually never of clinical importance.

Chronic lithium nephropathy. In a retrospective analysis of data from Oxford University Hospitals, UK, the presence of lithium in serum was associated with an increased risk for stage 3 CKD (hazard ratio 1.93), with women younger than 60 years and those with lithium concentrations higher than median at increased risk.[11] Nephrogenic diabetes insipidus induced by lithium may persist despite the cessation of treatment, indicating irreversible renal damage.

In one study, the mean serum creatinine concentration of patients with biopsy-proven chronic lithium nephrotoxicity was 2.8 mg/dl (247 μmol/l) at the time of biopsy, and 42% of patients had proteinuria greater than 1 g/day.[12] After renal biopsy, all but one patient discontinued treatment with lithium, but seven patients nevertheless progressed to ESRD. A study of 74 lithium-treated patients in France showed that lithium-induced nephropathy developed slowly over several decades, with an average latency between the start of therapy and ESRD of 20 years.[11]

Magnetic resonance imaging, in particular the half-Fourier acquisition single-short turbo spin-echo T2-weighted sequence, without the use of gadolinium, or ultrasound may help in detection of the characteristic microcysts in the kidney.[13]

Treatment

After other potential causes of polyuria and polydipsia have been excluded, particularly psychogenic polydipsia, the first step to consider is a reduction in lithium dosage. The potassium-sparing diuretic amiloride improves the polyuria and also blocks lithium uptake through sodium channels in the collecting duct. Thiazide diuretics should be avoided because they increase the risk for acute lithium intoxication because of the resultant volume contraction and an increase in sodium and lithium reabsorption in the proximal tubule.

Patients undergoing long-term lithium treatment should have renal function (serum creatinine and estimated GFR [eGFR]) and 24-hour urine volume measured yearly. Lithium has a narrow therapeutic index, so levels should be monitored and maintained between 0.6 and 1.25 mmol/l. The severity of chronic lithium intoxication correlates directly with the serum lithium concentration and may be categorized as mild (1.5 to 2.0 mmol/l), moderate (2.0 to 2.5 mmol/l), or severe (>2.5 mmol/l). Once-daily regimens are less toxic than multiple daily administration schedules, perhaps because of the possibility of renal tubular regeneration with a once-daily administration schedule.[14] Prevention of volume depletion is also important.

Because progressive renal injury with reduced GFR in patients without prior acute lithium intoxication is relatively unusual, raised serum creatinine concentration initially should be treated by a dose reduction. If serum creatinine is persistently elevated, a renal biopsy should be considered, although the findings rarely mandate the complete cessation of lithium treatment. At all times, the risk for discontinuation in a patient with a severe unipolar or bipolar affective disorder needs to be balanced with the relatively low risk for progressive renal injury.

Analgesic Nephropathy

Definition and Epidemiology

Analgesic nephropathy resulted from the abuse of analgesics, commonly mixtures containing phenacetin, aspirin, and caffeine, that were available as over-the-counter preparations in Europe and Australia. It is now extremely rare; indeed, some doubt that new cases are still presenting, after restrictions in compound analgesic sales.[15] A large study in the United States showed no association between use of current analgesic preparations and increased risk for chronic renal dysfunction,[16] although it does increase the risk for acute kidney injury (see Chapter 66).

Pathogenesis and Pathology

The primary injury in analgesic nephropathy is medullary ischemia caused by toxic concentrations of phenacetin metabolites combined with relative medullary hypoxia, aggravated by inhibition of vasodilatory prostaglandin synthesis and glutathione (an antioxidant) levels. The main pathologic consequence is papillary necrosis, with secondary tubular atrophy, interstitial fibrosis, and a mononuclear cellular infiltrate (Fig. 62.2).

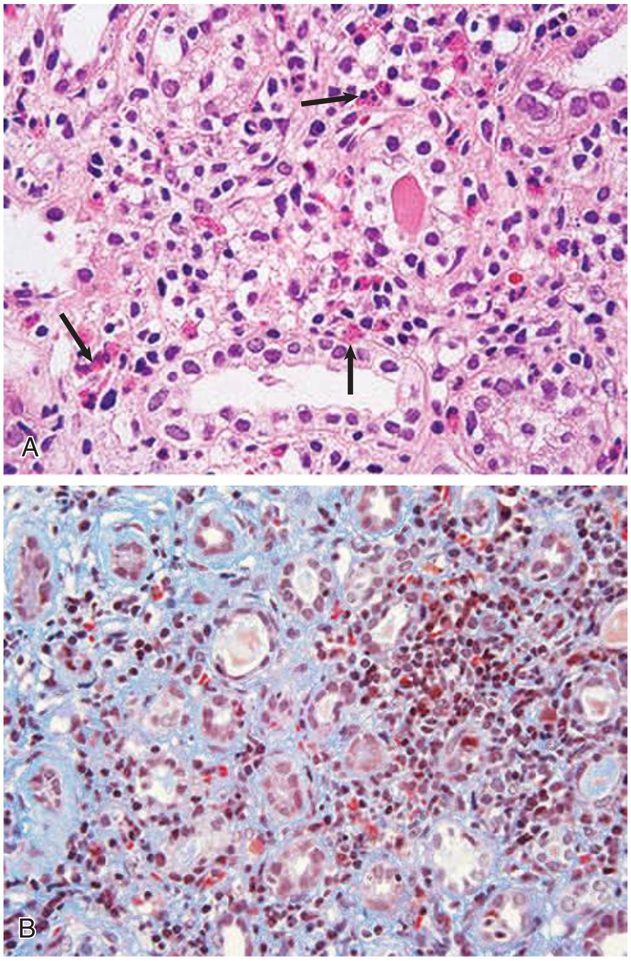

Fig. 62.2 Histologic changes in analgesic nephropathy. (A) Interstitial nephritis in a patient with analgesic nephropathy associated with marked mononuclear cellular infiltrate including eosinophils *(arrows)*. (HE stain; original magnification ×600.) (B) Analgesic nephropathy with interstitial fibrosis and inflammatory cell infiltration. (Masson trichrome stain; original magnification ×400.) (Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)

Clinical Manifestations

Analgesic nephropathy is five to seven times more common in women than in men. Renal manifestations are nonspecific and consist of slowly progressive CKD with impaired urine concentrating ability, urinary acidification defects, and impaired sodium conservation. Patients may present with hypertension, reflecting the use of nonsteroidal antiinflammatory drugs (NSAIDs) and degree of renal parenchymal injury. Urinalysis shows sterile pyuria and mild proteinuria. Patients with analgesic nephropathy are at increased risk for transitional cell carcinoma of the uroepithelium. Recent prospective analysis of the Nurses' Health Study and the Health Professionals Follow-up Study also showed association of regular use of nonaspirin NSAIDs with an increased renal cell carcinoma risk, whereas aspirin and acetaminophen use were not.[17]

Diagnosis

Papillary necrosis is present histologically in almost all patients, but it can be detected radiologically only if part or all of the papilla has sloughed. Papillary necrosis is not pathognomonic of analgesic nephropathy; it is also seen in diabetic nephropathy (particularly during an episode of acute pyelonephritis), sickle cell nephropathy, urinary tract obstruction, and renal tuberculosis. Non–contrast-enhanced computed tomography (CT) demonstrates a decrease in renal mass with either bumpy contours or papillary calcifications (Fig. 62.3; see also Chapter 52).[18]

Treatment

Management consists of stopping or at least reducing the intake of analgesic medications. Because of the increased incidence of uroepithelial

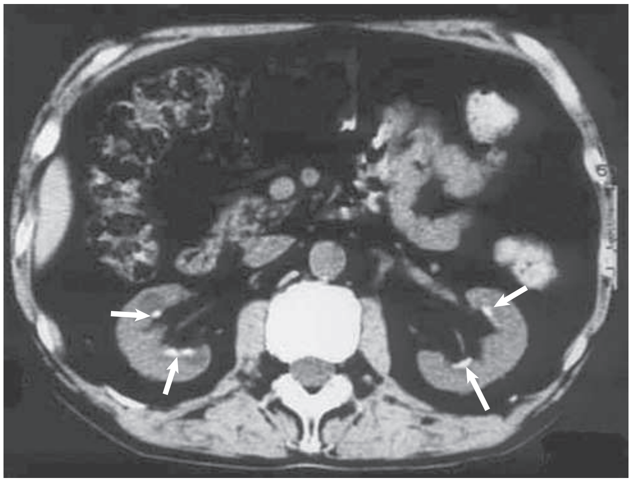

Fig. 62.3 **Papillary calcifications in analgesic nephropathy.** Non–contrast-enhanced CT scan of a patient with long-time analgesic abuse shows thinning of the renal parenchyma and typical papillary calcifications *(arrows).* (Courtesy Dr. Yoshifumi Ubara, Toranomon Hospital, Tokyo.)

tumors, close follow-up including regular urinalysis is necessary. New hematuria requires early referral for urologic evaluation, which includes urinary cytology, cystoscopy, and CT scan. It will be most prudent to perform yearly urinary cytologic examination at least several years after cessation of analgesics.

Analgesic nephropathy associated with over-the-counter medicines is also discussed in Chapter 76.

CHRONIC INTERSTITIAL NEPHRITIS CAUSED BY METABOLIC DISORDERS

Metabolic disorders that cause interstitial nephritis are discussed here. Hyperoxaluria is described in Chapter 57 and cystinosis in Chapter 48.

Chronic Uric Acid Nephropathy

Definition and Epidemiology

Historically, chronic interstitial nephritis associated with chronic hyperuricemia was called *gouty nephropathy* and was ascribed to the medullary deposition of crystals with surrounding inflammation and fibrosis. Later this concept was challenged, and the renal disease associated with gout was thought to be secondary to coexistent hypertension, vascular disease, or aging-associated renal injury. In addition, independent of intrarenal crystal deposition, recent epidemiologic studies document that an elevated serum uric acid is a risk factor for de novo development of CKD.[19] These increases in risk remain significant even after adjustment for eGFR, proteinuria, age, and components of the metabolic syndrome. These studies suggest that chronic hyperuricemia may be a risk factor for the development of CKD and progression of established CKD.[20]

Pathogenesis

Chronic gout and severe hyperuricemia can be associated with the deposition of uric acid crystals in the renal medulla (Fig. 62.4). However, independent of crystal deposition, experimental studies indicate that hyperuricemia causes chronic renal injury by activating the renin-angiotensin system and inducing oxidative stress, resulting in glomerular hypertension and impaired renal autoregulation.[21] Although uric acid can function as an antioxidant in the extracellular environment, within the cell uric acid has prooxidant effects and can lead to endothelial and mitochondrial dysfunction.

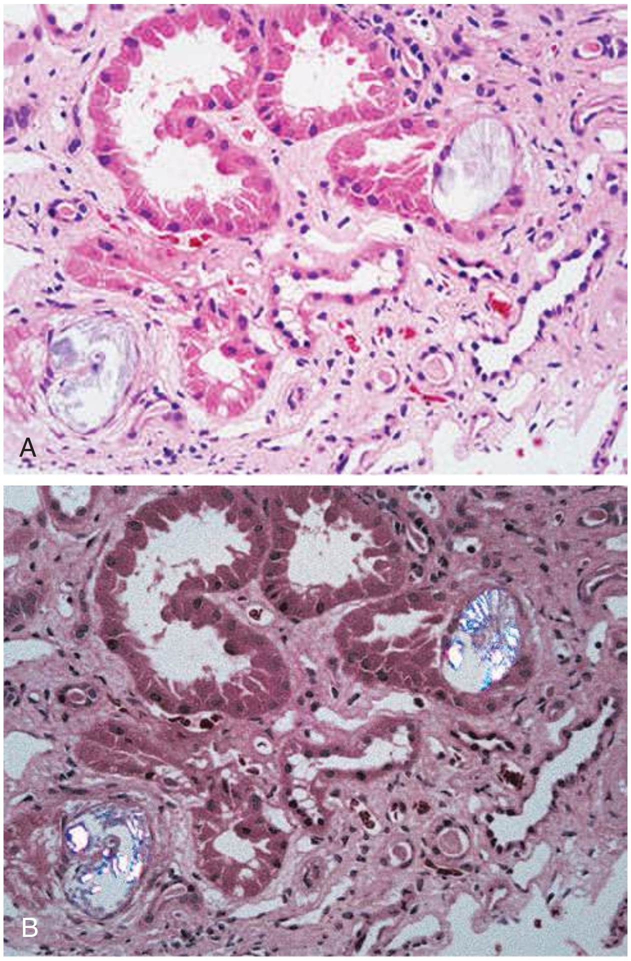

Fig. 62.4 **Chronic uric acid nephropathy.** (A) Large collections of elongated or fragmented uric acid crystals are present in association with atrophic tubules. (HE stain; original magnification ×400.) (B) The crystalline masses are refractile under polarized light. (Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)

Pathology

Renal functional abnormalities are observed in 30% to 50% of patients who have had gout for many years, and histologic changes are observed in more than 90%.[22] The most consistent histologic findings are arteriolosclerosis, focal or global glomerulosclerosis, and chronic tubulointerstitial disease. Uric acid crystals also can be occasionally found within tubules and in the interstitium (see Fig. 62.4), especially in the outer medulla, and on rare occasions medullary renal tophi can be found on gross anatomic dissection. Experimental studies question whether the uric acid crystals themselves are responsible for the renal functional abnormalities.

Clinical Manifestations

Patients with chronic uric acid nephropathy present with hypertension with mildly impaired renal function, mild proteinuria, unremarkable urinary sediment, and minor tubular dysfunction (usually impairment of urine concentrating ability manifested as isosthenuria). Uric acid nephropathy should particularly be considered if there is a disproportionate elevation in serum uric acid in relation to the degree of renal impairment (Table 62.2).[23]

Diagnosis

The most important differential diagnosis for chronic uric acid nephropathy is chronic lead nephropathy. Familial juvenile hyperuricemic

TABLE 62.2 Serum Creatinine and Uric Acid Levels in Chronic Kidney Disease

SERUM CREATININE		SERUM URIC ACID	
mg/dl	µmol/l	mg/dl	µmol/l
<1.5	<132	9	536
1.5-2.0	132-176	10	595
>2.0	>176	12	714

Serum uric acid levels are increased with decreased renal function, but if uric acid levels are especially high for the level of creatinine, then chronic urate nephropathy should be considered. Shown are threshold levels of uric acid for which higher levels should increase the suspicion for chronic urate nephropathy.
Modified from reference 22.

nephropathy is a rare autosomal dominant disease that mimics chronic gouty nephropathy but manifests in adolescence or during early childhood (see Chapter 48).

Treatment

It remains controversial whether lowering uric acid can improve kidney disease in patients with gout or hyperuricemia. One randomized trial demonstrated that allopurinol therapy is associated with preservation of eGFR in CKD, although the treatment did not show any effects on the defined study end-point, which was ESRD.[24] Withdrawal of allopurinol from patients with stable CKD has resulted in worsening of hypertension and acceleration of kidney dysfunction, especially in patients who were not on ACE inhibitors.[25] Lowering uric acid in patients with asymptomatic hyperuricemia is also associated with an increase in eGFR.[26] There also have been reports that lowering uric acid may reduce the risk for cardiovascular disease in patients with CKD.[24,27] However, to date all studies have involved small numbers of patients and more definitive studies are required before treatment of hyperuricemia with uric acid–lowering therapy can be recommended routinely.

One reason for caution is the accumulation of xanthine in renal failure, which will be aggravated by the xanthine oxidase inhibitor allopurinol. When precipitated in the kidney, xanthine can cause acute kidney injury. To minimize this complication, it is recommended to initiate allopurinol at a dose of 50 to 100 mg/day, increasing to 200 or 300 mg/day after several weeks as tolerated. Another adverse effect of allopurinol use is a hypersensitivity reaction (Stevens-Johnson–like syndrome) that may be more common in patients with reduced eGFR. The newer xanthine oxidase inhibitor febuxostat does not require modification of dose at lower eGFR and appears to be less frequently associated with hypersensitivity or nephrotoxicity, but there are some studies that suggest that its use may be associated with greater cardiovascular mortality than that observed with allopurinol.

Hypokalemic Nephropathy

Definition and Epidemiology

Hypokalemia, if persistent for prolonged periods, can induce renal cysts, chronic interstitial nephritis, and progressive loss of renal function, known as *hypokalemic nephropathy,* which can be inherited or acquired. Hypokalemic nephropathy occurs in 15% to 20% of individuals with anorexia nervosa.[28]

Pathology

The characteristic finding is vacuolation of the renal tubules as a result of dilation of cisternae of the endoplasmic reticulum and basal folding, which is usually limited to the proximal tubular segments (Fig. 62.5). This abnormality generally requires at least 1 month to develop and is reversible with potassium supplementation. More prolonged hypokalemia can lead to more severe changes, predominantly in the renal medulla, including interstitial fibrosis, tubular atrophy, and cyst formation. There is experimental evidence that hypokalemic injury may be caused by hypokalemia-induced renal vasoconstriction with ischemia. Local ammonia production stimulated by hypokalemia also may lead to intrarenal complement activation that may contribute to the renal injury. Furthermore, the associated intracellular acidosis can stimulate cell proliferation, which may account for the occasional development of cysts in hypokalemic patients.

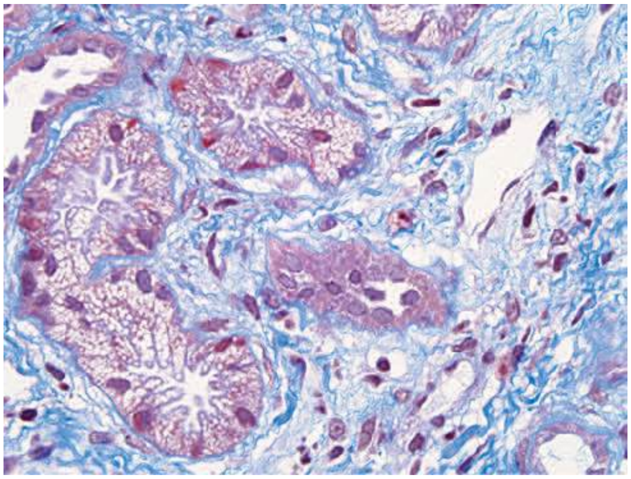

Fig. 62.5 Hypokalemic nephropathy. Vacuolization of the renal tubules is observed in association with interstitial fibrosis in a patient with hypokalemic nephropathy. (Masson trichrome stain; original magnification ×400.) (Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)

Clinical Manifestations

Impaired urine concentration, manifesting with nocturia, polyuria, and polydipsia, may occur, particularly when serum potassium concentration is consistently below 3.0 mmol/l for months or years. The average duration of hypokalemia reported in patients with chronic hypokalemic nephropathy is 3.5 to 9 years. The renal defect is associated with decreased collecting tubule responsiveness to vasopressin, possibly because of decreased expression of aquaporin 2.

Diagnosis

Although degenerative changes in proximal tubular cells are a consistent but nonspecific finding in hypokalemic nephropathy, a particularly characteristic finding is vacuolar changes in the proximal tubules (see Fig. 62.5). Similar vacuolization of the convoluted tubules is observed in ethylene glycol poisoning.

Treatment

Hypokalemia usually can be treated with oral potassium supplements. The treatment of hypokalemia is discussed in Chapter 9. Coarse cytoplasmic vacuoles may persist for some time after normalization of serum potassium values.

Hypercalcemic Nephropathy

Definition and Epidemiology

Hypercalcemia can cause transient and reversible renal vasoconstriction with a decrement in renal function as well as chronic interstitial nephritis secondary to tubular cell necrosis and intratubular obstruction. In addition, hypoparathyroidism (especially after surgical treatment of

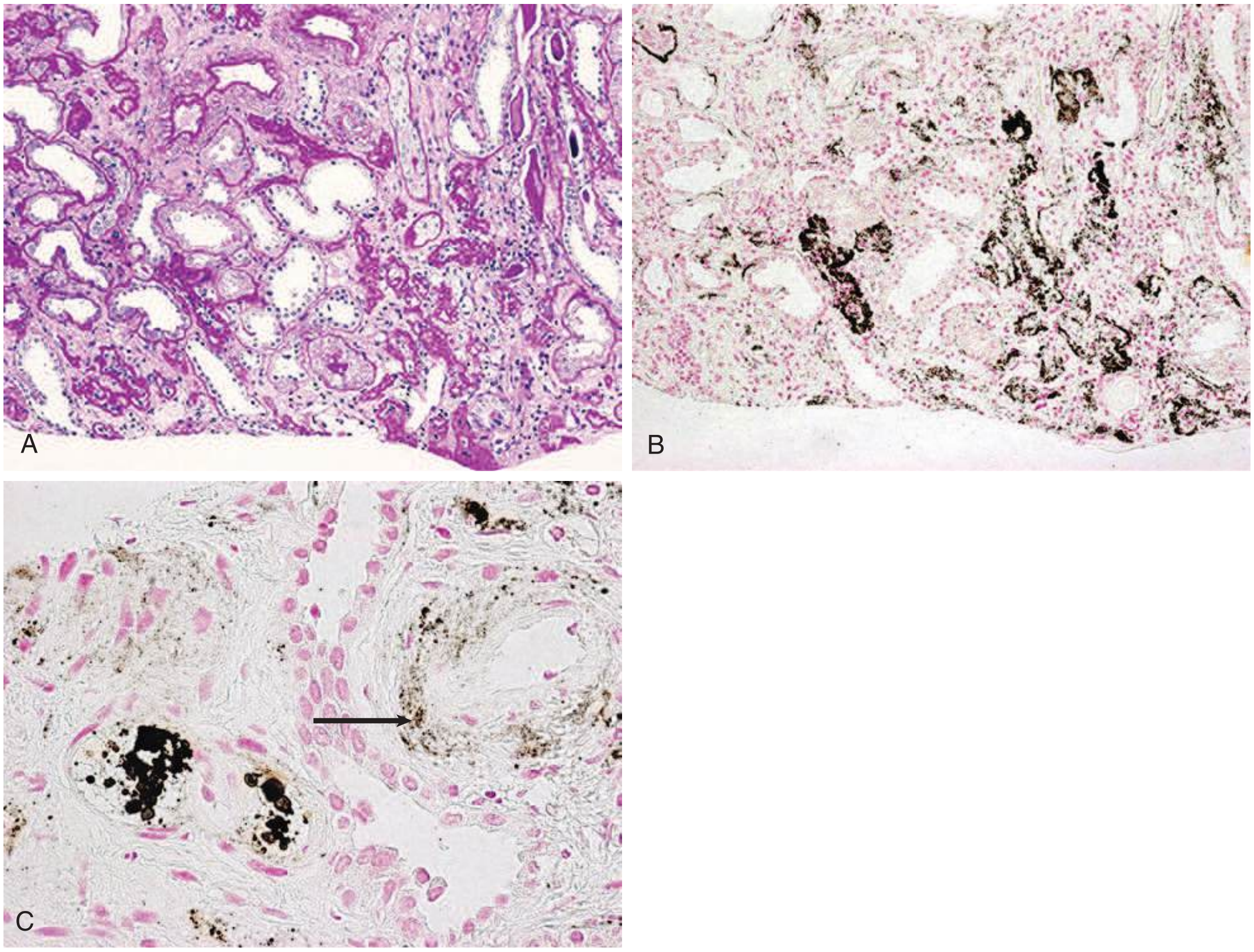

Fig. 62.6 **Hypercalcemic nephropathy caused by sarcoidosis.** (A) Marked tubular atrophy and interstitial fibrosis with mild lymphocytic infiltrate. (B) Dense calcium deposits are seen in the thickened basement membrane of the atrophic tubules and in the fibrotic area of interstitium (serial section of A). (C) Intraluminal calcium plaque in the atrophic tubules. Granular calcium deposits are observed in the arterial wall *(arrow).* (*A,* Periodic acid–Schiff stain; *B* and *C,* von Kossa stain.) (Courtesy Dr. Noriko Uesugi, Ibaraki, Japan.)

hyperparathyroidism) can result in marked hypercalciuria and a similar syndrome in the absence of hypercalcemia.

Pathology

Focal degeneration and necrosis of the tubular epithelium, primarily in the medulla, where calcium is concentrated, develop soon with persistent hypercalcemia. Although focal degenerative and necrotic lesions of the tubular epithelium can be observed with acute hypercalcemia, the most distinctive histologic feature of long-standing hypercalcemia is calcific deposits in the interstitium (nephrocalcinosis; Fig. 62.6). Deposition begins in the medullary tubules, followed by deposition in the cortical proximal and distal tubules and within the interstitial space, and secondarily leads to mononuclear cell infiltration and tubular necrosis.

Clinical Manifestations

Macroscopic nephrocalcinosis is often detected on radiography or ultrasound. A defect in urinary concentration is the most notable tubular dysfunction and manifests as polyuria and polydipsia. The mechanism is incompletely understood, but the impairment relates both to a reduction in medullary solute content and to interference with the cellular response to vasopressin. Reversible impairment of eGFR can result from either acute or chronic hypercalcemia by decreased renal blood flow. Irreversible, advanced CKD is a rare consequence of long-standing hypercalcemia and is almost invariably associated with calcium crystal deposition in the interstitium of the kidney.

CHRONIC INTERSTITIAL NEPHRITIS CAUSED BY HEREDITARY DISEASES OF THE KIDNEY

Nephronophthisis (NPHP) and medullary cystic kidney disease (MCKD) (or the NPHP-MCKD complex) are hereditary diseases associated with renal cysts at the corticomedullary junction. Karyomegalic interstitial nephritis is a hereditary form of chronic tubulointerstitial nephritis histologically characterized by nuclear enlargement with irregular outlines, hyperchromatic aspect, and prominent nucleoli. These disorders are described in detail in Chapters 45 and 48.

CHRONIC INTERSTITIAL NEPHRITIS ASSOCIATED WITH HEAVY METAL EXPOSURE

Lead Nephropathy

Definition and Epidemiology

Acute lead intoxication is rare but may manifest with abdominal pain, encephalopathy, hemolytic anemia, peripheral neuropathy, and proximal tubular dysfunction (Fanconi syndrome). In contrast, chronic low-level exposure to lead is associated with CKD, often with hyperuricemia.

Because lead has a biological half-life of several decades, both intermittent acute poisoning and low-level environmental exposure result in chronic cumulative lead poisoning.

Although some epidemiologic studies have suggested that low-level exposure may be associated with CKD or hypertension,[29-31] data indicating that lead causes CKD leading to ESRD are relatively sparse.[32] It should be noted, however, that there may be regional differences on this issue and a closer look will be needed to obtain an epidemiologic heatmap. The pathogenesis of the renal disease may be related to the accumulation of reabsorbed lead in the proximal tubule cells, effects of chronic lead exposure on the vasculature, or lead-induced hyperuricemia. Additional well-controlled longitudinal studies with adequate exposure and effect variables are awaited to confirm that lead exposure causes deterioration of renal function and eventual ESRD.

Pathology

The kidneys are granular and contracted. The characteristic morphology is chronic interstitial nephritis demonstrating nonspecific tubular atrophy, interstitial fibrosis, and a paucity of inflammatory cells. The earliest histologic finding is proximal tubular injury, with intranuclear inclusion bodies composed of a lead-protein complex. Glomerular scarring can be observed as a secondary event, and arteries and arterioles demonstrate medial thickening and luminal narrowing, probably related to hypertension. Immunofluorescence studies are noncontributory.

Clinical Manifestations

Chronic lead nephropathy is usually identified when a source of high exposure is known (occupational hazard or consumption of illicitly distilled spirits [moonshine]). Hyperuricemia is common because of impaired uric acid excretion. Urine sediment is benign, and urinary protein excretion is less than 2 g/day. Hypertension is almost always present, and in the absence of appropriate testing or a careful exposure history, lead nephropathy is often misdiagnosed as hypertensive kidney disease. Gouty arthritis ("saturnine gout") affects about half of patients. Patients with chronic lead intoxication may occasionally manifest other signs, including peripheral motor neuropathies, anemia with basophilic stippling, and perivascular cerebellar calcifications.

Diagnosis

Lead nephropathy may be underdiagnosed because no simple diagnostic blood test is available. Lead nephropathy is easily confused with chronic uric acid nephropathy, in which uric acid deposits (tophi) may form in the renal interstitium. All patients with hyperuricemia and renal impairment should have a history of occupational lead exposure excluded. The blood lead concentration is an insensitive measure of cumulative body stores. A clinical diagnosis of lead nephropathy is based on a history of exposure, evidence of renal dysfunction, and an abnormal calcium disodium edetate ($CaNa_2$ EDTA) lead chelation test. The association with gout and CKD is strong enough to merit lead chelation testing in patients with CKD who have gout and risk for lead exposure. $CaNa_2$ EDTA is administered (2 doses of 0.5 g in 250 ml 5% dextrose given 12 hours apart), and urine is collected for 3 days because urinary excretion is slower when eGFR is reduced. Normal urinary lead levels are less than 650 μg/3 days. X-ray fluorescence, which provokes the emission of fluorescent photons from the target area, is an alternative method that detects increased bone lead levels, which are also a reflection of cumulative lead exposure. Although x-ray fluorescence measurements allow a rapid, noninvasive estimation of lead in bone, detection equipment is available at only a small number of centers.

Treatment

Treatment involves infusions of $CaNa_2$ EDTA together with removal of the source of lead. The likelihood of a satisfactory response to $CaNa_2$ EDTA is influenced by the degree of interstitial fibrosis that has already occurred.

In industrial and occupational settings, such as in foundry workers and individuals working with lead-based paints and glazes, preventive measures to minimize exposure and low-level absorption are essential. Some studies in children show success with the oral chelating agent succimer (Chemet). Chelation therapy may slow progressive CKD, even in patients with mild lead intoxication.[33] However, chelation therapy has not been widely used because of adverse drug effects and concerns about the effects of remobilized lead. It is generally not indicated for adults with blood lead concentrations of less than 45 μg/dl. Because of a lack of controlled clinical trials demonstrating efficacy of chelation and concerns about potential side effects, recommendations for treatment with chelating agents are empiric and decisions to use chelation therapy for lead intoxication can be controversial.

Other Heavy Metal–induced Nephropathies

Cadmium is a metal with a wide variety of industrial uses, including the manufacture of glass, metal alloys, and electrical equipment. Cadmium is preferentially concentrated in the kidney, principally in the proximal tubule, in the form of a cadmium-metallothionein complex that has a biological half-life of about 10 years. Cadmium contamination may be an important contributor to the high risk for chronic interstitial nephritis in some agricultural communities in the developing world. A major outbreak of cadmium toxicity occurred in Japan as a result of industrial contamination. The disease was called *itai-itai,* or "ouch-ouch," because bone pain was the major clinical manifestation. Other manifestations included proximal tubular dysfunction (Fanconi syndrome), hyperphosphaturia, and vitamin D–resistant rickets with osteomalacia. The mechanism by which cadmium elicits chronic inflammation and fibrosis in the kidney is relatively unstudied. The diagnosis is suggested by a history of occupational exposure, increased urinary β_2-microglobulin, and increased urinary cadmium levels (>7 μg of cadmium per gram creatinine). Once manifested, renal injury tends to be progressive, even if exposure is discontinued. Chelation has not been effective in humans, and prevention is the only effective treatment.

Arsenic, used as a poison gas in World War I, is present in insecticides, weed killers, wallpaper, and paints. Chronic arsenic toxicity from inorganic arsenic most commonly manifests as sensory and motor neuropathies, distal extremity hyperkeratosis, palmar desquamation, diarrhea and nausea, Aldrich-Mees lines (white bands on the nails), and anemia. In rare cases, it may cause renal disease, manifested by proximal RTA and chronic interstitial fibrosis. Diagnosis is made by demonstration of an elevated urinary inorganic arsenic level.

Mercury is found in alloy plants, mirror plants, and some batteries, and mercury intoxication usually occurs as a result of accidental exposure to mercury vapor. Mercury has been shown to induce membranous nephropathy (MN) in experimental animals and has been reported with the use of mercury-containing skin-lightening creams.[34] Neither elemental mercury nor the mercurous salt (Hg_2Cl_2) produces sustained renal tubular injury, but mercury dichloride ($HgCl_2$) may produce acute tubular necrosis and subsequent chronic interstitial nephritis in laboratory animals. However, a report of endemic methyl mercury poisoning in Japan revealed a clinical picture dominated by neurologic sequelae; renal disease in these patients was surprisingly benign, consisting only of tubular proteinuria without changes in serum creatinine.

RADIATION NEPHRITIS

Definition and Epidemiology

Although radiation nephritis was relatively common decades ago, the incidence has decreased considerably because recognition of radiation-induced renal damage has altered protocols for the administration of therapeutic radiation. In general, direct exposure of the kidney to 20 to 30 Gy (1 Gy = 100 rad) over 5 weeks or less will produce radiation nephritis.

Pathology

In general, vascular and glomerular lesions of thrombotic microangiopathy may predominate. The initial target of ionizing radiation within the kidney appears to be endothelial cells, leading to endothelial cell swelling. Electron microscopy reveals a split appearance of the capillary wall caused by the mesangial interposition and widening of the subendothelial space by a nondescript fluffy material. These features are shared by hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, suggesting a common pathogenic mechanism originating from endothelial injury. However, tubulointerstitial changes are also usually present. Vascular occlusion leads to tubular atrophy, and severe disease is characterized by progressive interstitial fibrosis and the presence of interstitial inflammatory cells.

Clinical Manifestations

Hypertension is commonly observed. Progression to a chronic form of radiation nephritis may occur if resolution of acute radiation nephritis is incomplete. These patients present with proteinuria, progressive CKD, and eventual development of ESRD several years after irradiation in the absence of an acute phase.

Treatment

Prevention is the best approach; risk can be minimized by shielding the kidneys or fractioning the total-body irradiation into several small doses over several days. No specific treatment is available for established radiation nephritis. The general approach is control of hypertension and supportive treatment of CKD.

INTERSTITIAL NEPHRITIS MEDIATED BY IMMUNOLOGIC MECHANISMS

Sjögren Syndrome

Definition and Epidemiology

Sjögren syndrome may be associated with chronic interstitial nephritis. The reported prevalence of renal involvement in Sjögren syndrome varies from 2% to 67%, principally owing to different definitions between studies. Recent analysis of 130 patients with primary Sjögren syndrome in China showed an 80% incidence of biopsy-proven chronic interstitial nephritis.[35]

Pathology

The lesion is characterized histologically by infiltration of lymphocytes and plasmacytes in the interstitium with tubular cell injury and, rarely, granuloma formation. This progresses to tubular atrophy and interstitial fibrosis over time. Immunofluorescence reveals granular deposits of immunoglobulin G (IgG) and C3 along the tubular basement membrane (TBM).

Clinical Manifestations

The clinical and biochemical manifestations of interstitial nephritis may be the presenting or only features of Sjögren syndrome. Serum creatinine concentration is generally only mildly elevated in association with a bland urine sediment and abnormalities in tubular function, including Fanconi syndrome, distal RTA, hypokalemia, and nephrogenic diabetes insipidus. Sjögren syndrome is one of the most common causes of acquired distal (type 1) RTA in adults, and the hypokalemia may be marked, resulting in a clinical presentation of severe weakness. Hypokalemia may occur in the absence of RTA, resulting from salt wasting and secondary hyperaldosteronism.

Treatment

Treatment with corticosteroids at the stage of cellular infiltration is frequently beneficial for protecting renal function. Although the renal disease has a slow and protracted course and CKD develops over time, progression to ESRD is rare.

Sarcoidosis

Definition and Epidemiology

Histologic evidence of interstitial nephritis with noncaseating granulomas is common in patients with sarcoidosis, but the frequency of clinically significant disease is low.[36] It may manifest as either acute interstitial nephritis or chronic interstitial nephritis.

Pathogenesis and Pathology

Renal biopsy reveals normal glomeruli; interstitial infiltration, mostly with mononuclear cells; tubular injury; and, with more chronic disease, interstitial fibrosis. Whereas the classic finding is noncaseating granulomas in the interstitium, they are uncommon and nonspecific. An analysis of 18 patients with granulomatous interstitial nephritis showed that in 5 the disorder was associated with sarcoidosis; in 2, tubulointerstitial nephritis and uveitis; in 2, medication; and in 9, the condition was idiopathic.[37] Immunofluorescence and electron microscopic studies typically show no immune deposits.

Recent studies suggest that renal sarcoidosis may reflect an impaired immune response to certain bacteria, especially *Propionibacterium acnes*. Confirmatory studies are needed, and it is not known if antibiotic treatment aimed at *P. acnes* provides any benefit.

Clinical Manifestations

Most affected patients have clear evidence of diffuse active sarcoidosis, although some present with an isolated elevation in serum creatinine and only minimal extrarenal manifestations. The urinalysis may be normal or show only sterile pyuria or mild proteinuria.

In addition, hypercalcemia induced by increased production of calcitriol (1,25-dihydroxyvitamin D_3) by activated mononuclear cells (particularly macrophages) in the lung and lymph nodes occasionally results in renal problems (see the previous discussion of hypercalcemic nephropathy).

The serum ACE level is used best not as a primary diagnostic tool but as a marker of disease activity and response to therapy. A normal serum ACE level does not exclude renal sarcoidosis.

Treatment

Corticosteroid therapy tends to improve renal function, although recovery is often incomplete. Limited data are available concerning the optimal protocol for corticosteroid therapy, but initial dose is usually predniso(ol)one 0.5 to 1 mg/kg/day, which is followed by a slow taper. Rapid tapering of corticosteroids can result in relapse.

Systemic Lupus Erythematosus

Definition and Epidemiology

Interstitial nephritis with immune complexes is defined by granular deposits of immunoglobulins and complement in the TBM, interstitium, or both. Systemic lupus erythematosus is the most common reason for this type of interstitial nephritis (Fig. 62.7), and interstitial involvement is present in half of kidney biopsy specimens in lupus. Tubulitis serves as an independent predictive factor for eGFR decline in lupus nephritis.[38] Rarely, tubulointerstitial immune complex disease may be the only manifestation of lupus nephritis.

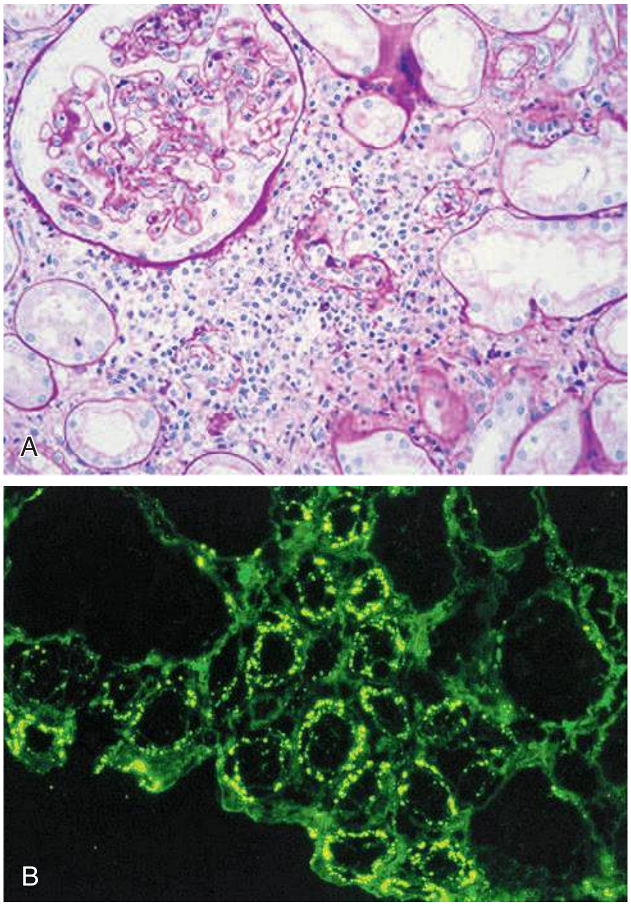

Fig. 62.7 Chronic interstitial nephritis in systemic lupus. (A) Interstitial nephritis observed in patients with systemic lupus erythematosus. (Periodic acid–Schiff stain; original magnification ×400.) B, Immunofluorescence study of the same patient revealed deposition of immunoglobulin G in the interstitium, in tubular cells, and along the tubular basement membrane. (Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)

Clinical Manifestations

The presentation may be as acute or chronic interstitial nephritis. The possibility of interstitial involvement (without glomerular disease) is suggested by a rising serum creatinine concentration and a bland urine sediment. Interstitial involvement may be accompanied by signs of tubular dysfunction, such as distal RTA (type 1 or type 4); by isolated hyperkalemia resulting from impaired distal potassium secretion; or by hypokalemia resulting from salt wasting. The potentiating effects of sodium wasting on potassium secretion include an increase in sodium delivery to the potassium secretory site in the collecting tubules and associated volume depletion with subsequent stimulation of aldosterone secretion.

Treatment

Corticosteroid therapy is usually effective in suppressing tubular dysfunction and preserving renal function.

Inflammatory Bowel Disease

Although the most frequent renal complications of Crohn disease are calcium oxalate stones and renal amyloidosis, interstitial nephritis has been reported in patients treated for chronic inflammatory bowel disease. Aminosalicylates (5-aminosalicylic acid, mesalazine, and sulfasalazine) are responsible for most of these cases, but nephrotoxicity of these agents is very uncommon (mean rate only 0.3% per patient-year).[39] The median time for development of renal injury after commencing aminosalicylates is 3 years.[40] There is no clear relationship between aminosalicylate dose and the risk for nephrotoxicity, suggesting that this is an idiosyncratic response. Some patients have been reported to have biopsy-proven interstitial nephritis before the diagnosis of Crohn disease.

Aminosalicylates should be withdrawn when renal impairment develops in a patient with inflammatory bowel disease; if this does not result in a fall in serum creatinine, renal biopsy should be considered. Only one third of cases recover completely after drug withdrawal.[40] Corticosteroids are recommended when renal function does not respond to drug withdrawal.

IgG4-Related Kidney Disease

Definition and Epidemiology

On the basis of histologic and immunohistochemical examination of various organs of patients with autoimmune pancreatitis, a novel clinicopathologic entity of IgG4-related sclerosing disease has been proposed.[41] This is a systemic disease that is characterized by extensive IgG4-positive plasma cells and T-lymphocyte infiltration of various organs (Fig. 62.8). Initial reports of IgG4-related sclerosing disease came from Japan, but it has now been described in Europe and the United States and is considered to be a worldwide entity.

Pathogenesis

Whether IgG4 is pathogenic or is a "bystander" remains unknown. IgG4 does not activate the classical complement pathway effectively. However, immune complex formation may play a pathogenic role, raising the possibility of complement fixation via the lectin pathway or activation of the classical pathway of complement by some unknown mechanism.

Pathology

The most common pattern of involvement by IgG4-related kidney disease is tubulointerstitial nephritis with dense infiltration of IgG4-positive mononuclear cells. Distinctive features of the tubulointerstitial nephritis include (1) well-demarcated borders between involved and uninvolved areas; (2) involvement of the cortex and deep medulla, often extending beyond the renal capsule; (3) interstitial inflammatory cells comprising predominantly plasma cells and lymphocytes, with a high prevalence of IgG4-positive cells often admixed with fibrosis; (4) peculiar features of interstitial fibrosis called *storiform fibrosis* or *bird's-eye* pattern; and (5) deposits visible by light microscopy and immunofluorescence in the TBM, Bowman capsule, and interstitium.[42] Recent pathologic analysis revealed perivascular inflammation or fibrosis of medium- and small-sized vessels as a newly identified pathologic feature of IgG4-related kidney disease and proposed the term *interstitial fibrosclerosis* because storiform fibrosis contains mainly nonfibrillar collagens.[43] Immunofluorescence shows granular TBM staining for IgG accompanied by C3 of lesser staining intensity. MN also has been described as a manifestation of IgG4-related kidney disease.[44]

Clinical Manifestations

Clinical manifestations are observed in various organs, with presentations including sclerosing cholangitis, cholecystitis, sialadenitis, and retroperitoneal fibrosis. IgG4-related tubulointerstitial nephritis can be mass forming, similar to IgG4-related inflammatory lesions in other organs. Of patients with IgG4-related disease, 80% are reported to have had radiographic renal abnormalities: bilateral and multiple small low-attenuation lesions, a mass, or bilateral renal enlargement.[45] Whereas most IgG4-related sclerosing disease is associated with autoimmune

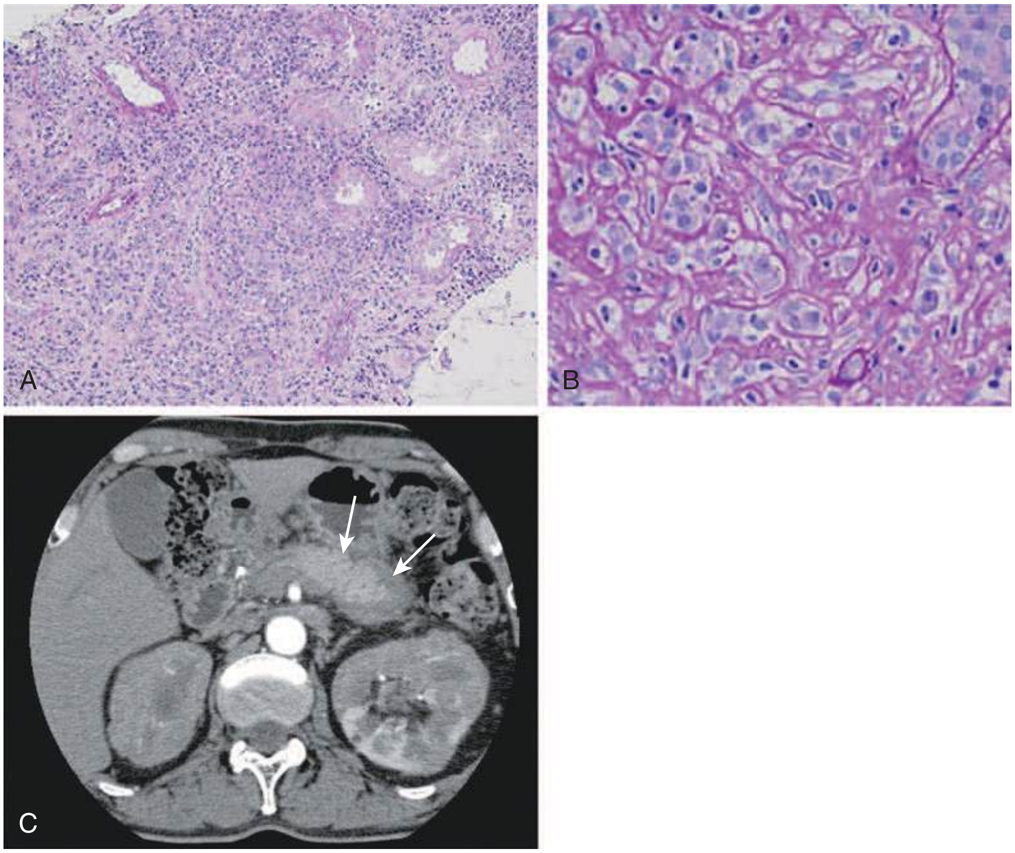

Fig. 62.8 **Chronic interstitial nephritis in IgG4-related sclerosing disease.** (A) Interstitial nephritis with numerous mononuclear cell infiltrates observed in a patient with autoimmune pancreatitis. Many of these cells are positive for IgG4 in typical cases. (Periodic acid–Schiff stain; original magnification ×200.) (B) Small nests of swollen plasma cells or individual plasma cells are encircled by collagenous tissue. The features resemble a maple wood grain pattern called *bird's eye*. Plasma cells look like birds' eyes in the wood, whereas fibrotic tissues correspond to branches of the wood. (C) CT scan of the patient revealed pancreatic swelling *(arrows)*. (**A** and **C,** courtesy Dr. Hiroshi Nishi, University of Tokyo, Tokyo. **B,** from reference 42.)

pancreatitis, cases without pancreatic involvement have been described. The disease occurs predominantly in older men. Serum IgG4 levels are raised, and IgG4-positive cells are found in the interstitium. According to a recent meta-analysis, a cut-off value of serum IgG4 ranging from 135 to 144 mg/dl confers a sensitivity of 87% and a specificity of 83%.[46] However, the finding of an elevated serum IgG4 is not specific, because this may occur in 5% of the normal population. The patients often show hypocomplementemia and eosinophilia. Recently proposed diagnostic criteria are shown in Table 62.3.

Treatment

The response to corticosteroids is generally favorable, but relapse is common. The protocol has not been established, but a starting dose of approximately 40 mg/day may be prudent. There is no correlation between histologic pattern and response to therapy, and even patients with extensive fibrosis on biopsy have shown a response to corticosteroid therapy.

Other Forms of Immune-Mediated Interstitial Nephritis

Primary anti-TBM nephritis is an extremely rare form of interstitial nephritis that usually is acute and characterized by linear deposits of immunoglobulins, commonly IgG, and complement in the TBM, together with tubular interstitial inflammation and anti-TBM antibodies in the serum. Anti-TBM antibodies, usually IgG, may be found in 50% to 70% of patients with anti–glomerular basement membrane nephritis and occasionally in patients with MN, systemic lupus, IgA nephropathy, minimal change disease, and malignant hypertension.

OBSTRUCTIVE UROPATHY

Complete or partial urinary tract obstruction is accompanied by pathologic changes in both the tubulointerstitium and glomeruli consisting of interstitial fibrosis, tubular atrophy, and occasionally focal glomerular sclerosis. Details are discussed in Chapter 58.

VASCULAR DISEASES

Ischemia resulting from intrarenal vascular involvement causes tubular atrophy, interstitial fibrosis, and cellular infiltration. This is further discussed in Chapter 41. Chronic ischemia in the tubulointerstitial compartment also plays a crucial role in the progression of a variety of glomerular and tubulointerstitial diseases.[2]

INFECTION-ASSOCIATED CHRONIC INTERSTITIAL NEPHRITIS

Although a variety of bacterial and viral infections can be associated with acute interstitial nephritis (see Chapter 60), chronic interstitial

TABLE 62.3 Diagnostic Criteria for IgG4-Related Tubulointerstitial Nephritis

Histology	Plasma cell–rich tubulointerstitial nephritis with >10 IgG4-positive plasma cells per high-power field in the most concentrated field* Tubular basement membrane immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy†
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement Diffuse marked enlargement of kidneys
Serology	Elevated serum IgG4 or total IgG level
Other organ involvement	Includes autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis

Diagnostic criteria for IgG4-related tubulointerstitial nephritis (TIN). diagnosis of IgG4 TIN requires the histologic feature of plasma cell–rich TIN with increased IgG4-positive plasma cells and at least one. Other feature from the categories of imaging, serology, or other organ involvement.
From reference 45.
*Mandatory criterion.
†Supportive criterion, present in >80% of cases.

nephritis secondary to infectious agents appears to be rare. Insidious *Mycobacterium tuberculosis* infection can cause chronic granulomatous tubulointerstitial nephritis.[47] Chronic bacterial infections can result in xanthogranulomatous pyelonephritis or renal malacoplakia (see Chapter 51).

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SELF-ASSESSMENT QUESTIONS

1. A 29-year-old woman was admitted to the hospital because of anorexia, binge eating, and self-induced vomiting. On admission, her body mass index was 12.2 and she presented with nocturia and polyuria. The serum potassium level was 2.8 mEq/l. Which *one* of the following do you expect as the pathologic change of the renal biopsy specimen of this patient?
   A. Calcific deposits in the interstitium
   B. Vacuolation of the renal tubules
   C. Noncaseating granulomas
   D. Infiltration of IgG4-positive mononuclear cells
   E. Acellular interstitial nephritis with intranuclear inclusion bodies in the proximal tubules
2. IgG4-related tubulointerstitial nephritis is an emerging clinicopathologic entity that is a part of the systemic disease characterized by infiltration of IgG4-positive plasma cells in various organs. Which *one* of the following is *most* likely to be associated with this disease?
   A. Uroepithelial carcinoma
   B. Inflammatory bowel disease
   C. Cerebral aneurysm
   D. Autoimmune pancreatitis
   E. Angiokeratoma
3. A 58-year-old woman with a 30-year history of bipolar affective illness was admitted to hospital because of thirst, polyuria, and weight loss. Lithium had been prescribed for the preceding 18 years. On admission, she presented with hypernatremic dehydration. Which *one* of the following represents the *best* next step to diagnose the characteristic morphologic changes in the kidney?
   A. Non–contrast-enhanced magnetic resonance imaging
   B. Blood oxygen level–dependent magnetic resonance imaging (MRI)
   C. Non–contrast-enhanced computed tomography
   D. Scintigraphy
   E. Intravenous urography

63

Endemic Nephropathies

Ramón Garcia-Trabanino, Richard J. Johnson

Localized epidemics of chronic kidney disease (CKD) have been reported in various parts of the world and are known as *endemic nephropathies*. The word *endemic* is used in a lay rather than epidemiologic sense, to emphasize the regionally confined nature of such nephropathies. By definition, these nephropathies are distinct from CKD of usual causes and tend to manifest insidiously. Although both aging and metabolic syndrome are also associated with the insidious reduction in estimated glomerular filtration rate (eGFR), endemic nephropathies are distinguished by earlier onset, fewer classic risk factors, and more rapid progression to end-stage renal disease (ESRD).

There have been some spectacular examples in which the cause of endemic nephropathy has been identified. For example, in the 1920s there was a dramatic increased frequency of CKD in children and young adults in Queensland, Australia, that was shown to be due to lead poisoning, such as from exposure to paints. The children presented with either Fanconi syndrome from acute lead intoxication or CKD and hypertension associated with chronic lead intoxication. Likewise, an epidemic of CKD resulting from chronic interstitial nephritis and associated with Fanconi syndrome with hypophosphatemia and osteomalacia was discovered in the Toyama prefecture of Japan in the 1950s and 1960s and was shown to be caused by cadmium poisoning. A factory was found to be dumping cadmium into the Jinzu River, leading to contamination of the rice and soybeans. The disease was called *itai-itai* (“ouch-ouch”) by the locals due to the severe joint pains, and manifested over decades, especially among the older women. For more information on nephropathies associated with heavy metals see Chapter 64. Finally, Balkan endemic nephropathy is another example in which the cause, the herb *Aristolochia clematis* contaminating wheat, has been identified. *Aristolochia* is also the cause of Chinese herbs nephropathy that was related to an epidemic of chronic tubulointerstitial disease first identified in individuals taking Chinese herbs for weight loss in the early 1980s. Diseases caused by *Aristolochia* (*Aristolochia*-associated nephropathy) are discussed in Chapter 78.

MESOAMERICAN NEPHROPATHY

Definition and Epidemiology

Mesoamerican nephropathy was first described in 2002 when physicians from reference Hospital Rosales in San Salvador noted a large number of young agricultural workers from the Bajo Lempa region presenting with CKD of unknown cause and a distinct epidemiologic pattern.[1] Subsequently, the disease was found to be endemic mainly along the Pacific coast, particularly involving Guatemala, Nicaragua, El Salvador, and Costa Rica (Fig. 63.1). Most of those affected are young men between ages 20 and 60 who are working manually in the fields, but there is evidence that women and even children are also at increased risk. Although manual work in the sugarcane fields carries the highest risk, the disease also has been reported among banana and cotton farmers, miners, construction and transportation workers, and others. Review of historical records suggest the disease has been present since the early 1970s but has increased progressively over recent decades, especially in men (Fig. 63.2).[2] In some areas, such as in Chichigalpa, Nicaragua, the prevalence of CKD (defined as eGFR <60 ml/min/1.73 m^2) approaches 40% of men between the ages of 20 to 40.[3] Although the true extent of the epidemic is veiled by the lack of comprehensive renal registries in the afflicted countries, this contrasts with an overall prevalence of 8.3% for all adults and with less than 0.4% for males ages 20 to 40 in the United States.

Pathogenesis

Although there have been rare reports linking the disease with carbamate pesticides or methyl parathion, most studies have been negative and there are no identified associations with aristolochic acid and heavy metals. One common risk factor is heat stress and recurrent dehydration, leading some to suggest it might be a type of heat stress nephropathy.[4,5] Heat stress is well known to cause acute kidney injury from a variety of mechanisms, including heat stroke and rhabdomyolysis, but the concept of a chronic kidney injury occurring from heat stroke is new. Consistent with this possibility, however, is the observation that Mesoamerican nephropathy is much more common in sugarcane workers who work at low altitude where it is warmer than at higher altitudes, despite similar working conditions and pesticide exposure. Experimentally, recurrent heat stress and dehydration also have been shown to induce CKD in animals because of hyperosmolarity-induced activation of the polyol-fructose and vasopressin pathways,[6] and the renal injury is amplified if animals are rehydrated with sugary (fructose-containing) beverages as opposed to water.[7] Heat stress also may result in subclinical rhabdomyolysis, uric acid overproduction, and supersaturation of urine resulting in intermittent uric acid crystalluria.[8] Leptospirosis, an infection that affects the kidney and is spread by rats, also has been proposed as a causal or potentiating factor.

Pathology

Few renal biopsies have been performed, often in patients who already have advanced CKD. The primary finding is chronic tubulointerstitial fibrosis with variable degrees of glomerulosclerosis (Fig. 63.3).[9] Immune deposits are absent. There remains debate over whether the glomerular changes are secondary to chronic disease or represent a primary glomerular injury. Potential mechanisms of glomerular injury include glomerular ischemia (the findings of shrinkage of the

Mesoamerican Nephropathy is Common in Hotter Areas of Central America

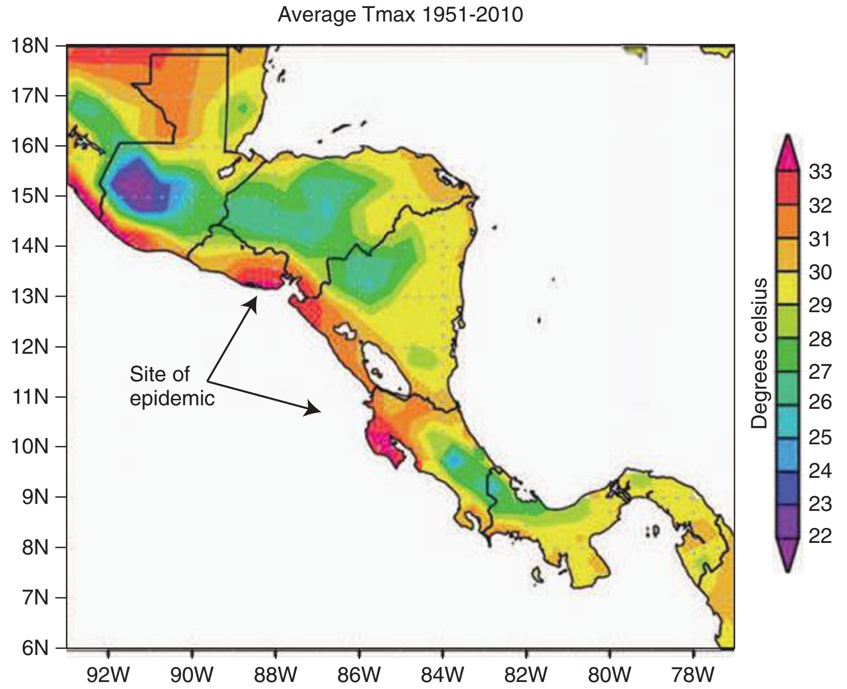
Average Tmax 1951-2010
18N
17N
16N
15N
14N
13N
12N
11N
10N
9N
8N
7N
6N
92W
90W
88W
86W
84W
82W
80W
78W
Site of epidemic
Degrees celsius
33
32
31
30
29
28
27
26
25
24
23
22

Fig. 63.1 Mesoamerican nephropathy. The major areas where Mesoamerican nephropathy has been observed along the Pacific Coast, especially involving the Guanacaste region of Costa Rica, the Bajo Lempa region of El Salvador, and the Chinandega Region of Nicaragua. These are also the hottest areas in Central America. (With permission from reference 13.)

Epidemiology of Mesoamerican Nephropthy in Costa Rica

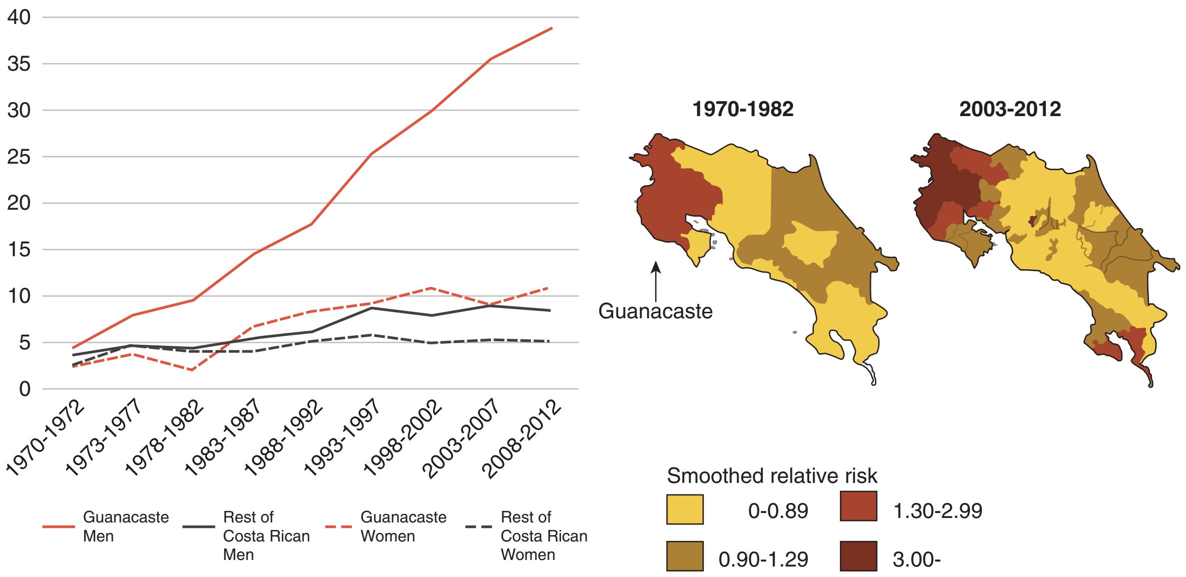

Fig. 63.2 Prevalence of CKD in Guanacaste, Costa Rica. Mesoamerican nephropathy was first noted in the 1970s in Guanacaste Region of Costa Rica. Shown is the increasing prevalence of chronic kidney disease in the Guanacaste Region of Costa Rica in men compared with the rest of Costa Rica. (With permission from reference 2.)

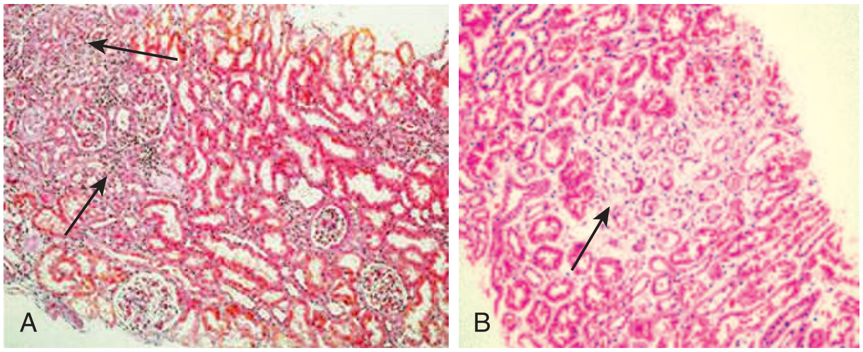

Fig. 63.3 Renal pathology in endemic nephropathy. Mesoamerican nephropathy is characterized by chronic tubulointerstitial fibrosis with localized inflammation *(arrows)*. Other findings include glomerular ischemia and variable glomerulosclerosis. Renal vascular disease is usually mild. Sri Lankan nephropathy (see Fig. 63.3B, hematoxylin and eosin stain) also has a similar histologic appearance with the tubulointerstitial fibrosis with some pockets of inflammatory cells. (**A,** Courtesy Dr. Annika Wernerson, Karolinska Institute Sweden. **B,** With permission from reference 14 [both 40× magnification].)

TABLE 63.1 **Characteristics of Patients With Mesoamerican Nephropathy**

No evidence for common causes of chronic kidney disease	Absence of diabetes (blood glucose <125 mg/dl or 7 mmol/l) BP normal or only slightly high Minimal evidence for GN (no RBC casts, urine protein <2 g/day) No evidence for obstruction (ultrasound) No evidence for polycystic kidney disease (ultrasound)
Clinical presentation	Asymptomatic rise in serum creatinine Minimal albuminuria Frequent hyperuricemia Serum potassium level often lower than expected Biopsy usually shows chronic tubulointerstitial disease and variable glomerulosclerosis (often performed late in disease)

BP, Blood pressure; *GN,* glomerulonephritis, *RBC,* red blood cell.

glomerular tuft and wrinkling of the basement membrane support this). In addition, hyperuricemia, which is commonly elevated in this disease, has been found experimentally to cause glomerular hypertension, and vasopressin induces hyperfiltration in addition to the effects on tubular injury.

Clinical Manifestations

Affected individuals are commonly manual workers, such as sugarcane cutters (Table 63.1). In early stages, some patients present with muscle weakness related to hypokalemia or aseptic dysuria possibly related to uric acid crystalluria. Other patients are asymptomatic but are identified when an elevated serum creatinine is found during health screening. Blood pressure is normal or only slightly elevated, and urine sediment shows low-grade (<1 g/day) proteinuria with occasional red cells and leukocytes. Serum sodium and potassium are often low early in the disease and appear to be associated with increased urinary losses; similarly, elevated magnesium and phosphate losses in the urine are also common, suggesting a tubular defect.[10] Serum uric acid is also elevated, often with levels greater than 9 mg/dl, typically 2 mg/dl higher than expected for the eGFR.[11]

Diagnosis, Treatment, and Prognosis

Diagnosis is made on clinical grounds and is based on living in the endemic area and presenting with CKD without clear cause (Fig. 63.4). The presence of hypokalemia and/or hyperuricemia aids diagnosis. Renal biopsies are generally not performed. Empiric treatment includes counseling on hydration and need for rest in shaded areas, avoidance of nonsteroidal antiinflammatory drugs (NSAIDs), and cessation of smoking. Given experimental data that rehydration with sugary beverages (>6% to 8%) markedly worsens renal injury,[7] avoidance of soft drinks or sugary beverages as hydration drinks is recommended. Although the therapy has not been proven, some local nephrologists (including the primary author) are treating subjects with low-dose angiotensin-converting enzyme inhibitors (especially if they are no longer working and at risk for dehydration) and with allopurinol and bicarbonate when serum uric acid levels are very elevated (>9 mg/dl) to reduce the formation of urine urate crystals and improve the aseptic dysuria. Treatment is empiric and controlled trials are needed. Dialysis is rarely available because of poverty and lack of insurance, and prognosis is guarded. It has been estimated that over 20,000 individuals have died to date.

SRI LANKAN NEPHROPATHY

Reports of an epidemic of CKD in the North Central Province of Sri Lanka began in the late 1980s. Today there over 100,000 individuals affected with the disease, with an ongoing mortality of 5000 per year.[12] Typically, affected individuals are males between the ages of 20 and 60 who are working in the rice paddies under extremely hot conditions. Women also may develop the disease. The clinical presentation is also similar to that of Mesoamerican nephropathy, with low-grade proteinuria and an asymptomatic elevation in serum creatinine or with late presentation in ESRD (see Table 63.1). Hyperuricemia is also common.[13] Renal biopsies early in the disease show chronic tubulointerstitial fibrosis, while later biopsies also show increasing glomerulosclerosis (see Fig. 63.3).[14] Many patients are very poor and have little access to medical care; thus treatment tends to be supportive and dialysis is only rarely provided. [12,15]

For decades the primary hypothesis has been that Sri Lankan nephropathy is due to a toxin, either an agrochemical or pesticide, or possibly heavy metal exposure such as cadmium or arsenic. Nevertheless, levels of heavy metals in the drinking water are within acceptable ranges,[16] and similarly it has been difficult to incriminate any specific agrochemical such as glyphosate.[12] However, those who drink local

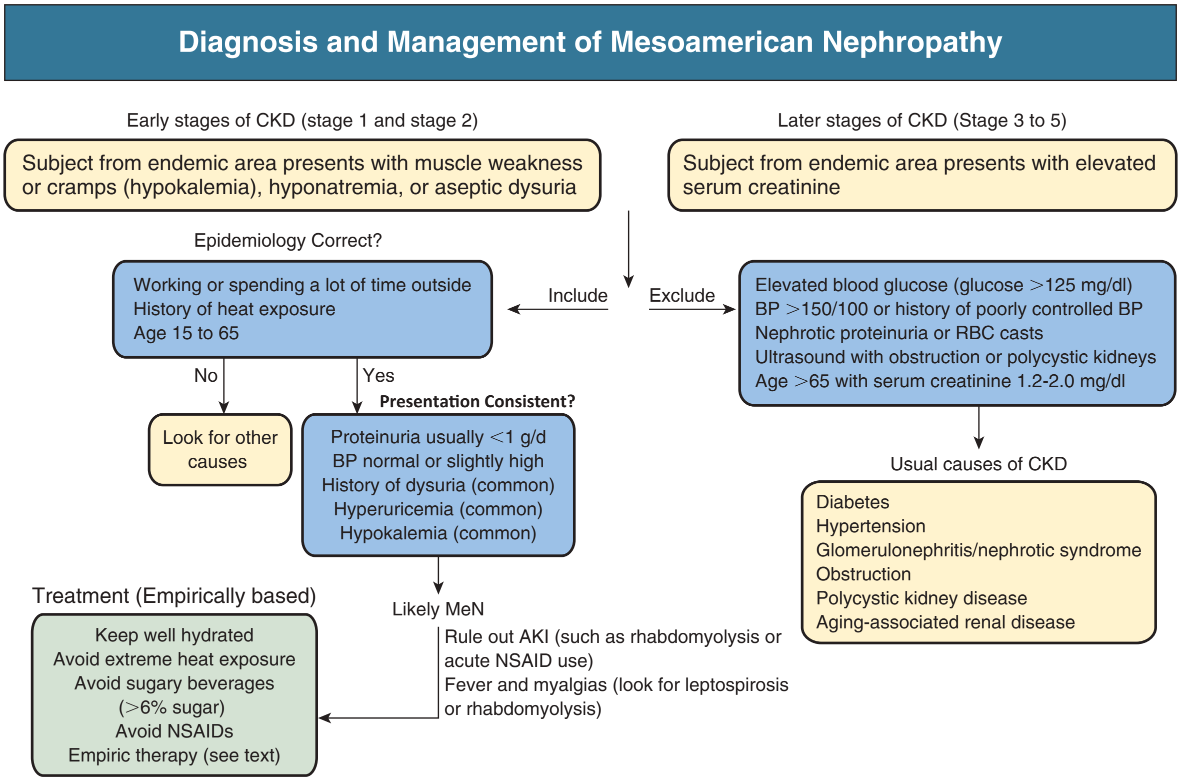
Diagnosis and Management of Mesoamerican Nephropathy
Early stages of CKD (stage 1 and stage 2)
Subject from endemic area presents with muscle weakness or cramps (hypokalemia), hyponatremia, or aseptic dysuria
Later stages of CKD (Stage 3 to 5)
Subject from endemic area presents with elevated serum creatinine
Epidemiology Correct?
Working or spending a lot of time outside
History of heat exposure
Age 15 to 65
Include
Exclude
Elevated blood glucose (glucose >125 mg/dl)
BP >150/100 or history of poorly controlled BP
Nephrotic proteinuria or RBC casts
Ultrasound with obstruction or polycystic kidneys
Age >65 with serum creatinine 1.2-2.0 mg/dl
No
Yes
Presentation Consistent?
Look for other causes
Proteinuria usually <1 g/d
BP normal or slightly high
History of dysuria (common)
Hyperuricemia (common)
Hypokalemia (common)
Usual causes of CKD
Diabetes
Hypertension
Glomerulonephritis/nephrotic syndrome
Obstruction
Polycystic kidney disease
Aging-associated renal disease
Treatment (Empirically based)
Likely MeN
Keep well hydrated
Avoid extreme heat exposure
Avoid sugary beverages (>6% sugar)
Avoid NSAIDs
Empiric therapy (see text)
Rule out AKI (such as rhabdomyolysis or acute NSAID use)
Fever and myalgias (look for leptospirosis or rhabdomyolysis)

Fig. 63.4 Diagnosis and management of Mesoamerican nephropathy (MeN). *AKI,* Acute kidney injury; *BP,* blood pressure; *CKD,* chronic kidney disease; *NSAID,* nonsteroidal antiinflammatory disease; *RBC,* red blood cell.

well water are at higher risk for CKD, suggesting the presence of some unidentified toxin.[17] Importantly, the risk for CKD was also increased in those highly exposed to the sun, those who worked more than 6 hours per day, and those who drank less than 3 l/day liquids.[17] Noteworthy, because many workers believe the well water contains toxins, it seems likely that those who drink well water might be the same subjects who were limiting their water intake. Thus these studies also raise the question whether heat stress and recurrent dehydration may be involved in this disease as well.[13]

OTHER ENDEMIC NEPHROPATHIES

An epidemic of CKD has been reported in the Uddanam region of Andhra Pradesh in southern India and may have been present since the early 1990s.[18] Uddanam nephropathy is observed primarily in males working in the agricultural fields where the primary crops are cashews, coconuts, and rice. Similar to the other epidemics, the patients present with minimal proteinuria and elevated serum creatinine and have chronic tubulointerstitial disease on renal biopsy.[19] Hyperuricemia is also common in this condition. Indeed, to date there are no distinguishing features among the various epidemics, and many authorities believe the disease may have similar etiologies worldwide.

Other similar epidemics are also emerging. This includes an epidemic among manual workers near Tierra Blanca in the Veracruz region of Mexico, where heat stress also has been a major risk factor.[20] There are also early reports that similar epidemics may be manifesting in northeastern Thailand, Egypt, and Sudan.

POTENTIAL ROLE OF CLIMATE CHANGE AND GLOBAL WARMING

The similarity between the various epidemics has placed special emphasis on the role of heat stress and dehydration in CKD. Indeed, studies have shown that the sites where epidemics of CKD are reported are frequently in areas that are extremely hot, especially between the equator and the Tropic of Cancer. It also remains possible that global warming has a role in accelerating the epidemics. Although mean temperatures have increased only 0.8 degrees centigrade in the last 50 years, the frequency of extreme heat events (exceeding the 99th percentile) has increased by nearly 75%.[21] It is interesting that the sites where reports are emerging of epidemic CKD in India correlate with areas of increased extreme heat events such as heat waves (Fig. 63.5). This has led to the hypothesis that these epidemics may represent a type of heat stress nephropathy. If true, the increase in frequency being observed is likely related to increasing world temperatures. The heat stress hypothesis is currently being tested and yet needs to be confirmed. Other factors could include better reporting and the possibility that rehydration with sugary beverages could be accelerating the renal injury.[7] It also remains possible that toxins may be contributing to the various epidemics, or may be acting in synergy with heat stress to cause CKD, as suggested by the presence of some Fanconi-like features in Mesoamerican nephropathy and other locales.

The causes of Mesoamerican and Sri Lanka nephropathy are still unknown. Strong renal registries need to be in place to determine the severity of the epidemics. Genetic and environmental studies need to

Sites of Endemic Nephropathy in India Correlate with Sites of Prolonged Heat Waves

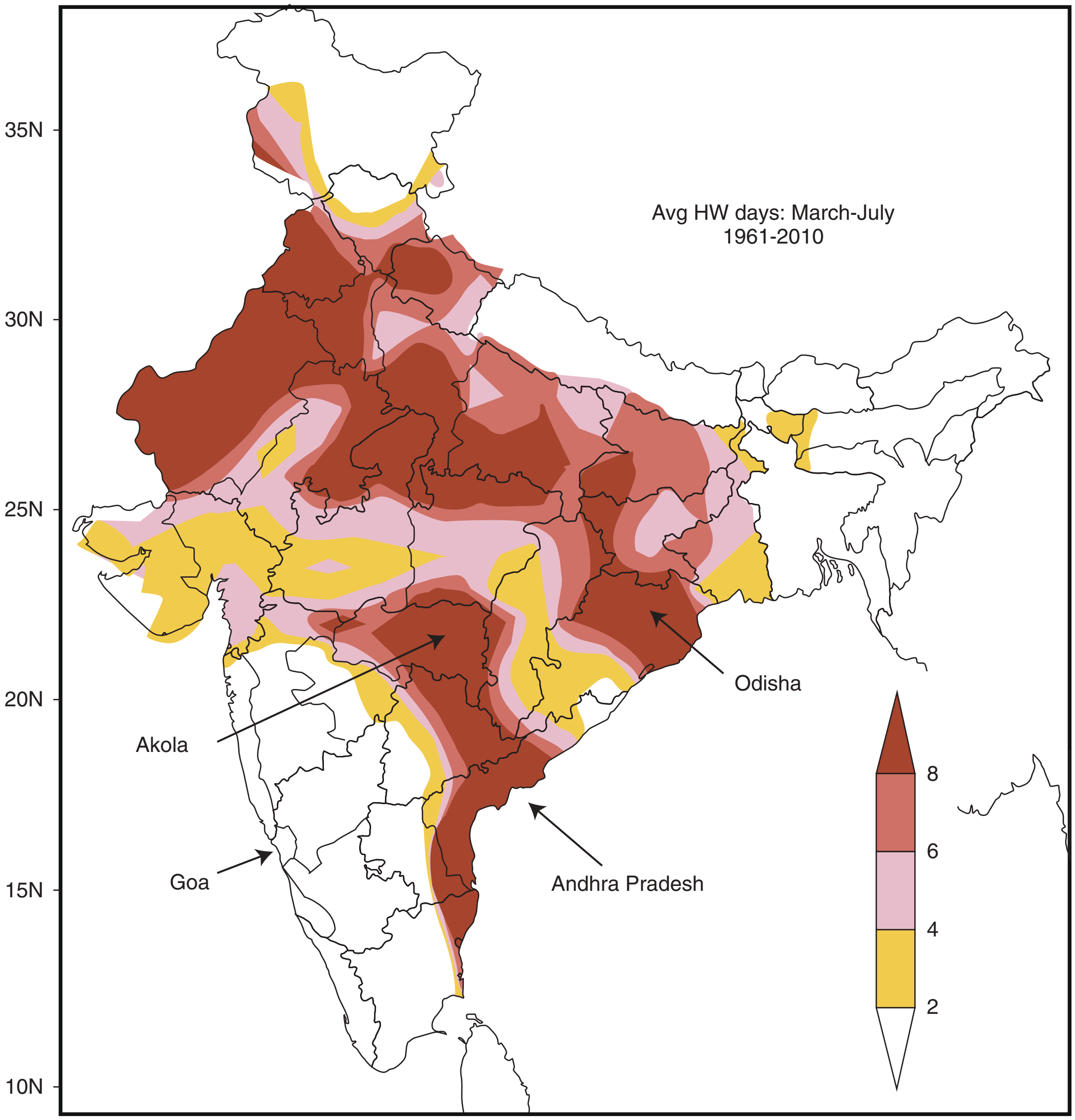

Fig. 63.5 **Reported sites in India with increased frequency of chronic kidney disease (CKD) correlate with sites of prolonged heat waves.** Shown is the average number of heat wave days between March and July (hottest time of the year) in India, based on the number of heat wave days over the 50-year period. Heat wave is usually defined as sustained temperatures of > 40 degrees C or an increase of 5–6 degrees C over the normal maximal temperature of that region. Andhra Pradesh (including the Uddanam region) has had some of the longest heat waves, with one recorded at 35 days. Other suspected sites of CKD of unknown etiology include the Akola district of Maharashtra, the central Odisha region and Goa. *HW,* heat wave. (Data originally from reference 22; reproduced from reference 13.)

be conducted as well. Given the linkage with heat stress and climate, there is also a need to determine whether similar epidemics are occurring in other hot regions where there are similar working conditions. The most successful research approach to these disorders will require strenghtening of local renal registries, controlled trials of current diagnosis and management protocols, and a multidisciplinary approach with contributions from nephrologists, epidemiologists, public health specialists, and agriculturalists.

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SELF-ASSESSMENT QUESTIONS

1. Endemic nephropathies refer to:
   - **A.** Regions where chronic kidney disease (CKD) of any cause is highly prevalent
   - **B.** Regions with a high prevalence of CKD that is unrelated to common causes such as hypertension and diabetes
   - **C.** Ethnic groups with high susceptibility to CKD
   - **D.** Ethnic groups with high prevalence of CKD
   - **E.** Regions with high prevalence of patients undergoing renal replacement therapy
2. Which statement best describes Mesoamerican nephropathy?
   - **A.** A type of CKD of undetermined cause highly prevalent in the Pacific coast of Central America
   - **B.** A type of CKD caused by exposure to aristolochic acid
   - **C.** A type of CKD related to exposure to cadmium
   - **D.** A type of CKD often seen in Mesoamerican Maya ethnicity patients
   - **E.** A type of CKD that locals call *itai-itai*
3. Which of the following are similarities between Sri Lankan endemic nephropathy and Mesoamerican endemic nephropathy?
   - **A.** Highly symptomatic, predominantly glomerular damage with proteinuria, young patients from hot regions
   - **B.** Mostly asymptomatic, predominantly tubulointerstitial damage with low proteinuria, young workers from hot regions
   - **C.** Fanconi-like syndrome with high mortality rates and exposure to lead
   - **D** Fanconi-like syndrome with high mortality rates and exposure to heat stress
   - **E.** Highly symptomatic, predominantly tubulointerstitial damage with proteinuria, elderly patients
4. The idea of a potential role of climate change and global warming is suspected in emerging endemic nephropathies because of which of the following?
   - **A.** Most emerging endemic regions correlate with areas of increased extreme heat.
   - **B.** CKD is much more common in workers in warmer areas despite similar working conditions.
   - **C.** Patients are exposed to extreme heat stress and dehydration. Dehydration may be fueled by the fear of water contamination.
   - **D.** Most emerging endemic regions are comprised between the equator and the Tropic of Cancer.
   - **E.** All of the above.

64

Myeloma and the Kidney

Ashley B. Irish

Myeloma is an uncommon malignancy; for example, it accounts for 1% to 2% of total and 10% to 15% of hematologic malignancies in the United States. African Americans have twice the incidence of Whites, and males predominate over females. It is a disease of older people with the median age of diagnosis greater than 65 years.[1] Myeloma is characterized by a neoplastic proliferation of plasma cell clones producing monoclonal immunoglobulin, which in 95% of cases, includes an excess of the light chain (LC) component, which can be nephrotoxic. Various causes and manifestations of acute kidney injury (AKI) are possible in myeloma (Table 64.1) but the major risk is myeloma cast nephropathy (MCN), which is a medical emergency that requires prompt diagnosis and intervention to avoid irreversible renal failure. Other monoclonal B cell–derived kidney disorders have been collectively described as monoclonal gammopathy of renal significance (MGRS) and differ from myeloma because they do not depend on expansion of the clonal mass for their nephrotoxicity and usually lack the additional features characteristic of myeloma such as bone disease.[2]

ETIOLOGY AND PATHOGENESIS OF MYELOMA

Plasma cells derive from mature uncommitted B cells and after antigen stimulus undergo heavy-chain class switching from μ (immunoglobulin M [IgM]) expression to α, δ, ε, γ. Whole immunoglobulin production requires the intracellular assembly of two heavy chains and two LCs, either kappa (κ) or lambda (λ), to derive whole IgG, IgA, IgD, and IgE. Normally LCs are excreted in slight excess, with a κ/λ ratio of approximately 2 : 1. In myeloma a clone of cells secretes excessive quantities of a specific immunoglobulin and/or LCs (the paraprotein or M-protein). All myelomas (whole immunoglobulin or LC only) arise from a preclinical phase of monoclonal gammopathy (MGUS) into a clinical or symptomatic phase as a consequence of somatic mutations. Mutations have important implications for prognosis and treatment and are incorporated into diagnostic and prognostic stratification tools.[3,4] Myeloma remains an incurable disease because of multiple subclones, which engender resistance to chemotherapy and account for the natural history of remission and relapse over time. Both deregulation of cell cycling and impaired apoptosis account for their progressive and dysfunctional accumulation within the bone marrow and occasionally other organs. Plasma cells express little surface immunoglobulin and are recognized by surface expression of CD38 and CD138; they normally reside only in the bone marrow. In myeloma, unrestrained plasma cell growth is supported by a complex milieu of autocrine and paracrine cytokines, especially interleukin-6 (IL-6). These cytokines are secreted from stromal cells, endothelial cells, and/or osteoclasts and maintain myeloma cell growth, survival, and migration; they also contribute to local organ dysfunction, such as bone resorption, fracture and anemia.[5]

ETIOLOGY AND PATHOGENESIS OF RENAL DISEASE IN MYELOMA

Free light chains (FLCs) circulate as monomers (predominantly κ ≅ 25 kDa) and dimers (predominantly λ ≅ 50 kDa) with a very short half-life (2-6 hours) because of free glomerular filtration, whereas the much larger whole immunoglobulin circulates intact for several weeks. The filtered FLC is reabsorbed in the proximal tubule cell (PTC) by receptor-mediated endocytosis after binding with the glycoprotein receptor cubilin[6] (Fig. 64.1). LCs in excess can induce an inhibitory effect on endocytosis in vitro and are associated with lysosomal overload and rupture, releasing enzymatic contents into the cytosol, manifest histologically by crystallization, vacuolation, and desquamation of the PTC. Endocytosis of LCs induces the release of the pro-inflammatory cytokines IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) by activation of nuclear factor κB (NF-κB) in the PTC.[7] Inhibition of proximal tubule uptake of LCs by silencing the megalin/cubilin genes with small interfering RNAs prevents proximal tubular toxicity.[8] This suggests that LC overload induces factors promoting interstitial injury and fibrosis, as described in other proteinuric states. Less common manifestations of PTC injury include the Fanconi syndrome, which is invariably associated with specific variant kappa LCs and often with pathologic evidence of crystalline inclusions.[9]

Injury to the PTC allows escape or overflow of LC to the distal nephron, where it can interact with the Tamm-Horsfall protein (THP) secreted by the cells of the thick ascending loop of Henle. Variations in the specificity of the binding region of different LCs modify the affinity of the LC for binding with THP, which could in part explain the variable nephrotoxicity of LCs.[10] This specificity of the individual LC for THP was illustrated by the finding that the intraperitoneal instillation of LCs isolated from humans with specific renal LC-associated disease induces the same renal injury in animals.[11] Inhibition of binding of the LC to THP prevents cast formation.[12] Not all LCs are associated with tubular injury, and neither the amount nor type of urinary LCs correlates with the severity of cast formation. Nevertheless, in general, the higher the urinary excretion of LCs, the greater is the risk for renal failure and reduced response to chemotherapy.[13-15] In addition to LC-specific factors, tubular solute composition and tubular flow rates modulate the risk for cast formation. In animals, urinary acidification, furosemide, and urinary sodium and calcium concentrations may affect the tendency to increased binding or aggregation of LCs with THP, whereas colchicine may reduce this tendency in animals but not in humans.[16,17] The formation and passage of casts distally can occlude the tubule and allow intratubular obstruction, with rupture and even backflow of contents (Fig. 64.2).

TABLE 64.1 **Etiology of Renal Injury and Clinical Manifestations in Myeloma**

		Cause	Manifestation
Prerenal	Volume depletion	Hypercalcemia	Polyuria and polydipsia
		Gastrointestinal losses (nausea and vomiting)	Hypotension
		Sepsis	Fever
	Hemodynamic	Hemodynamic from NSAIDs	Oliguria, hyperkalemia
	Other	Hyperviscosity (IgA, IgG3)	Mental state alterations
		Hyperuricemia	Tumor lysis
Renal		Proximal tubular injury from light chains, uric acid, distal tubular injury from casts	Fanconi syndrome Tubular proteinuria Crystalluria
		Glomerular disease (LCDD, amyloid)	Nephrotic proteinuria Hematuria, active sediment
Postrenal		Calculi	Colic

IgA, Immunoglobulin; *LCDD,* light chain deposition disease; *NSAIDs,* nonsteroidal antiinflammatory drugs.

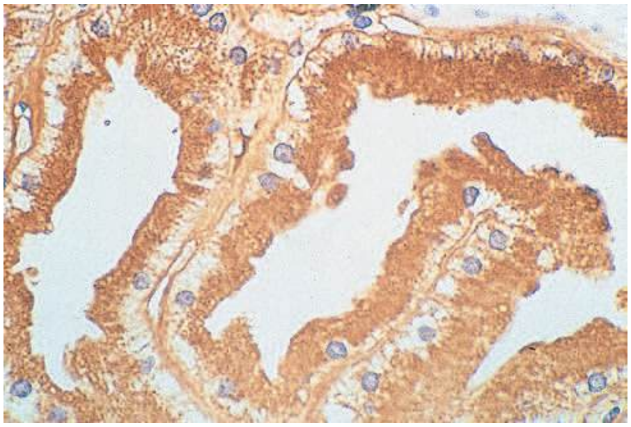

Fig. 64.1 Uptake of light chains by proximal tubular cells. Renal biopsy from a patient excreting kappa light chains. Immunoperoxidase staining (brown color) showing kappa light chains along the brush border and in the cytoplasm of proximal tubular cells.

EPIDEMIOLOGY

Most myeloma manifests de novo, although around 1% evolves from patients with a known MGUS each year. In patients with newly diagnosed myeloma, the prevalence of IgG, IgA, IgD, and FLC-only myeloma was 52%, 21%, 2%, and 16%, respectively.[13] IgM and IgE myeloma are extremely uncommon. Approximately 70% of patients with myeloma also have a urinary M-protein. At the time of diagnosis, up to 50% of patients have evidence of impaired renal function judged by increased serum creatinine, around 25% presenting with serum creatinine greater than 2 mg/dl (177 µmol/l).[13,14] In unselected series, 2% to 10% of patients present with severe renal failure requiring dialysis, this figure is higher in series reported from renal units. In contrast to the general distribution of M-protein types in myeloma, LC and IgD myeloma are particularly associated with the risk for renal disease, being present in nearly 50% of patients with severe renal disease requiring dialysis.[18]

CLINICAL PRESENTATION

Most patients present with constitutional symptoms (fatigue, weight loss) and skeletal pain, especially back pain. Renal impairment is common and has a variety of causes (see Fig. 64.1). In a smaller proportion of patients, renal failure is the presenting manifestation of myeloma and these patients often have more advanced disease with high morbidity/mortality.[18] Renal findings are nonspecific, typically normal-size kidneys and bland urine. Urinary protein excretion may be increased because of the presence of LCs (Bence Jones protein). Urinary dipstick, or albumin measurement, may indicate only small amounts of protein because they measure albumin only. Significantly increased levels of urinary albumin are suggestive of amyloidosis or other monoclonal kidney disorders, which affect the glomerulus (see Chapter 27). Normal or elevated ionized calcium, a decreased serum anion gap, lytic bone lesions on x-ray, hypogammaglobulinemia, reductions in levels of other immunoglobulin classes (immunoparesis), significant cytopenias, or blood film changes (plasma cells and/or leukoerythroblastic film) are suggestive of myeloma. Clinical and laboratory findings that may distinguish MCN from other monoclonal B cell disorders affecting the kidney are listed in (Table 64.2).

PATHOLOGY

Histologic examination of the kidney in myeloma and AKI has diagnostic and prognostic utility, although it is not always required.[19,20] The introduction of the serum (FLC) ratio as a rapid diagnostic tool has reduced the requirement for biopsy for diagnosis. MCN is the most common histologic finding, occurring in 30% to 50% of patients; however, a diverse range of diseases have been reported depending on the indication for biopsy (Table 64.3). MCN is characterized by many distal tubular casts, which are strongly eosinophilic and consist of the monoclonal LC and laminated THP, which often appear fractured after fixation. Casts promote local inflammation with giant cell formation.[21,22] In 30% of cases, cast formation may not be prominent despite extensive tubulointerstitial injury[23] (Box 64.1 and Fig. 64.3). Glomeruli are usually spared unless there is associated LC deposition disease or amyloidosis.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The International Myeloma Working Group (2014) diagnostic criteria for symptomatic myeloma require one or more myeloma-defining events in addition to bone marrow clonally restricted plasma cells of 10% or greater or biopsy-proven plasmacytoma. A myeloma-defining event is a CRAB event (hypercalcemia, renal failure, anemia or lytic bone lesions) or one of three biomarkers: clonal bone marrow plasma cells greater than 60%, serum FLC ratio of 100 or greater (involved to uninvolved LC *and* the involved LC absolute value >100 mg/l), or more than one focal bone lesion on magnetic resonance imaging. To meet the criteria

Renal Injury Caused by Light Chains

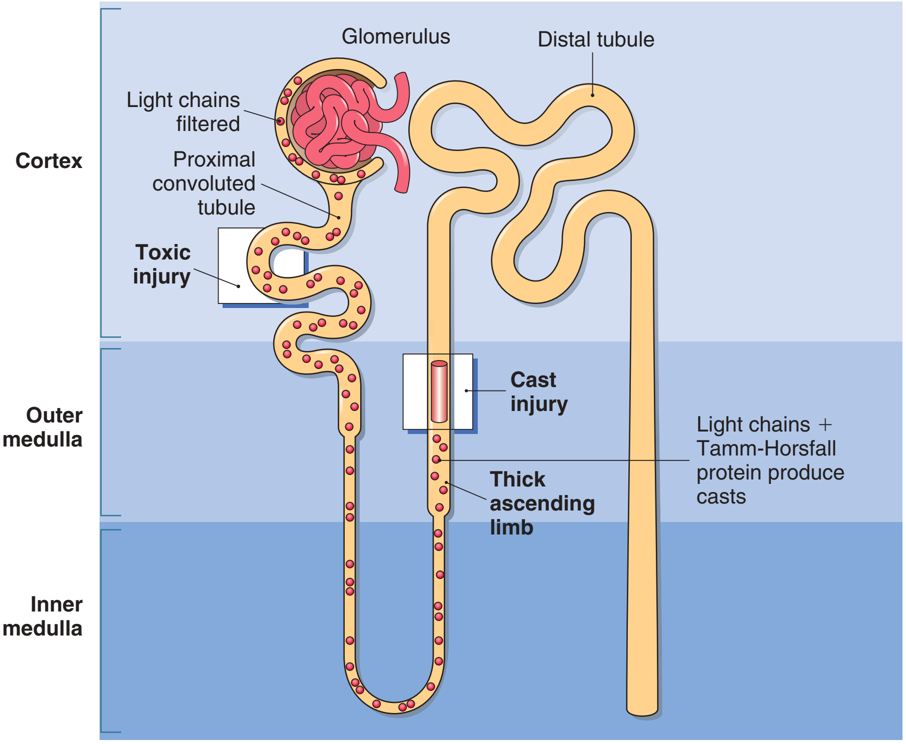

Fig. 64.2 **Renal injury caused by light chains.** Sites *(white boxes)* where light chains injure the tubule. In the proximal tubule, there is direct tubular cytotoxicity. In the distal tubule, there is cast injury.

for renal failure as a myeloma-defining event, a reduction in estimated glomerular filtration rate (eGFR) less than 40 ml/min/1.73 m^2, and a histologic diagnosis of cast nephropathy (or presumptive diagnosis based on a serum involved FLC of typically >1500 mg/l) is necessary to distinguish this from other paraprotein-defined renal diseases.[3] About 97% of patients with a diagnosis of myeloma have a detectable intact whole immunoglobulin and/or a free LC by serum protein electrophoresis (SEP) and immunofixation (IFE). The quantity of the M-protein is estimated from the SEP and may be used both for diagnosis and to monitor response to therapy. Urinary LC (Bence Jones protein) is determined from a concentrated sample, but despite this LC may be below the level of detection by IFE. The specific quantitative FLC assay (which measure only LC not bound to whole immunoglobulin in serum) is significantly more sensitive than SEP and IFE alone and is an automated assay that allows rapid diagnosis.[24,25] An abnormal monoclonal FLC increases the specific LC fraction and may suppress the other LC, which alters the normal ratio of FLC (0.26-1.65 κ/λ) to reflect the oversecretion of the abnormal LC clone (<0.26 for λ FLC clone, >1.65 for κ clone). The normal serum levels of FLC are very low (7 to 13 mg/l), but in patients with impaired renal function, accumulation of both (kappa and lambda) FLCs occurs as a result of reduced excretion, and because lambda free light chains tend to circulate as dimers, their clearance is reduced more than the monomeric kappa FLC. The use of an extended reference range of 0.37 to 3.1 improves diagnostic sensitivity for myeloma to 99% with 100% specificity in the presence of renal failure.[26] In patients with renal failure and biopsy-proven cast nephropathy, the ratios are highly abnormal and the absolute increase in the affected LC is on the order of 100 to 200 times normal with values usually greater than 1000 mg/l at presentation[26] (Fig. 64.4). Measurement of serum FLC has significant advantages over SEP and IFE and is now incorporated into international clinical guidelines for the diagnosis and management of myeloma.

Diagnostic difficulties can arise when elderly patients who are evaluated for newly diagnosed renal impairment have an M-protein on routine SEP. Approximately 3% of the population over 70 years of age will have a serum M-protein, most consistent with MGUS. A diagnosis of MGUS is more likely if the serum level of the M-protein is low (<3 g/dl), there is absent or very low urinary LC (<1 g/24 hours), and a normal FLC ratio with the absence of end organ injury (no lytic lesions, <10% plasma cells on bone marrow aspirate).[27] This distinction is important because most patients with MGUS will die of an unrelated disease, and only 1% a year progress to myeloma.[28] The majority of renal disease in patients with MGUS is unrelated to the M-protein.[29] However, it is now recognized that the spectrum of paraprotein and LC disorders associated with specific renal diseases histologically noted on biopsy is extensive and heterogeneous, but most are not associated with the malignant clonal expansion characteristic of myeloma. These disorders are now described as MGRS.[2] Evidence supportive of alternative causes of the renal disease (most commonly diabetes or vascular disease), along with a period of observation, may clarify the significance of the M-protein, although renal and/or bone marrow biopsy is often required when diagnostic uncertainty persists.

NATURAL HISTORY

Most patients with renal impairment at presentation will show resolution of these predominantly functional changes with therapeutic measures that include withdrawal of nephrotoxins, rehydration, treatment of

TABLE 64.2 Differentiating Features of Myeloma Kidney and Other Monoclonal Immune Deposition Diseases

	Myeloma Kidney	Other MIDDs
Proteinuria	<3 g/l	>3 g/l
Hematuria	Rare	LCDD, occasional Amyloidosis, rare
Hypercalcemia	Common	Absent
Hypertension	Uncommon	LCDD, common Amyloidosis, uncommon
Cytopenias	Anemia very common Leukopenia and thrombocytopenia, occasional	Uncommon
Immunoparesis*	Very common	Uncommon
Lytic bone lesions	Very common	Absent
Renal impairment	Common	Common
Associated whole immunoglobulin	IgA, IgD, IgG	None
Type of light chain	Either	Amyloid $\lambda > \kappa$, LCDD $\kappa > \lambda$
Serum light chain elevation	>500 mg/l	<500 mg/l

IgA, Immunoglobulin A; *LCDD,* light chain deposition disease; *MIDDs,* monoclonal immune deposition disease.

TABLE 64.3 Renal Pathology in Patients With Myeloma

Histologic Finding	Prevalence (%)
Myeloma kidney (myeloma cast nephropathy)	30-50
Interstitial nephritis/fibrosis without cast nephropathy	20-30
Amyloidosis	10
Light chain deposition disease	5
Acute tubular necrosis	10
Other (urate nephropathy, tubular crystals, hypercalcemia, focal segmental glomerulosclerosis)	5

From references 19, 20, 53, and 54.

BOX 64.1 Histologic Features of Myeloma Cast Nephropathy

Many eosinophilic, often fractured casts (medullary portion of the distal nephron predominantly)

Intratubular and interstitial macrophages and giant cells in response to casts

Interstitial inflammation, fibrosis, tubular atrophy, crystalline inclusions

Minimal glomerular abnormality

Minimal or no vascular changes

hypercalcemia, treatment of sepsis, and reduction in LC load with chemotherapy. Response to treatment with improvement in renal function is associated with improved clinical outcomes.[30] Reversibility occurs more frequently with lesser degrees of initial renal impairment, lower LC excretion and presentation with hypercalcemia. Although renal function improves in the majority of patients, approximately 10% of patients presenting with renal impairment at diagnosis may require dialysis. Before the introduction of modern chemotherapy strategies, patients requiring dialysis had reported rates of recovery of renal function as low as 5% to 15%. However, the introduction of specific LC reduction strategies has increased renal recovery in up to 80% of patients if a significant reduction in the FLC level is achieved by day 21, with improvement in renal function and independence from dialysis being associated with improved patient outcomes.[31,32]

TREATMENT

There are three key issues in the management of MCN. The first is to suspect and diagnose myeloma in the differential diagnosis of AKI. The inclusion of serum FLC measurement for routine evaluation of otherwise unexplained AKI in the appropriate clinical circumstances is essential. This is because renal injury in myeloma is directly related to FLC excess and the increased sensitivity and specificity of FLC measurement, along with its rapid availability, may implicate or refute myeloma as a likely diagnostic possibility days in advance of standard tests (SPE/IFE) or renal biopsy. Early diagnosis is crucial to allow implementation of the second strategy, which is to prevent or reverse oliguria by rapid identification and management of possible contributing factors to renal impairment, which are present in around 50% of patients. Hypercalcemia, sepsis, and nonsteroidal antiinflammatory agents (NSAIDs) are the most common precipitants. Intravenous volume expansion is helpful to increase glomerular filtration, reduce single-nephron LC concentration, and increase tubular flow. The use of furosemide to promote diuresis should be avoided because it may favor cast formation. There is no clinical evidence of the superiority of volume expansion with sodium bicarbonate over sodium chloride, although prevention of urinary acidification is in theory desirable and in severe renal failure may be necessary for management of metabolic acidosis. The maintenance of a high fluid intake (3 liters/day) with water after initial volume correction and restoration of urine output with intravenous crystalloid is recommended to maintain high urine flow rates.

The third key requirement is the rapid reduction of FLC in the serum by chemotherapy. The immediate commencement of high-dose dexamethasone 40 mg/day is recommended, because plasma cells are highly responsive to corticosteroids, which induce rapid apoptosis and lowering of LC concentration. The addition of newer chemotherapy strategies (see later discussion) with high immediate LC lowering effects in combination with corticosteroids is critical to achieving a rapid response.[33] The routine addition of plasma exchange to conventional treatment did not improve either recovery from renal failure or patient survival.[34] The large volume of distribution of LC (which freely cross cell membranes) is not well suited to plasma exchange, and its role is controversial.[35,36] The use of a Polyflux dialysis membrane (HCO1100, Gambro) with a high cut-off of molecular weight up to 50 kDa, in conjunction with chemotherapy, was shown to be associated with a reversal of renal failure associated with the rapid reduction in circulating FLC in patients with cast nephropathy.[32,37,38] The benefit and role of high cut-off dialysis is still controversial and two small controlled trials did not confirm an independent benefit when combined with bortezomib chemotherapy.[38a,38b] A suggested algorithm for management of myeloma with AKI is shown in Fig. 64.5.

Chemotherapy

Although myeloma is incurable, chemotherapy will induce clinical improvement by control of the underlying disease in most patients. Bortezomib, a reversible proteasome inhibitor whose clearance is independent of renal function, has been successfully and safely used in

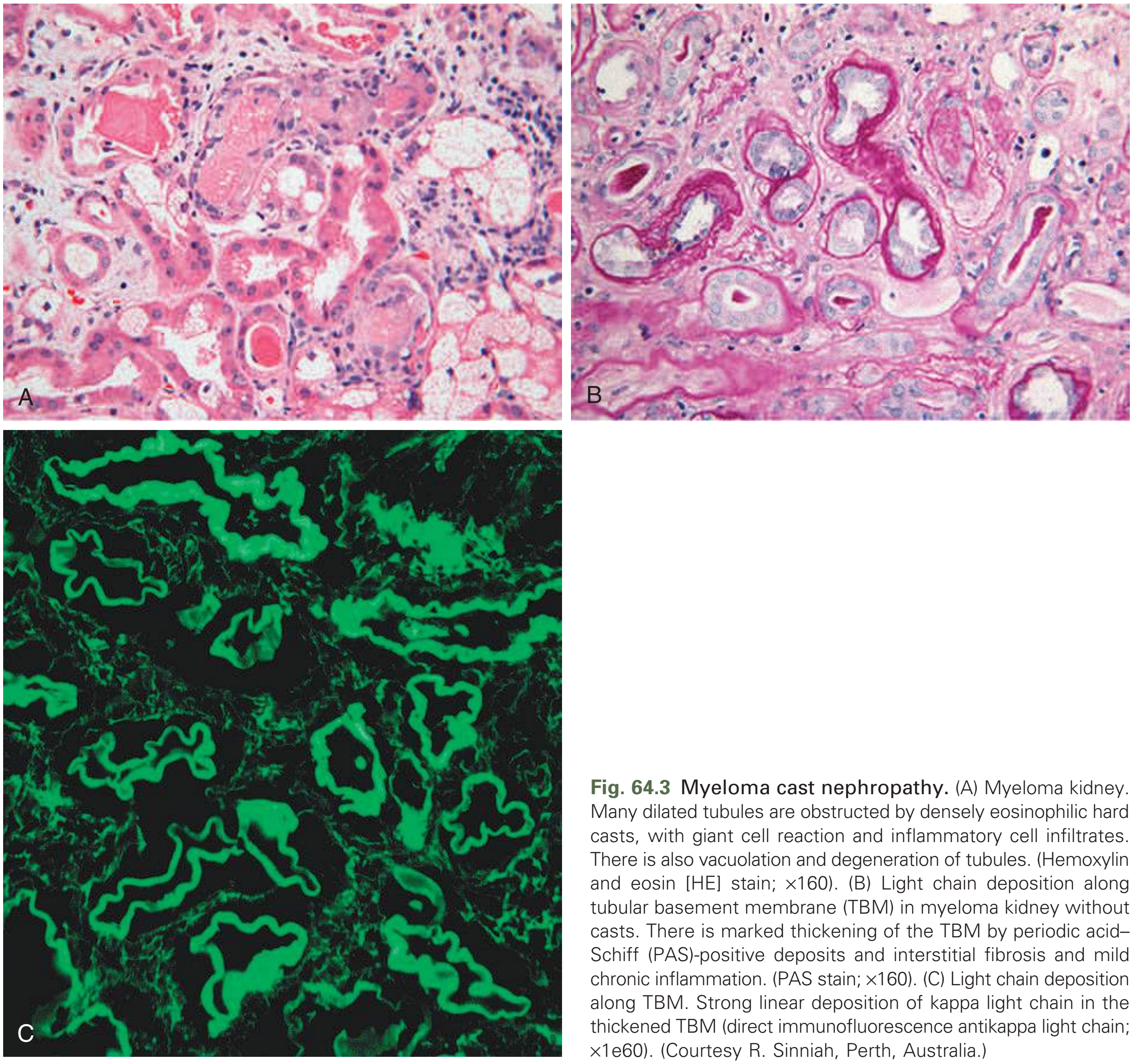

Fig. 64.3 Myeloma cast nephropathy. (A) Myeloma kidney. Many dilated tubules are obstructed by densely eosinophilic hard casts, with giant cell reaction and inflammatory cell infiltrates. There is also vacuolation and degeneration of tubules. (Hemoxylin and eosin [HE] stain; ×160). (B) Light chain deposition along tubular basement membrane (TBM) in myeloma kidney without casts. There is marked thickening of the TBM by periodic acid–Schiff (PAS)-positive deposits and interstitial fibrosis and mild chronic inflammation. (PAS stain; ×160). (C) Light chain deposition along TBM. Strong linear deposition of kappa light chain in the thickened TBM (direct immunofluorescence antikappa light chain; ×1e60). (Courtesy R. Sinniah, Perth, Australia.)

patients with severe degrees of renal failure and myeloma without significant toxicity and is the agent of choice for rapid reduction of LCs in combination with dexamethasone.[33] Bortezomib lowers the LC load by direct effects on plasma cells and also may protect renal proximal tubular cells by inhibiting activation of IL6 and NF-κB induced by LC endocytosis.[39] Immunomodulatory drugs such as thalidomide, lenalidomide, and pomalidomide are frequently used as consolidation/maintenance therapy or for relapsed disease in conjunction with dexamethasone. Agents used for management of myeloma in patients with AKI are summarized in Table 64.4. Autologous stem cell transplantation (ASCT) significantly extends survival and is now the treatment of choice for eligible patients.[33] Patients on dialysis are suitable for ASCT, although increased morbidity and mortality is recognized and are associated with renal recovery and freedom from dialysis.[40-42] For patients unsuited for ASCT, chemotherapy selection depends on comorbidity, and melphalan/prednisolone or dexamethasone/thalidomide may be useful. Close multidisciplinary management and discussion with hematology and oncology staff is required to individualize decision making because of the continuous advances in this area.

Infection and progression of disease remain the major impediments to survival, especially within the higher risk ESRD group. Median survival in recent ESRD series with conventional chemotherapy before ASCT was only 4 to 8 months; however, survival of up to 7 years is reported in selected cases of ESRD managed with ASCT and overall patient survival has improved with the advent of newer treatment strategies.[43] The improved overall management of myeloma with prolonged survival of patients will increase the referral of patients with relapsed and treatment-refractory disease presenting with MCN. The management of this patient group is challenging and must be individualized based on overall prognosis and potential for salvage chemotherapy and likelihood of benefit from dialysis.

Adjunctive Therapies

Patients with CKD/ESRD and myeloma respond to erythropoiesis-stimulating agents, and these should be used along with other hematopoietic agents, including granulocyte colony-stimulating factor (G-CSF) as required, although early in the disease frequent transfusion may be necessary.[44] Intravenous bisphosphonates rapidly correct hypercalcemia

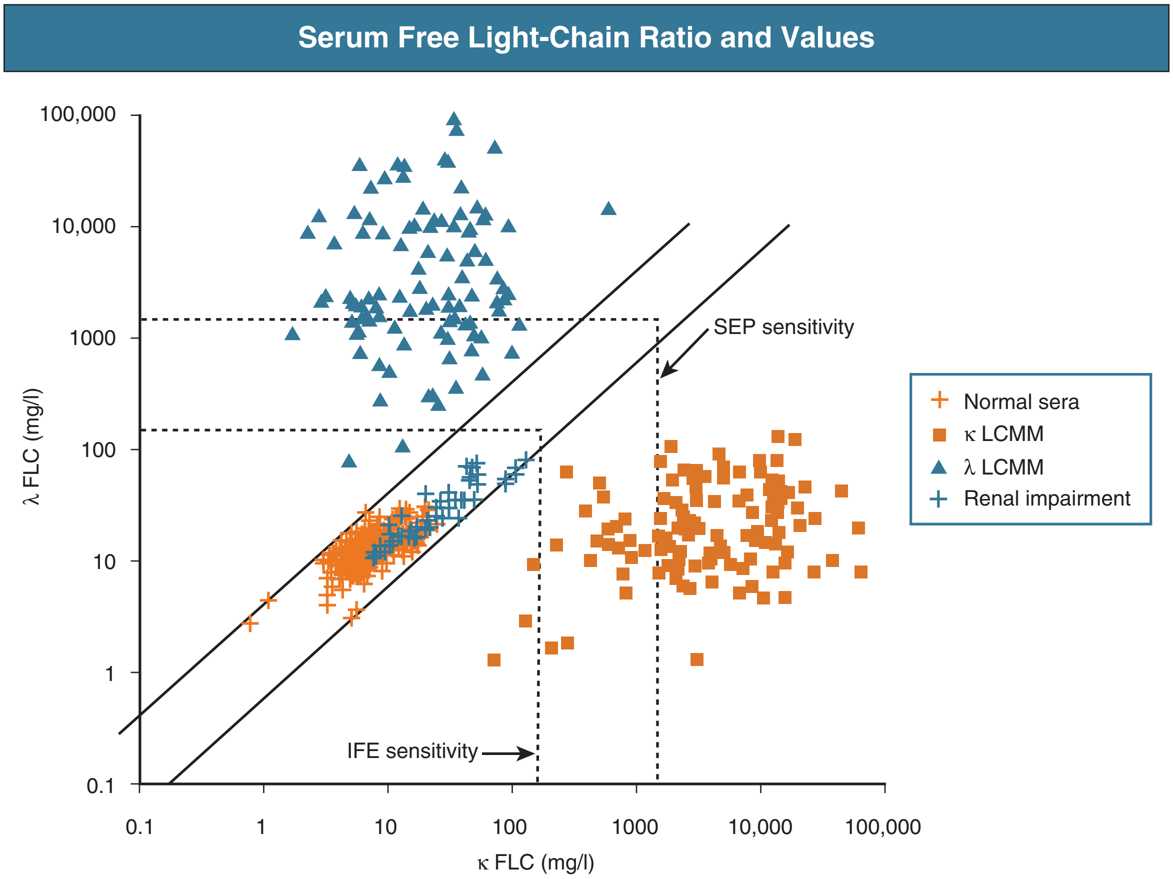
Serum Free Light-Chain Ratio and Values

Fig. 64.4 **Serum free light chain ratio and values in normal individuals, patients with renal impairment, and light chain myeloma.** *FLC,* free light chain; *IFE,* immunofixation; *LCMM,* light chain multiple myeloma; *SEP,* serum protein electrophoresis.

TABLE 64.4 Chemotherapeutic Drugs Used in Myeloma and Renal Failure

Class	Agent	Route of Administration	Dose Reduction for CrCl <30 ml/min/1.73 m^2	Side Effects
Corticosteroids	Dexamethasone, Prednisone	PO/IV	None	Standard
Alkylating agents	Melphalan	PO/IV	Yes	Bone marrow suppression, infection
	Cyclophosphamide	PO/IV	No	
Immunomodulatory drugs	Thalidomide	Oral	No	Neuropathy, venous thrombosis, hyperkalemia, cytopenias
	Lenalidomide	Oral	Yes	
	Pomalidomide	Oral	Uncertain	
Proteasome inhibitors	Bortezomib	IV/SC	None	Neuropathy and cytopenias
	Carfilzomib	IV	No	
	Ixazomib	PO	Suggested	

CrCl, Creatinine clearance; *IV,* intravenously; *PO,* orally.

and are preferred to furosemide (which may aggravate tubular LC injury) and in the longer term reduce bone fracture.[45] However, there are several reports of toxicity (acute tubular necrosis, proteinuria) with full dose and/or rapid infusion of pamidronate and zoledronic acid; the use of reduced doses (pamidronate 30 to 60 mg, zoledronic acid 4 mg) and slower infusion rates are recommended.[46,47] Alternatively, bisphosphonates could be avoided in patients with an eGFR less than 30 ml/min/1.73 m^2 by using denosumab to manage hypercalcemia.[48] Replacement of profound immunoglobulin deficiency with regular intravenous immunoglobulin (IVIG) has been proven to reduce infectious complications in stable treated myeloma patients but is not widely adopted although recommended.[49] Caution is required to avoid further AKI because of the hyperosmolarity of IVIG, because renal impairment and diabetes represent known risk factors for this complication.[50]

DIALYSIS AND TRANSPLANTATION

Where renal replacement therapy is required long-term, both hemodialysis and peritoneal dialysis have been successfully used and there are no data to indicate that outcome is influenced by dialysis modality.

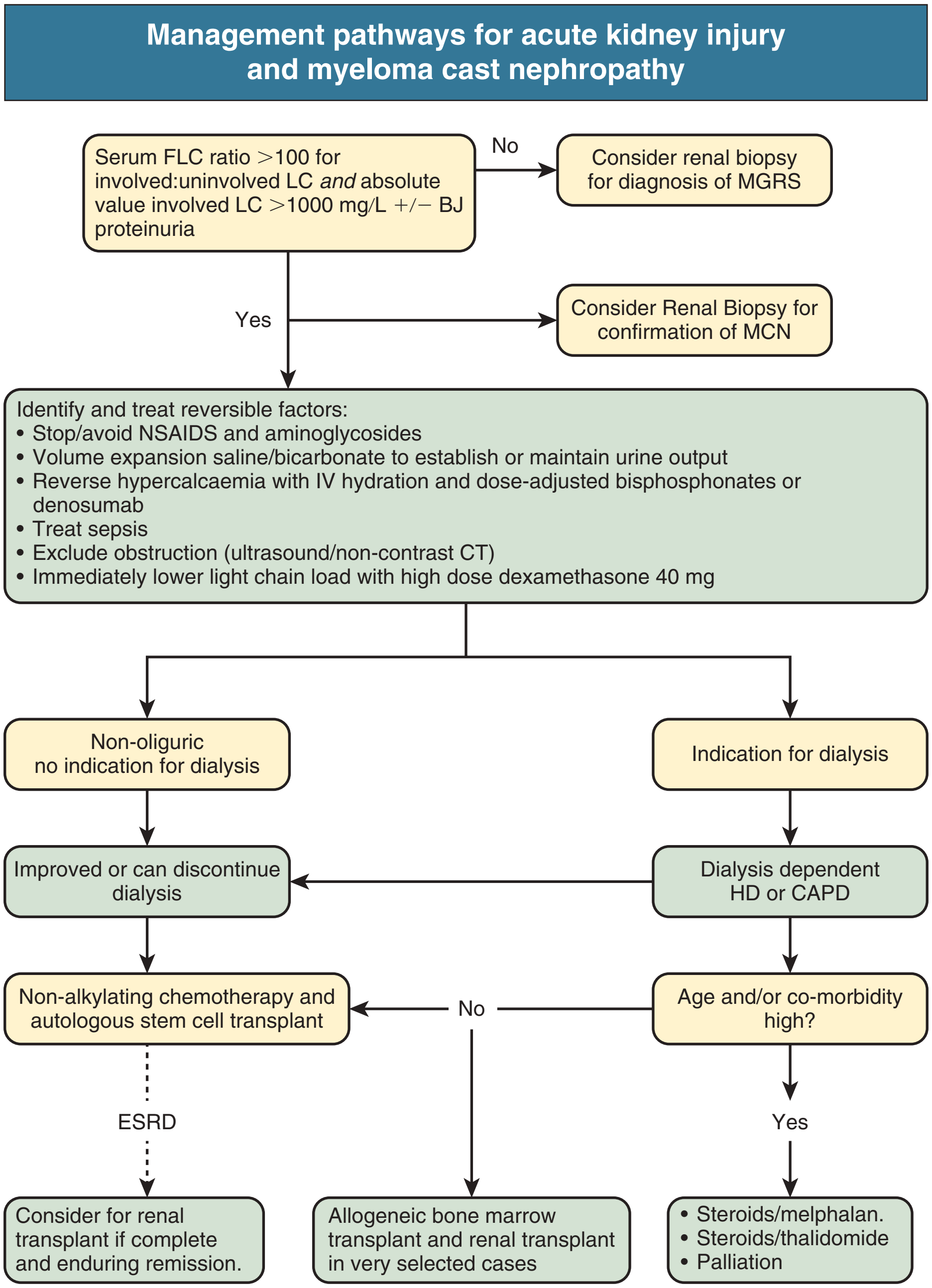
Management pathways for acute kidney injury and myeloma cast nephropathy
Serum FLC ratio >100 for involved:uninvolved LC *and* absolute value involved LC >1000 mg/L +/− BJ proteinuria
No
Consider renal biopsy for diagnosis of MGRS
Yes
Consider Renal Biopsy for confirmation of MCN
Identify and treat reversible factors:
• Stop/avoid NSAIDS and aminoglycosides
• Volume expansion saline/bicarbonate to establish or maintain urine output
• Reverse hypercalcaemia with IV hydration and dose-adjusted bisphosphonates or denosumab
• Treat sepsis
• Exclude obstruction (ultrasound/non-contrast CT)
• Immediately lower light chain load with high dose dexamethasone 40 mg
Non-oliguric no indication for dialysis
Indication for dialysis
Improved or can discontinue dialysis
Dialysis dependent HD or CAPD
Non-alkylating chemotherapy and autologous stem cell transplant
No
Age and/or co-morbidity high?
ESRD
Yes
Consider for renal transplant if complete and enduring remission.
Allogeneic bone marrow transplant and renal transplant in very selected cases
• Steroids/melphalan.
• Steroids/thalidomide
• Palliation

Fig. 64.5 **Management pathways for acute kidney injury and multiple myeloma.** *BJ,* Bence Jones; *CAPD,* continuous ambulatory peritoneal dialysis; *CT,* computed tomography; *ESRD,* end-stage renal disease; *FLC,* free light chain; *HD,* hemodialysis; *IV,* intravenous; *LC,* light chain; *MCN,* myeloma cast nephropathy; *MGRS,* monoclonal gammopathy of renal significance; *NSAIDs,* nonsteroidal antiinflammatory drugs.

Choice of long-term therapy requires individual assessment of patient circumstances. Aggressive measures to reduce the risk for systemic infection (antibiotic catheter locking solutions; mupirocin at exit sites; IVIG replacement) should be routinely considered because initially central venous catheters are often required for dialysis, plasma exchange, and chemotherapy. The timing of arteriovenous fistula placement requires an individualized risk assessment because it may be several months before irreversibility of renal failure or a response to chemotherapy is proven. Renal transplantation has a high risk for disease recurrence in the allograft and patient mortality, and given the incurability of the disease has rarely been appropriate.[51] Allogeneic bone marrow and renal allograft transplant have been reported, demonstrating the ability to induce allograft tolerance in haploidentical pairs.[52] This treatment is limited in availability and is not suitable for the majority of patients. The use of renal transplant after successful induction therapy and ASCT is unknown but may be suitable for younger patients when disease remission by standard criteria and normalization of the serum FLC ratio is achieved.

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SELF-ASSESSMENT QUESTIONS

1. Kidney injury in patients with myeloma is most usually due to an excess of which of the following?
   - **A.** Calcium
   - **B.** Uric acid
   - **C.** Light chains
   - **D.** Immunoglobulins
   - **E.** β_2-Microglobulin
2. What is the most common histologic lesion noted in patients with acute kidney injury and myeloma?
   - **A.** Amyloidosis
   - **B.** Light chain deposition disease (LCDD)
   - **C.** Cast nephropathy
   - **D.** Urate nephropathy
   - **E.** Tubular crystals
3. In addition to corticosteroids, which therapy should be commenced urgently for the management of myeloma cast nephropathy?
   - **A.** Vincristine
   - **B.** Adriamycin
   - **C.** Melphalan
   - **D.** Cyclophosphamide
   - **E.** Bortezomib
4. A 72-year-old man has a 3-month history of back pain and is managed with nonsteroidal antiinflammatory agents. He presents with anemia, hypercalcemia, and acute kidney injury. You suspect myeloma. What is the most appropriate investigation to rapidly confirm the diagnosis?
   - **A.** Urine Bence Jones protein
   - **B.** Serum protein electrophoresis
   - **C.** Serum immunoglobulins
   - **D.** Serum free light chains
   - **E.** Renal biopsy

65

Onconephrology
Kidney Disease in Cancer Patients

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CANCER AND KIDNEY DISEASE

Malignant diseases are commonly associated with acute and chronic kidney disease (Box 65.1), which in turn increase morbidity and mortality in cancer patients.[1-3] Rapid advancements in oncology over the past two decades have turned many previously fatal cancers into chronic diseases. This relates mainly to recognition of gene mutations in various malignancies that are prime targets of anticancer therapies and using drugs to leverage the immune system for killing tumor cells. Cancer therapy with tried and true chemotherapeutic agents as well as targeted agents, immunotherapies, cytotoxic T cell therapies, and stem cell transplantation underpins this transition. However, these positives come with a price, including acute and chronic kidney disease. Nephrologists have been inundated with information on the nephrotoxicity of new drugs as well as the need to manage chronic kidney disease (CKD) in cancer survivors. An increased knowledge gap for many clinicians providing kidney care for these patients and the need for targeted education in this area has fueled the birth of onconephrology, an area of subspecialization within nephrology.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is a common complication in cancer patients, particularly in those who are hospitalized or admitted to the intensive care unit (ICU). In these settings, AKI is associated with increased lengths of stay and higher costs. The 1-year risk for AKI as defined by RIFLE. *Risk* in a large Danish study of incident cancer patients was 17.5%.[1] The 1-year risk for more severe AKI, defined as the *Injury* and *Failure* categories, was 8.8% and 4.5%, respectively. Moreover, the 5-year risks for the *Risk, Injury,* and *Failure* AKI categories were even higher, at 27%, 14.6%, and 7.6%, respectively. AKI incidence was highest in patients with renal cell cancer, liver cancer, multiple myeloma, and leukemia. Among 9613 cancer patients with any AKI stage, 5.1% required renal replacement therapy (RRT) within 1 year of AKI onset. Unsurprisingly, older patients were most heavily represented in this analysis. In patients admitted to a comprehensive cancer center, AKI was 12%, nearly threefold higher than most noncancer settings, and was associated with worse clinical outcomes.[4] AKI developed in 55% of these cancer patients after being in the hospital for at least 48 hours.[4]

Critically ill cancer patients are at even higher risk to develop AKI than critically ill patients without cancer. Of 288 patients admitted to a cancer-focused ICU from 2006 to 2008, 54.1% developed AKI.[5] RIFLE *Risk* category occurred in 33.3% of patients, and the *Injury* and *Failure* categories each developed in 10.4% of patients. In addition to an increased risk for AKI, critically ill cancer patients have a higher incidence of RRT-requiring AKI compared with patients without cancer. Depending on AKI definition employed and underlying case-mix, 13% to 42% of critically ill patients with cancer may develop AKI and 8% to 60% require RRT.[6] Those with hematologic malignancies, myeloma, and septic shock are at highest risk to develop AKI.

Causes of hospital-acquired AKI in cancer patients include prerenal, intrarenal, and postrenal AKI (see Chapter 69). Risk factors for AKI in cancer patients includes typical comorbidities such as underlying diabetes mellitus and CKD, as well as exposure to radiocontrast, chemotherapy, and antibiotics.[4] It is therefore critical to identify at-risk cancer patients to allow prophylactic measures. This will allow clinicians to avert AKI and improve clinical outcomes for this fragile group.[4]

Prerenal Acute Kidney Injury

Nearly one third of AKI in cancer patients is prerenal and results from volume depletion from chemotherapy-induced nausea, vomiting, and diarrhea; chemotherapy-associated hypoalbuminemia contributes to the reduction in effective plasma volume and to compromised renal perfusion. Extracellular volume depletion as a result of third-spacing, as in malignant ascites or pleural effusion, or insensible losses from neutropenic fever also can lead to prerenal AKI. Abdominal compartment syndrome from tense ascites can lead to AKI from renal underperfusion.

Intrarenal Acute Kidney Injury

Intrarenal AKI is one of the most common forms of renal injury in cancer patients. The cause is often multifactorial (Chapter 69). Several chemotherapeutic agents and other nephrotoxic medications commonly used in cancer patients may cause toxic acute tubular necrosis (ATN).

BOX 65.1 Kidney Disease Associated With Common Cancers and Cancer Treatments

Leukemia

Common: Acute kidney injury (AKI) from sepsis, volume depletion, drug toxicity

Rare: Infiltrative disease, glomerulonephritis (GN), AKI from tumor lysis syndrome (TLS) and leukostasis

Multiple Myeloma

Common: Cast nephropathy, AKI from volume depletion and drug toxicity

Rare: Amyloidosis, light chain deposition disease (LCDD), Fanconi syndrome, AKI from hypercalcemia, C3 glomerulopathy, proliferative GN with monoclonal immunoglobulin deposits (PGNMIgD)

Lymphoma

Common: AKI from TLS and volume depletion

Rare: Obstructive uropathy, infiltrative disease, minimal change disease (Hodgkin's), membranoproliferative GN (non-Hodgkin's lymphoma)

Renal Cell Carcinoma

Common: Anti–vascular endothelial growth factor toxicity, postnephrectomy chronic kidney disease

Rare: Obstructive uropathy, membranous GN

Lung and Head and Neck Cancer

Common: Platinum toxicity

Rare: Syndrome of inappropriate antidiuretic, membranous GN

Genitourinary and Gynecologic Cancers

Common: Obstructive uropathy

Rare: Platinum toxicity

Kidney Disease in Commonly Used Cancer Treatments

Common: AKI, tubulopathy and CKD from chemotherapeutic agents (e.g., cisplatin, ifosfamide, methotrexate), complications of conditioning regimen and hemopoietic stem cell transplantation, and from toxicities of targeted anticancer therapies (includes proteinuria, thrombotic microangiopathy [TMA] and hypertension)

Rare: Radiation nephritis, TMA, GN.

Obstructive Uropathy

Common: Genitourinary and gynecologic cancers

Rare: Lymphoma

Cancer patients with sepsis are also at risk to develop severe ischemic ATN.[7] High and repetitive doses of chemotherapy, concurrent with other nephrotoxic agents, may increase AKI risk. Drug-induced acute interstitial nephritis (AIN) is a common cause of AKI in cancer patients, and exposure to the new immunotherapies and targeted therapies is increasing the prevalence of AIN.[8]

Postrenal Acute Kidney Injury

Genitourinary cancers may cause urinary tract obstruction and postrenal AKI. Cancers commonly associated with urinary tract obstruction are bladder, prostate, cervix, and ovary. Among these, pelvic irradiation or urogenital surgery procedures for cancer is more likely to cause urinary obstruction. Cervical and ovarian cancers with metastatic spread involving the ureters or bladder are associated with postrenal AKI. In hematopoietic stem cell transplantation (HSCT) recipients with BK infection, ureteral obstruction is a common cause of renal impairment and bulky retroperitoneal adenopathy associated with lymphomas may cause obstruction.

CHRONIC KIDNEY DISEASE

CKD is also a complication of many cancers and their therapy, and like AKI, is also associated with increased morbidity and mortality. Preexisting CKD from underlying comorbidities is highly prevalent in patients with various types of malignancy. Additionally, CKD may develop after multiple episodes of AKI, after nephrectomy for renal cancer, and from nephrotoxic medications that cause glomerulosclerosis and tubulointerstitial fibrosis. The Renal Insufficiency and Anticancer Medications (IRMA)-1 and -2 studies observed that 52.9% (IRMA-1) and 50.2% (IRMA-2) of patients with active malignancy had an estimated glomerular filtration rate (eGFR) less than 90 ml/min/1.73 m^2, respectively.[9] In this group, the prevalence of stage 3 CKD was 12% (IRMA-1) and 11.8% (IRMA-2), whereas stage 4 CKD was rare in these two studies (0.9% and 0.7%, respectively). In an Australian cohort with various cancers ($n = 4077$), an eGFR less than 60 ml/min/1.73 m^2 was observed in 30% of patients and 8.3% had an eGFR less than 45 ml/min/1.73 m^2.[10] In a cohort of Chinese patients with cancer, stage 3 CKD was noted in 12.8% (1051 of 8223) of patients.[11] The relatively common occurrence of CKD in many cancer patients has been confirmed in other studies.

The relationship between kidney disease and cancer appears to be bidirectional. Although there is an increase in CKD prevalence in cancer patients, both CKD and end-stage renal disease (ESRD) are risk factors for development of a number of malignancies[1] (see Chapter 88). In a retrospective cohort study of more than 1 million adults, lower eGFR was associated with an increased risk for renal cancer after adjustment for time-updated confounders. In addition, the adjusted hazard ratio was 2.28 (95% confidence interval [CI], 1.78-2.92) for eGFR less than 30 ml/min/1.73 m^2.[12] In patients with ESRD on dialysis, there is an increased risk for renal parenchymal cancer in patients with acquired renal cystic disease.

MORTALITY IN CANCER PATIENTS WITH KIDNEY DISEASE

The increased mortality associated with cancer-related AKI and CKD is related to a number of factors. AKI occurrence may require cessation of effective chemotherapeutic regimens, allowing unhindered tumor growth. Preexisting CKD may limit use of chemotherapeutic agents or promote underdosing of curative anticancer regimens. CKD and AKI may alter the bioavailability and/or safety profile of some anticancer drugs leading to use of suboptimal therapies. In addition, CKD and ESRD may impair immune surveillance, allowing cancers to grow and metastasize, especially when combined with insufficient drug dosing. It is also possible that anticancer agent nephrotoxicity is associated with worsening of preexisting CKD, which leads to increased all-cause mortality unrelated to cancer.

IMPORTANT MALIGNANCIES ASSOCIATED WITH KIDNEY DISEASE

Multiple Myeloma and Amyloidosis

Renal involvement occurs in about 50% of patients with myeloma but varies depending on the myeloma type[13] (see Chapter 64). Monoclonal light chain (LC) overproduction is commonly associated with kidney injury, with as many as 50% of patients requiring dialysis.[14] The LC type is also important; cast nephropathy and renal amyloidosis are common with lambda LCs, whereas severe proximal tubular injury causing Fanconi syndrome and LC deposition disease are common with kappa LCs. Cast nephropathy has been diagnosed in 41% of patients with myeloma and kidney disease.[15] Primary systemic (AL) amyloidosis in patients with LC disease is another infrequent manifestation of myeloma (see Chapter 27). When amyloidosis complicates myeloma, it carries a grave prognosis. Renomegaly, gross proteinuria, and amyloid deposition are hallmarks of renal amyloidosis, and, based on autopsy studies, occurs in about 5% to 10% of patients with myeloma.[16]

Leukemia and Lymphoma

Various forms of kidney disease occur in patients with lymphoma and leukemia. Those admitted to an ICU had an AKI hazard ratio of 2.23 for AKI, compared with otherwise comparable patients without ICU admission.[17] In 200 patients with newly diagnosed high-grade lymphoma and leukemia, the incidence of RIFLE AKI was 68.5%, with 50% requiring RRT.[18] Possible causes of AKI in patients with leukemia and lymphoma include prerenal processes,[19] intrarenal causes such as ATN (especially from sepsis and nephrotoxic medications),[20] or postrenal causes such as mechanical obstruction from lymphadenopathy or retroperitoneal fibrosis.[21] Patients with leukemia or lymphoma commonly develop infiltrative disease of the kidney.[22] Most often, renal infiltration is asymptomatic or subclinical as noted in autopsy studies in which 34% of patients were found to have lymphomatous infiltration of the kidneys.[22] Leukemic or lymphoma cell infiltration is suggested by renomegaly on imaging (Fig. 65.1A), and urinalysis shows bland urine sediment and tubular proteinuria.[23] When AKI does occur, it is thought to be due to tubular compression and increased interstitial pressure from the massive malignant cell infiltration (see Fig. 65.1B).[24] Overproduction of lysozyme, which is a freely filtered cationic protein reabsorbed in the proximal tubule, may cause ATN and/or proximal tubular injury with full-blown Fanconi syndrome.[25] Intrarenal leukostasis may cause AKI in patients with acute myeloid leukemia (white blood cells >100,000 cells). Renal leukostasis is associated with reduced renal perfusion, blast aggregation within the renal microvasculature, and endothelial damage triggered by soluble cytokines. Emergent treatment with cytoreductive chemotherapy and leukopheresis is generally required.[26]

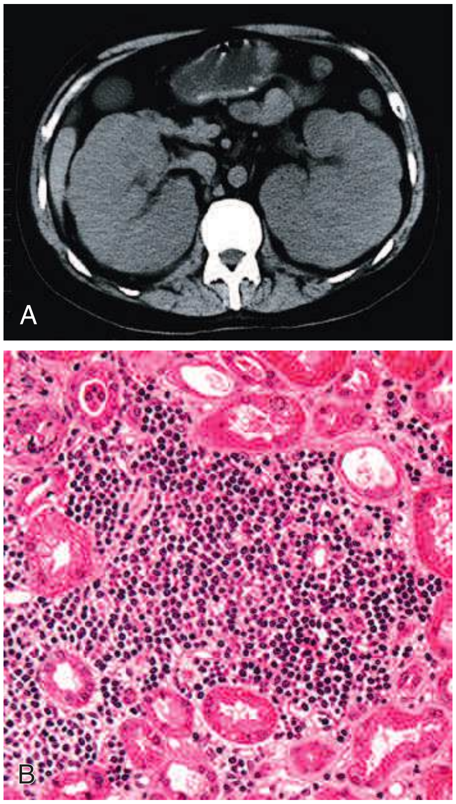

Fig. 65.1 (A) CT scan demonstrating renomegaly from lymphomatous infiltration of the kidneys. (B) Renal biopsy demonstrating low-grade B cell lymphoma cells within the renal parenchyma (Hematoxylin and eosin stain; ×400.)

ANTICANCER DRUGS AND KIDNEY DISEASE

Chemotherapeutic Agents

Oncologists generally assess kidney function before initiation of chemotherapeutic agents. Nevertheless chemotherapy-related nephrotoxicity has become an important area for the nephrologist. Understanding renal metabolism and excretion of these drugs is critical in ensuring efficacy while also avoiding toxicity. Nephrotoxicity associated with the more common chemotherapeutic drugs includes AKI primarily from ATN and AIN, as well as other metabolic perturbations (Table 65.1). However, emergence of targeted therapies and immunotherapies has been associated with an increase in various nephrotoxicities (Table 65.2).[27]

Immunotherapies

Immune Checkpoint Inhibitors

Leveraging the immune system to destroy cancer cells has become an attractive strategy for several different malignancies. Immune checkpoint inhibitors (ICIs) impair the checkpoints that function to suppress adaptive immune response and prevent autoimmunity. T cells possess surface receptors, such as programmed death-1 protein (PD-1) and cytotoxic T lymphocyte–associated antigen-4 (CTLA-4), which bind to their ligands on antigen-presenting cells, leading to T cell exhaustion. This normally prevents the development of autoimmunity. Tumor survival may be enhanced in malignancies that overexpress ligands that bind these inhibitory T cell receptors, thereby decreasing activated T cell infiltration into the tumor microenvironment and inhibiting antitumor T cell responses. To combat this, monoclonal antibody drugs that block ligand binding to PD-1 and CTLA-4 receptors were designed to facilitate T cell rescue and restore antitumor immunity. Ipilimumab, a fully human, immunoglobulin G1 (IgG)1 monoclonal antibody blocking CTLA-4; nivolumab, a fully human IgG4 antibody blocking the PD-1 receptor; and pembrolizumab, a humanized monoclonal IgG4-κ isotype antibody against PD-1, are the ICIs available in clinical practice. However, blocking immune checkpoints risks development of pathologic autoimmunity and end-organ injury, such as AIN. Twenty-six cases of AIN, some with granulomatous changes, have been described with the use of PD-1 receptor blockers.[8] Although some patients develop rash and eosinophilia, AKI is the only consistent clinical manifestation. A small number of cases have required RRT, but most respond to drug discontinuation and steroid therapy.

Interferon Therapy

Treatment with interferon (IFN) is associated with proteinuria secondary to glomerular injury that is primarily a podocytopathy.[28] Minimal change disease (MCD) was first described, but more recent reports describe collapsing and noncollapsing focal segmental glomerulosclerosis (FSGS). Nephrotic-range proteinuria and AKI are observed within weeks of commencing IFN therapy. Although proteinuria declines with IFN discontinuation, complete resolution is more common with MCD than with FSGS. Steroids are associated with complete remission in fewer than one third of patients with FSGS. IFN-related glomerular injury may be due to direct binding of IFN to podocyte receptors and alteration of normal cellular proliferation. Macrophage activation and skewing of the cytokine profile toward IL-6 and IL-13, which are possible permeability factors in MCD and FSGS, are also possible.

TABLE 65.1 **Commonly Used Cancer Therapies Associated With Renal Toxicity**

Tubular Injury	Glomerular Injury	Renal Vascular Injury
Acute Tubular Injury Platinums, zoledronate, ifosfamide, mithramycin, pentostatin, imatinib, diaziquone, pemetrexed, zoledronate	**Focal Segmental Glomerulosclerosis** Interferon (IFN) Pamidronate, tyrosine kinase inhibitors	**Thrombotic Microangiopathy** Bevacizumab (anti-VEGF monoclonal antibody)
Tubular Syndromes ***Renal Tubular Acidosis*** Ifosfamide, amphotericin, calcineurin inhibitors	***Minimal Change Disease*** IFN, pamidronate	**Tyrosine Kinase Inhibitors** Sorafenib, sunitinib, imatinib
Fanconi Syndrome Cisplatin, ifosfamide, azacitidine, diaziquone, imatinib, pemetrexed	***Proteinuria*** Sorafenib, sunitinib, vatalanib, axitinib	**Other Agents** Gemcitabine, mitomycin C, interferon-α, calcineurin inhibitors
Salt Wasting Cisplatin, azacitidine		
Magnesium Wasting Cetuximab, cisplatin, panitumumab		
Nephrogenic Diabetes Insipidus Cisplatin, ifosfamide, pemetrexed		
Acute Interstitial Nephritis Sorafenib, sunitinib, checkpoint inhibitors		
Crystalline Nephropathy Methotrexate, acyclovir, sulfa-based drugs		
Syndrome of Inappropriate Antidiuretic Hormone Cyclophosphamide, vincristine		

Targeted Therapies

Antiangiogenesis Therapy

The discovery that vascular endothelial growth factor (VEGF) is an important mediator of tumor growth and angiogenesis led to the development of drugs targeting this pathway for cancer therapy. However, VEGF is also an essential growth factor to maintain glomerular endothelial health. VEGF is secreted by podocytes and traverses the basement membrane, where it binds to VEGF receptors on endothelial cells and maintains glomerular endothelial cell integrity and filtration barrier function (Fig. 65.2). Anti-VEGF drugs (e.g., the monoclonal antibody bevacizumab) and drugs that inhibit tyrosine kinase (e.g., sunitinib) both block VEGF function. This leads to glomerular endothelial cell dysfunction and filtration barrier disruption, resulting in proteinuria, thrombotic microangiopathy, hypertension, and AKI.[29] Mild and asymptomatic proteinuria is common, and heavy proteinuria occurs in less than 10% of subjects.[30] Hypertension or aggravation of preexisting hypertension is common. The reported incidence varies between 17% and 80%.[31] Development of hypertension reflects efficacy of VEGF blockade therapy, perhaps explaining why bevacizumab-induced hypertension correlates with clinical outcomes.[32] Hypertension is managed with standard antihypertensive medications, although the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is preferable in patients with proteinuria. Renal side effects that develop with anti-VEGF therapy may require dose reduction or drug discontinuation.[30]

B-RAF Inhibitors

Malignant melanoma frequently has a B-RAF V600 mutation that can be effectively targeted by the selective B-RAF inhibitors vemurafenib and dabrafenib. Although effective anticancer agents, these drugs produce nephrotoxicity. A GFR decline at 1 and 3 months of therapy occurred in 15 of 16 patients, which was complicated by persistent kidney injury after 8 months of follow-up. Eight patients developed AKI after vemurafenib with ATN seen in 1 patient. AKI that was clinically suggestive of AIN was observed in 4 patients treated with vemurafenib with 3 of 4 patients recovering kidney function after drug discontinuation, although no biopsy data were available. Nearly 60% of 74 patients treated with vemurafenib developed AKI, primarily Kidney Disease: Improving Global Outcomes (KDIGO) stage 1, within 3 months of drug exposure.[33] Kidney biopsy revealed tubulointerstitial injury in 2 patients. Kidney function recovered within 3 months of B-RAF discontinuation. AKI and metabolic disturbances from B-RAF inhibitors have been described in the U.S. Food and Drug Administration Adverse Events Reporting System.[34] Although the mechanism of kidney injury is unknown, these drugs may interfere with the downstream MAPK pathway, increasing susceptibility to ischemic tubular injury.

Anaplastic Lymphoma Kinase Inhibitors

Anaplastic lymphoma kinase 1 (ALK-1) is a member of the insulin receptor tyrosine kinase family, for which small molecule inhibitors include crizotinib and ceritinib. Crizotinib is an effective agent for treatment of advanced ALK-positive non–small cell lung cancer and appears to be associated with two major issues, AKI and an increased risk for the development and progression of renal cysts.[35] In addition, this agent is also associated with development of peripheral edema and, rarely, electrolyte disorders. Crizotinib is associated with true and pseudo-AKI, the latter due to drug-induced reduced tubular creatinine secretion.

TABLE 65.2 **Renal Toxicities Associated With Targeted Therapies**

			EVIDENCE FOR DOSE REDUCTION IN CKD		
Drug Class	**Renal Excretion**	**Most Frequent Renal Adverse Events**	**Mild/ Moderate***	**Severe**[†]	**Dialysis**
VEGF/VEGF-R–Targeting Agents					
Bevacizumab	No	Hypertension, proteinuria	No	No	No
Aflibercept	No	Hypertension, proteinuria	No	No	No
Sunitinib	16%	Hypertension, proteinuria	No	No	No
Pazopanib	<4%	Hypertension, proteinuria	No	No	No
Axitinib	23%	Hypertension, (proteinuria)	No	No	No
Other Multikinase Inhibitors					
Sorafenib	19%	Hypertension, proteinuria, hypophosphatemia	No	No	No
Regorafenib	19%	Hypertension, proteinuria, electrolyte disorders	No	No	No
Vandetanib	25%	Hypertension, proteinuria, AKI	No	Yes	No
Imatinib	13%	More renoprotective effects, AKI described	No	No	No
Mtor Inhibitors					
Everolimus	2%	Proteinuria, AKI, electrolyte disorders	No	No; suspend if AKI	No
Temsirolimus	4.6%	Proteinuria, AKI, electrolyte disorders	No	No; suspend if AKI	No
eGFR Inhibitors					
Gefitinib	<4%	Electrolyte disorders	No	No	No
Erlotinib	<9%	Electrolyte disorders	No	No	No
Afatinib	<5%	Electrolyte disorders	No	No	No
Cetuximab	No	Hypomagnesemia, other electrolyte disorders	No	No	No
Panitumumab	No	Hypomagnesemia, other electrolyte disorders	No	No	No
B-Raf Inhibitors ± MEK Inhibitors					
Vemurafenib	1%	AKI (tubular necrosis?)	No	No	Possible (risk for arrhythmia)
Dabrafenib	23%	Hypophosphatemia, (granulomatous nephritis?)	No	No	No
Trametinib	<20%	Hypertension, hyponatremia (with dabrafenib)	No	No	No
ERBB2-Targeting Agents					
Trastuzumab	No	Hypertension, AKI (with cisplatin)	No	No	No
Pertuzumab	No	No issues	No	No	No
Lapatinib	2%	No issues	No	No	No
Trastuzumab emtansine	<5%	Hypokalemia	No	No	No
Antibodies Against CTLA-4					
Ipilimumab	No	Autoimmune nephritis, (potential drug reaction with eosinophilia and systemic symptom syndrome)	No	No	No
Other Agents					
Crizotinib	No	Reduction of eGFR (tubular necrosis?), renal cysts	Possible, with caution	Possible, with caution	No
Catumaxomab	No	No issues	No	No	No

*30 to 90 ml/min/1.73 m^2.

[†] <30 ml/min/1.73 m^2.

AKI, Acute kidney injury; *CKD,* chronic kidney disease; *CTLA-4,* cytotoxic T lymphocyte–associated antigen-4; *eGFR,* estimated glomerular filtration rate; *mTOR,* mammalian target of rapamycin complex; *VGEF,* vascular endothelial growth factor; *VEGF-R,* vascular endothelial growth factor receptor.

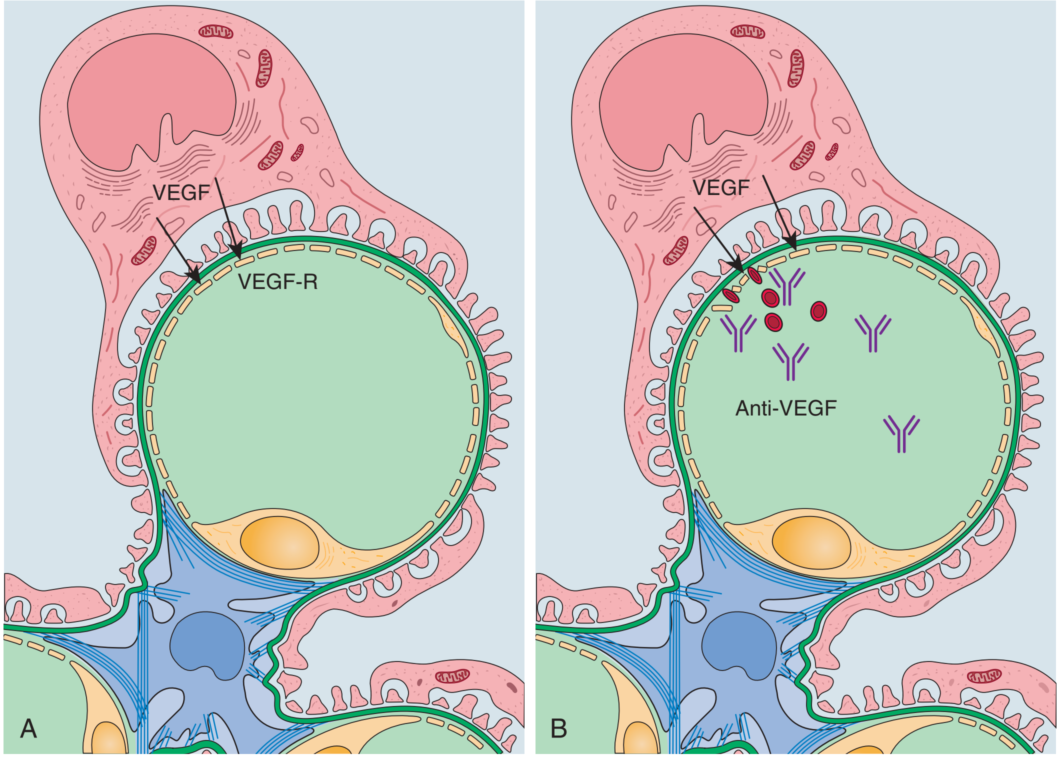

Fig. 65.2 Anti–vascular endothelial growth factor *(VEGF)* therapy and thrombotic microangiopathy. (A) Under normal circumstances, VEGF is produced constitutively by the podocyte and crosses the glomerular basement membrane to bind VEGF receptors *(VEGF-R)* on the endothelial cells, where it maintains endothelial health and integrity. (B) When *anti-VEGF* antibody is administered, the antibody binds to the VEGF and blocks binding to the endothelial cell, resulting in endothelial cell injury and thrombotic microangiopathy.

METABOLIC COMPLICATIONS

Tumor Lysis Syndrome

High-grade lymphomas, acute leukemias, and other rapidly proliferating tumors are prone to tumor lysis syndrome (TLS). Among these, patients with Burkitt lymphoma are particularly at risk. Volume depletion, hypotension, large primary or metastatic tumor load, preexisting CKD, and concurrent exposure to potential nephrotoxic agents are common risk factors for TLS-induced AKI. Cell lysis leads to hyperuricemia, hyperkalemia, hyperphosphatemia, and acidosis causing AKI, primarily from urate crystal deposition in the tubules. Hyperuricemia may also play a role in TLS-associated AKI independent of crystals, possibly as a result of inflammation and endothelial dysfunction.[36] Myocardial deposition of calcium-phosphate crystals may contribute to the development of life-threatening arrhythmias. TLS prevention in high-risk patients involves hydration to maintain a high urine output (>100 ml/h) and allopurinol or rasburicase to reduce hyperuricemia. Rasburicase, which degrades uric acid to water-soluble allantoin, more effectively lowers uric acid levels but has not been shown to be superior to allopurinol for prevention of TLS-associated AKI.[37] Early dialysis should be considered when progressive AKI develops in patients with TLS who will be unable to handle the excessive cellular contents (e.g., potassium, phosphate) to prevent life-threatening electrolyte abnormalities. Furthermore, accumulation of tumor lysis products can aggravate renal injury. In patients with severe TLS and oliguric AKI, continuous RRT (CRRT) may be required to control hyperkalemia and persistent hyperphosphatemia (Fig. 65.3).

Common Electrolyte Disorders

Although electrolyte abnormalities are common in cancer patients, factitious laboratory findings may occur. Paraproteins, especially IgM, may cause assay interferences with several tests that are mostly due to their physical interferences with reagents, reactions, or both.[38] Pseudohyperkalemia secondary to in vitro release of potassium from cells may occur in patients with acute leukemia, chronic lymphocytic leukemia, and chronic myeloproliferative disorders. When factitious values are suspected, careful collection and prompt analysis of repeat samples are required.

Hyponatremia is the most common electrolyte abnormality and affects nearly 50% of hospitalized cancer patients.[39,40] Hyponatremia is frequently due to the syndrome of inappropriate antidiuretic hormone (SIADH), which occurs with many malignancies, including lung cancers, head and neck cancers, and some hematologic cancers.[41] Nausea, pain, and analgesics such as morphine and its derivatives, antidepressants, and several chemotherapeutic agents may cause hyponatremia either by increasing arginine vasopressin secretion or enhancing its effect. Although SIADH is common, one third of cancer cases develop hyponatremia from volume depletion (Chapter 70), which is responsive to normal saline repletion. Treatment with fluid restriction is difficult in cancer patients with SIADH, especially in subjects receiving chemotherapy or HSCT, because these procedures require high intravenous fluid intake. Oral sodium chloride (titrated to target sodium correction) and loop diuretics are sometimes effective in those not receiving large intravenous fluid volumes, whereas V2-receptor antagonists may be an option to correct hyponatremia in such patients.[41] Hypernatremia is much less frequent compared with hyponatremia (3% vs. 47%) but is

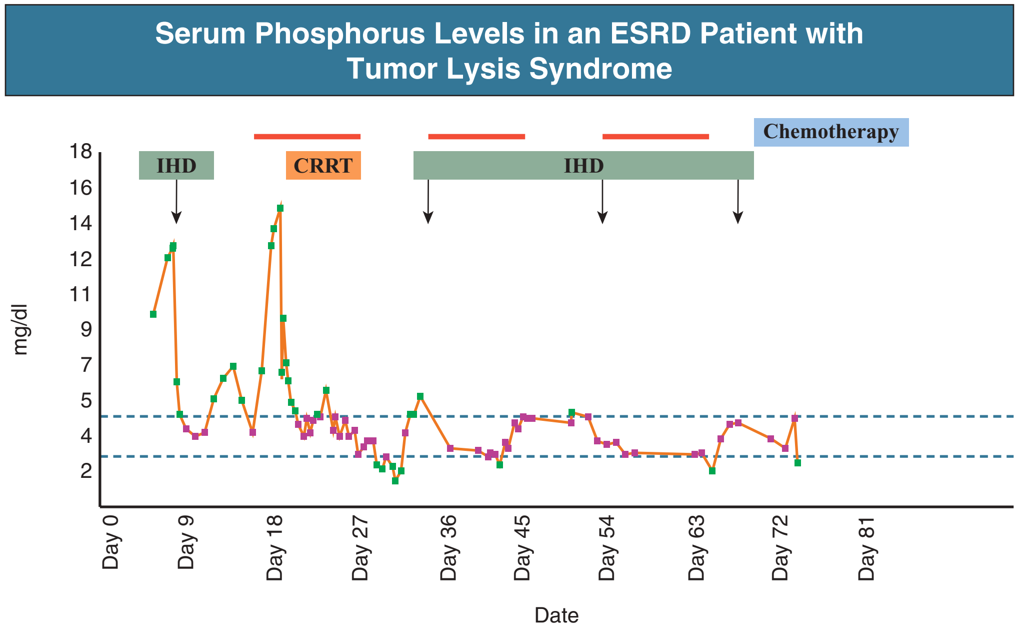
Serum Phosphorus Levels in an ESRD Patient with Tumor Lysis Syndrome

Fig. 65.3 Serum phosphorous levels in a patient with end-stage renal disease (ESRD) with tumor lysis syndrome being treated with continuous renal replacement therapy *(CRRT)* or intermittent hemodialysis *(IH)* *(arrows)*.

associated with higher mortality and longer hospital stays.[42] Most hypernatremia occurs in the hospital and is observed primarily in critically ill leukemia and HSCT patients who are receiving loop diuretics.

Other common electrolyte abnormalities in cancer patients, especially those who are receiving chemotherapy, include hypokalemia, hypomagnesemia, and hypophosphatemia. Nausea/vomiting, diarrhea, and poor nutrition from chemotherapy account for many of these abnormalities. However, severe abnormalities are usually due to drug-induced Fanconi syndrome. Ifosfamide and cisplatin are the most common agents, but kappa LC myeloma also can cause this syndrome. Cetuximab causes hypomagnesemia that occasionally can be severe. In health, epidermal growth factor (EGF) binds its receptor (EGFR) and stimulates distal tubular magnesium reabsorption. Cetuximab (EGFR antibody) competes with EGF for its receptor, thereby inhibiting normal reabsorption of luminal magnesium and causing hypermagnesiuria.

Hypercalcemia is common in patients with advanced cancer with bone metastasis and heralds a poor prognosis. Hypercalcemia is frequently associated with multiple myeloma and can be the presenting feature. Several mechanisms may underlie tumoral hypercalcemia such as elevated parathyroid hormone (PTH)-related peptide (PTHrP) levels associated with lung cancer, ectopic vitamin D in certain lymphomas, or tumor resorption of bones as in advanced cancer (Chapter 10). Treatment of hypercalcemia mandates vigorous intravenous fluid administration (Box 65.2). Although corticosteroids (for myeloma and vitamin D–related hypercalcemia) and calcitonin are useful, persistent hypercalcemia often requires bisphosphonate therapy for long-term control. Rarely, hemodialysis with low calcium dialysate alone is sufficient to control severe hypercalcemia in symptomatic patients. Use of bisphosphonates, especially zoledronate and pamidronate, can be complicated by AKI and collapsing FSGS, respectively. Ibandronate may be a less nephrotoxic option.[43]

BOX 65.2 Management of Cancer-Related Hypercalcemia

1. General measures: Intravenous fluids followed by loop diuretics if hypervolemia.
2. Administer calcitonin (4 IU/kg SQ every 6 to 12 hours based on calcium response), corticosteroids (prednisone 20 to 40 mg/day PO depending on cause) or both for acute and short-term calcium control.
3. If patient severely symptomatic and with reduced urine output and impaired renal function, consider dialysis with low bath calcium.
4. Start bisphosphonates (pamidronate 30 to 90 mg IV over 2 to 4 hours depending on GFR; zoledronate 4 mg IV over 15 minutes, dose adjusted for GFR, contraindicated for GFR <30 ml/min) for longer term hypercalcemia control (adjust for renal dysfunction).
5. Treat the underlying malignancy.
6. For bone resorption–associated hypercalcemia: Humanized anti-RANKL antibody (denosumab 60 to 120 mg SQ) maybe more effective than bisphosphonates (under evaluation)
7. For PTHrP-related hypercalcemia: Humanized monoclonal antibody against human PTHrP may be more effective than bisphosphonates (under evaluation)

GFR, Glomerular filtration rage; *IU,* international units; *IV,* intravenously; *PO,* orally; *PTHrP,* parathyroid hormone–related protein; *RANKL,* receptor activator of nuclear factor kappa-B ligand; *SQ,* subcutaneously.

CANCER-RELATED GLOMERULONEPHRITIS

Cancer-related glomerulonephritis is a relatively rare but important entity in patients with certain malignancies. Proteinuria or nephrotic syndrome, rarely, can be the manifesting feature of cancer. Membranous nephropathy (MN) (Chapter 20) is the most common glomerular pathology associated with solid tumors. In the largest series of 240 patients with biopsy-proven MN, a cancer diagnosis was noted in 10%.[44] Common cancers associated with MN are lung, gastric, colon, and renal carcinomas, but several other solid tumors, such as prostate and breast cancer, are also linked (Table 65.3). In Hodgkin disease, the most common lesion is MCD (Chapter 17), possibly related to tumor-related T cell dysfunction. Chronic lymphocytic leukemia is commonly associated with membranoproliferative glomerulonephritis (Chapter 21), especially

TABLE 65.3 Cancer-Associated Glomerular Diseases

Malignancy	Glomerular Diseases
Lung cancer	MN*, MCD, MPGN, IgAN, FSGS, CGN, TMA
Colon cancer	MN*, MCD, CGN
Stomach cancer	MN
Pancreas cancer	MN*, MCD, IgAN
Bladder cancer	MCD
Renal cell cancer	AAA*, CGN, IgAN, MCD, FSGS, MPGN
Prostate cancer	MN*, CGN
Breast cancer	MN*, FSGS, MPGN, TMA
Esophageal cancer	MPGN*, FSGS
Gastrointestinal stromal tumor	AAA
Gastric cancer	MPGN*, CGN, TMA
Spleen sarcoma	AAA
Head and neck cancer	MN*, IgAN
Wilms tumor	MN*, MPGN
Teratoma	MN
Ovarian cancer	MN*, MCD
Cervical cancer	MN
Endometrial cancer	MN
Tongue cancer	IgAN
Mesothelioma	MCD
Melanoma	MN*, MPGN
Skin cancers (basal cell, squamous cell)	MN
Pheochromocytoma	MN
Thymoma	MCD*, FSGS, CGN, MPGN
Hodgkin disease	MCD*, MN, MPGN, IgAN, FSGS, CGN, AAA, Anti GBM
Non-Hodgkin disease	MPGN*, MCD, MN, IgAN, FSGS
CLL	MPGN*, MCD, MN, FSGS, CGN
AML	MN*, FSGS
CML	MN*, MCD, MPGN
MGUS	MPGN
T cell leukemia	FSGS

With permission from reference 28.
*Most common glomerular lesion
AAA, AA amyloidosis; *AML,* acute myelogenous leukemia *CGN,* crescentic glomerulonephritis; *CLL,* chronic lymphocytic leukemia; *CML,* chronic myelogenous leukemia; *FSGS,* focal segmental global sclerosis; *GBM,* glomerular basement membrane; *IgAN,* IgA nephropathy; *MCD,* minimal change disease; *MGUS,* monoclonal gammopathy of unclear significance; *MN,* membranous nephropathy; *MPGN,* membranoproliferative glomerular nephritis; *TMA,* thrombotic microangiopathy.

in the presence of cryoglobulinemia. HSCT is associated with membranous nephropathy, and, rarely, MCD can be a manifestation of chronic graft-versus-host disease (GVHD).[45] Use of IFN-α, anti-VEGF therapies, and bisphosphonates in cancer therapy are associated with various glomerular diseases and thrombotic microangiopathy.[46]

TABLE 65.4 Causes of Acute Kidney Injury and Other Kidney Disease in Relation to the Timing of Hemopoietic Stem Cell Transplantation

Before and hours after HSCT	Tumor lysis syndrome from conditioning regimen (rare) Systemic toxicity from conditioning regimen (e.g., volume depletion [common]) DMSO toxicity from hemolysis, acidosis, and pigment nephropathy (rare)
Days to weeks after HSCT	Prerenal AKI from volume depletion, AKI from neutropenic-sepsis and drug toxicity (common) AKI related to engraftment syndrome (rare)
Weeks to months after HSCT	AKI from sepsis, volume depletion, drug and radiocontrast toxicity (common) AKI from sinusoidal obstruction syndrome of the liver, graft-versus-host disease (GVHD), thrombotic microangiopathy, and BK virus nephropathy (rare)
Months to years after HSCT	CKD from previous AKIs, continuous use of calcineurin inhibitors especially with GVHD, and from preexisting cancer, such as myeloma (common)

AKI, Acute kidney injury; *CKD,* chronic kidney disease; *DMSO,* dimethyl sulfoxide; *GVHD,* graft-versus-host disease; *HSCT,* hemopoietic stem cell transplantation.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Among the types of HSCT (see Chapter 111), the myeloablative allogeneic form requires higher doses of irradiation, chemotherapy, or a combination and carries the highest risk for developing AKI (up to 70%). AKI can have multiple causes in HSCT recipients and is associated with poor clinical outcomes in patients receiving any form of HSCT.[47] In addition to usual causes of AKI (volume depletion, intravenous contrast, sepsis, and drug toxicity), there are several specific renal syndromes that should be suspected based on the length of time since they developed after HSCT (Table 65.4).

CANCER THERAPY IN CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE

Impaired kidney function complicates the selection and administration of chemotherapy and may lead to unduly high doses and drug accumulation.[48] Careful dosing and dialysis timing are critical because overdosing can aggravate systemic toxicities, whereas underdosing can lead to ineffective cancer treatment. Common risk factors for chemotherapy-induced nephrotoxicity include volume depletion, hypoalbuminemia, metabolic derangements, older age, presence of diabetes and other comorbid conditions, underlying AKI or CKD, presence of sepsis, and concomitant use of other potential nephrotoxins. Therefore optimizing kidney function in those with CKD before chemotherapy (correcting volume status, renal adjustment of chemotherapeutic doses, removing potential nephrotoxic agents, addressing tumor lysis early) can reduce risk for AKI and chemotoxicity. Moreover, administration of platinum compounds requires dose adjustments and timing with dialysis. Other commonly used agents for cancer treatment that need dose adjustment for GFR and dialysis are melphalan, methotrexate, pemetrexed, capecitabine, hydroxyurea, fludarabine, etoposide, irinotecan, and

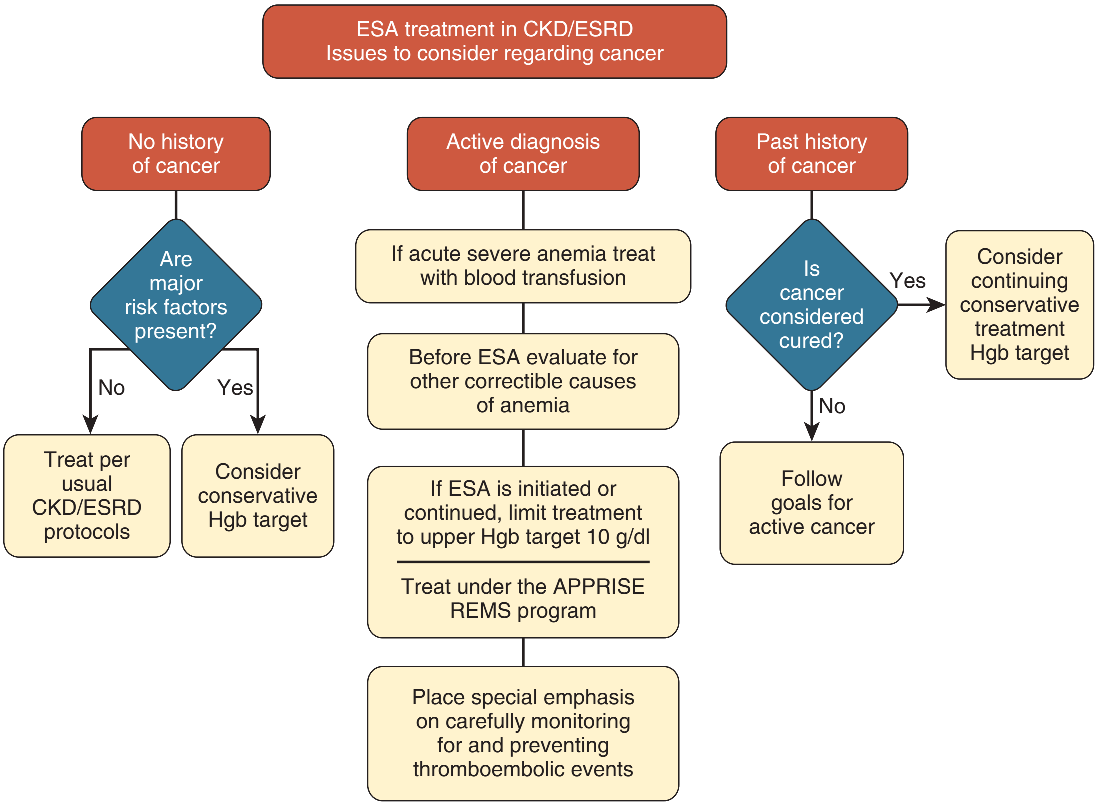
ESA treatment in CKD/ESRD
Issues to consider regarding cancer
No history of cancer
Are major risk factors present?
No
Yes
Treat per usual CKD/ESRD protocols
Consider conservative Hgb target
Active diagnosis of cancer
If acute severe anemia treat with blood transfusion
Before ESA evaluate for other correctible causes of anemia
If ESA is initiated or continued, limit treatment to upper Hgb target 10 g/dl
Treat under the APPRISE REMS program
Place special emphasis on carefully monitoring for and preventing thromboembolic events
Past history of cancer
Is cancer considered cured?
Yes
Consider continuing conservative treatment Hgb target
No
Follow goals for active cancer

Fig. 65.4 Recommended approach to erythropoietin-stimulating agent *(ESA)* use in cancer patients with anemia and chronic kidney disease *(CKD)*/end-stage renal disease *(ESRD). APPRISE,* Assisting Providers and cancer Patients with Risk information for the Safe use of ESAs; *Hgb,* hemoglobin; *REMS,* risk evaluation and mitigation strategy.

lenalidomide.[49] Tumor lysis developing in CKD/ESRD patients can be particularly challenging because the reduced ability to eliminate the tumor products can be life-threatening. In this situation, institution of daily dialysis or CRRT may become necessary. Moreover, in CKD/ESRD patients on active cancer treatment, erythropoietin (EPO) should be used judiciously because higher doses may be associated with poorer cancer outcomes.[50] A suggested approach is noted in Fig. 65.4.[51]

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SELF-ASSESSMENT QUESTIONS

1. Which one of the following statements is *true* regarding patients with cancer and acute kidney Injury (AKI)?
   - **A.** AKI incidence in cancer patients has been reported the highest in lung cancer, adrenal cancer, and breast cancer.
   - **B.** AKI develops in 5% of patients hospitalized in the first 48 hours.
   - **C.** AKI in cancer patients had similar clinical outcomes compared with cancer patients without AKI.
   - **D.** Critically ill cancer patients have an increased incidence of AKI requiring renal replacement therapy (RRT) compared with AKI patients without cancer.
2. A 55-year-old man with a history of metastatic melanoma is admitted with acute kidney injury (serum creatinine at 5.3 mg/dl) after therapy with ipilimumab and pembrolizumab. At this time, which *one* of the following treatments should be ordered?
   - **A.** Glucocorticoids
   - **B.** Plasma exchange
   - **C.** Eculizumab
   - **D.** Supportive therapy with possible dialysis
   - **E.** Cyclophosphamide
3. A 65-year-old man presented with abdominal fullness and weight loss. A computed tomography scan of the chest and abdomen demonstrated a 12-cm soft tissue mass in the midabdomen with mild bilateral hydronephrosis. Pathologic analysis of tissue obtained by percutaneous biopsy of the mass revealed large B cell lymphoma. The patient was admitted for initiation of chemotherapy. Laboratory test results revealed the following: sodium 135 mEq/l, potassium 5.6 mEq/l, chloride 104 mEq/l, bicarbonate 15 mEq/l, blood urea nitrogen 79 mg/dl, creatinine 4.0 mg/dl (baseline 1.0 mg/dl), calcium 6.0 mg/dl, phosphorus 7.3 mg/dl, and uric acid 10.0 mg/dl. Urinalysis showed specific gravity of 1.020, pH 5.0, and a negative dipstick examination. Urine output decreased to 10 to 15 ml/h. At this point before chemotherapy, which of the following is the most important intervention at this time?
   - **A.** 2 grams intravenous calcium gluconate, 10 units intravenous insulin, and 1 ampule of D50
   - **B.** Urine alkalinization with intravenous sodium bicarbonate
   - **C.** Hemodialysis
   - **D.** Percutaneous nephrostomy tube placement
   - **E.** Intravenous fluid challenge (1 liter) with normal saline
4. Which of the following statements concerning hyponatremia in cancer patients is *most* correct?
   - **A.** Hyponatremia in cancer patients is not a complication of cisplatin therapy.
   - **B.** Hyponatremia in cancer patients had increased hospital length of stay and 90-day mortality.
   - **C.** Hyponatremia in cancer patients is less common than in the general population.
   - **D.** Hyponatremia in cancer patients is not associated with pain and nausea.

66

Pathophysiology and Etiology of Acute Kidney Injury

Leah Haseley, J. Ashley Jefferson

DEFINITION

Acute kidney injury (AKI) is denoted by an abrupt decline in glomerular filtration rate (GFR) sufficient to decrease the elimination of nitrogenous waste products and other uremic toxins. This has traditionally been referred to as *acute renal failure,* but in recent years, this has been replaced with the term *acute kidney injury* and standardized definitions of AKI have been developed (see Table 68.1).[1] Staging criteria have been developed based on the magnitude of the rise in serum creatinine and changes in the volume of urine output over 1 week.[1]

ETIOLOGY OVERVIEW

Although AKI is defined by reduced GFR, the underlying cause of the renal impairment is most frequently tubular and vascular factors. AKI can be caused by a broad range of etiologies, and the differential diagnosis must be considered in a systematic fashion. The traditional paradigm divides AKI into prerenal, renal, and postrenal causes. Prerenal causes may be hypovolemia or a decreased effective arterial volume. Postrenal renal failure is usually due to obstruction. Intrinsic renal causes of AKI should be considered under the different anatomic components of the kidney (vascular supply, glomerular, tubular, and interstitial disease; Fig. 66.1). Major extrarenal artery or venous occlusion must be considered in the differential diagnosis (see Chapter 38). Similarly, disorders of the small intrarenal vasculature can result in AKI (e.g., vasculitis, thrombotic microangiopathy, malignant hypertension, eclampsia, postpartum states, disseminated intravascular coagulation [DIC], scleroderma; see Chapters 25, 29, 37, 42, and 62). All forms of acute glomerulonephritis (GN) can manifest as AKI, as can acute inflammation and space-occupying processes of the renal interstitium (e.g., drug-induced, infectious, and autoimmune disorders, leukemia, lymphoma, sarcoidosis).

Among inpatients, prerenal azotemia and acute tubular necrosis (ATN) account for the majority of AKI cases[2] (Fig. 66.2), often in the setting of AKI superimposed on chronic kidney disease (CKD), so-called "acute-on-chronic kidney disease." The term *acute tubular necrosis,* although commonly used, is a misnomer because the alterations are not limited to the tubular structures and true cellular necrosis in human ATN is often minimal. ATN should be reserved for cases of AKI in which a renal biopsy (if performed) shows the characteristic changes of tubular cell injury (Fig. 66.3) or for patients with findings of tubular injury (such as renal tubular epithelial cells in the urine sediment) in an appropriate clinical setting. There are also significant geographical differences in the causes of AKI with the spectrum of causes in tropical countries described in Chapter 67.

PATHOPHYSIOLOGY AND ETIOLOGY OF PRERENAL ACUTE KIDNEY INJURY

Impaired renal perfusion with a resultant fall in glomerular capillary filtration pressure is a common cause of AKI. In this setting, tubular function is typically normal, renal reabsorption of sodium and water is increased, and consequently the urine exhibits low sodium concentration (<20 mmol/l) and high osmolality (>500 mOsm/kg), presuming a diuretic has not been administered. A marked reduction in renal perfusion may overwhelm autoregulation and precipitate an acute fall in GFR. With lesser degrees of renal hypoperfusion, glomerular filtration pressures and GFR are maintained by afferent arteriolar vasodilation (mediated by vasodilatory eicosanoids) and efferent arteriolar vasoconstriction (mediated by angiotensin II [Ang II]). In this setting, AKI may be precipitated by agents that impair afferent arteriolar dilation (nonsteroidal antiinflammatory drugs [NSAIDs]) or efferent vasoconstriction (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]).

Prerenal AKI is often secondary to extracellular fluid volume depletion as a result of gastrointestinal losses (diarrhea, vomiting, prolonged nasogastric drainage), renal losses (diuretics, osmotic diuresis in hyperglycemia), dermal losses (burns, extensive sweating), or sequestration of fluid, sometimes known as *third-spacing* (e.g., acute pancreatitis, muscle trauma). Renal perfusion may be impaired in the setting of normal or increased extracellular fluid, when cardiac output is reduced (heart failure), or when there is systemic arterial vasodilation with redistribution of cardiac output to extrarenal vascular beds (e.g., sepsis, liver cirrhosis) (see Chapters 7, 72, and 73). An unusual cause of prerenal AKI is the infusion of large quantities of osmotically active substances such as mannitol, dextran, or protein, which can increase the glomerular oncotic pressure enough to exceed the capillary hydrostatic pressure stopping filtration.

Prerenal AKI can be corrected if the extrarenal factors causing the renal hypoperfusion are rapidly reversed. Failure to restore renal blood flow (RBF) during the functional prerenal stage will ultimately lead to tubular cell injury.

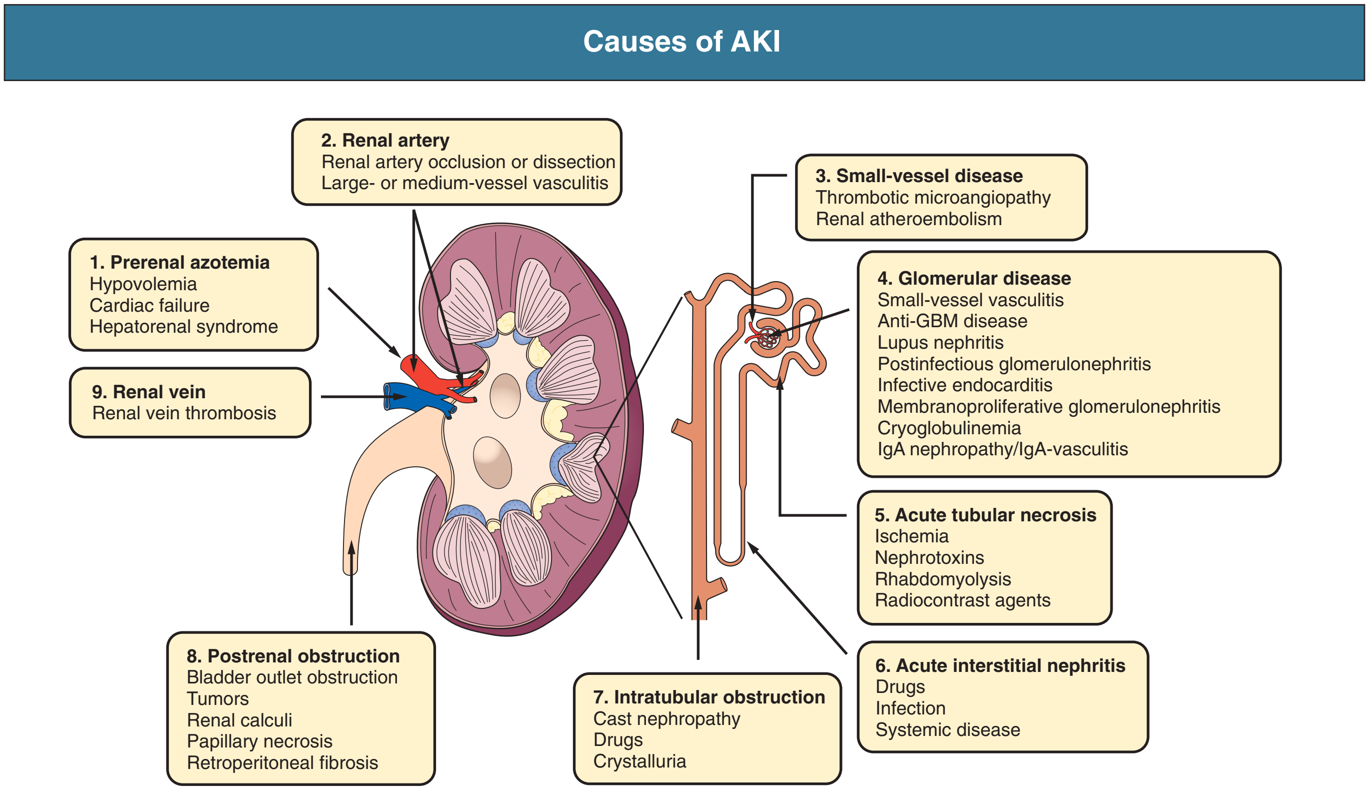
Causes of AKI
2. Renal artery
Renal artery occlusion or dissection
Large- or medium-vessel vasculitis
3. Small-vessel disease
Thrombotic microangiopathy
Renal atheroembolism
1. Prerenal azotemia
Hypovolemia
Cardiac failure
Hepatorenal syndrome
4. Glomerular disease
Small-vessel vasculitis
Anti-GBM disease
Lupus nephritis
Postinfectious glomerulonephritis
Infective endocarditis
Membranoproliferative glomerulonephritis
Cryoglobulinemia
IgA nephropathy/IgA-vasculitis
9. Renal vein
Renal vein thrombosis
5. Acute tubular necrosis
Ischemia
Nephrotoxins
Rhabdomyolysis
Radiocontrast agents
8. Postrenal obstruction
Bladder outlet obstruction
Tumors
Renal calculi
Papillary necrosis
Retroperitoneal fibrosis
7. Intratubular obstruction
Cast nephropathy
Drugs
Crystalluria
6. Acute interstitial nephritis
Drugs
Infection
Systemic disease

Fig. 66.1 Causes of acute kidney injury *(AKI).* AKI is classified into prerenal, renal, and postrenal causes. Renal causes of AKI should be considered under the different anatomic components of the kidney (vascular supply, glomerular, tubular, and interstitial disease). *GBM,* Glomerular basement membrane; *IgA,* immunoglobulin A.

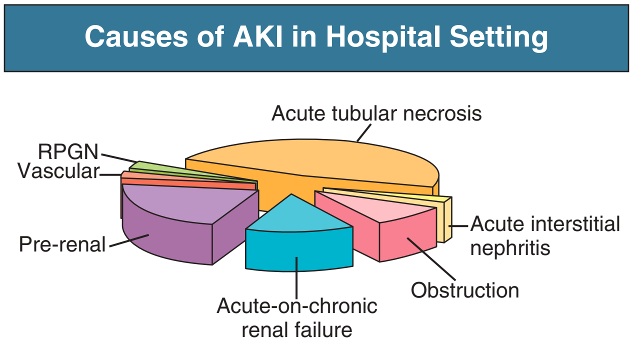

Fig. 66.2 Causes of acute kidney injury in the hospital setting. Madrid Acute Renal Failure Study (1996). *RPGN,* Rapidly progressive glomerulonephritis.

PATHOPHYSIOLOGY AND ETIOLOGY OF POSTRENAL ACUTE KIDNEY INJURY

Obstruction must be excluded in any patient with AKI because prompt intervention can result in improvement or complete recovery of renal function (see Chapter 58). Obstruction of the extrarenal collecting system at any level (renal pelvis, ureters, bladder, or urethra) can increase intratubular pressure, which opposes glomerular filtration pressure and decreases GFR. Obstructive nephropathy is more common in older men with prostatic disease, in patients with a single kidney, and in those with intraabdominal or pelvic cancer. Ureteral obstruction without hydronephrosis can occur with retroperitoneal fibrosis. All types of renal obstruction are also associated with inflammation and fibrosis and can result in permanent injury if the obstruction is prolonged. Nevertheless, most causes of obstructive nephropathy are amenable to therapy, and the prognosis is often good if treatment or intervention is early (Chapter 58).

PATHOPHYSIOLOGY OF ACUTE TUBULAR NECROSIS

ATN commonly occurs in patients with trauma, vascular and cardiac surgery, severe burns, pancreatitis, sepsis, and chronic liver disease. ATN is responsible for most cases of hospital-acquired AKI and is usually the result of ischemic or nephrotoxic injury or a combination of both. In the intensive care unit, two thirds of cases of AKI are due to the combination of impaired renal perfusion, sepsis, and nephrotoxic agents. The importance of combined injurious mechanisms is also highlighted by animal studies, in which severe and prolonged hypotension (<50 mm Hg for 2 to 3 hours in rats) or a single nephrotoxic agent may not cause ATN. Fever may exacerbate ATN by increasing the renal tubular metabolic rate, thereby increasing adenosine triphosphate (ATP) consumption. In renal artery occlusion in the rat, renal ischemia for 40 minutes resulted in minimal renal injury at 32° C, but marked renal injury at 39.4° C.

The typical course of uncomplicated ATN is recovery over 2 to 3 weeks; however, superimposed renal insults or multiple comorbidities often alter this pattern. For example, episodes of hypotension induced by hemodialysis may lead to additional ischemic lesions, potentially prolonging renal functional recovery.

Histology

The typical features of ATN include vacuolization and loss of brush border in proximal tubular cells. Sloughing of tubular cells into the

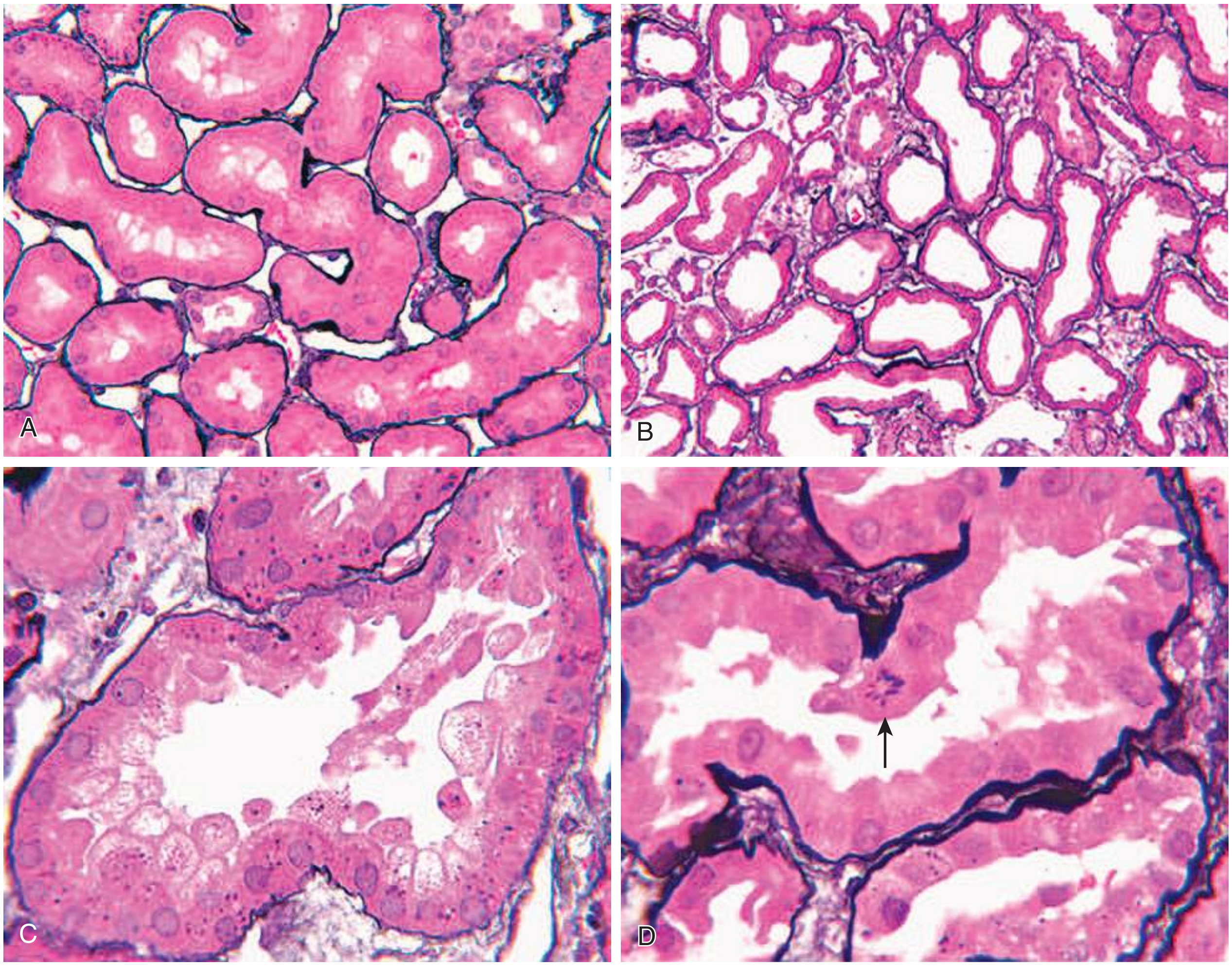

Fig. 66.3 Renal pathology in acute tubular necrosis (ATN). (A) Normal cortical renal tubules. (B and C) ATN: Note the flattened epithelium, bare basement membranes, and intraluminal cellular debris. (D) Recovering ATN showing a tubular epithelial cell mitotic figure *(arrow)*. (Courtesy Erika Bracamonte, MD, University of Arizona.)

lumen leads to cast obstruction, manifested by tubular dilation. Interstitial edema can produce widely spaced tubules, and a mild leukocyte infiltration may be present (see Fig. 66.3). Despite the term *acute tubular "necrosis,"* frankly necrotic cells are uncommon on renal biopsy and histologic evidence of injury frequently only involves 10% to 15% of the tubules despite marked functional impairment. This implies that additional factors such as vasoconstriction and tubular obstruction are important in the loss of GFR.

Site of Tubular Injury in Acute Tubular Necrosis

Tubular damage is usually due to a combination of ischemic injury resulting in depletion of cellular ATP and direct tubular epithelial cell injury by nephrotoxins. The S3 segment of the proximal tubule and the medullary thick ascending limb (mTAL) are particularly vulnerable to hypoxic injury (Fig. 66.4) for several reasons:

1. *Blood supply:* Most blood flow to the kidney is directed to the renal cortex for glomerular filtration, where tissue PO_2 is 50 to 100 mm Hg. By contrast, the outer medulla and medullary rays are watershed areas receiving their blood supply from vasa rectae. Countercurrent oxygen exchange occurs, leading to a progressive fall in PO_2 from cortex to medulla. This results in medullary cells living on the "brink of hypoxia" (PO_2 as low as 10 to 15 mm Hg). The S3 segments of proximal tubule cells and distal mTALs are thus exposed to chronic borderline oxygen deprivation.
2. *High tubular energy requirements:* The cells of the S3 region and mTAL have high metabolic activity because of sodium reabsorption driven by basolateral membrane Na^+,K^+-ATPase. Blocking sodium reabsorption in the mTAL with loop diuretics raises the medullary tissue PO_2 from about 15 to 35 mm Hg. The low GFR in AKI may be renoprotective by diminishing sodium filtration and hence limiting the need for ATP-dependent sodium reabsorption. The drop in GFR in this setting has been called *acute renal success*!
3. *Glycolytic ability of tubular cells:* Proximal tubular cells have minimal glycolytic machinery and rely almost solely on oxidative phosphorylation for the generation of ATP. In contrast, mTAL cells have a large glycolytic capacity and are more resistant to hypoxic or ischemic insults.

Hemodynamic Factors in the Development of Acute Tubular Necrosis

Impaired Renal Autoregulation

Autoregulation between systolic blood pressures of 80 and 150 mm Hg allows maintenance of RBF, glomerular pressures, and GFR in a stable range. Below 80 mm Hg, this autoregulation fails, and ischemic injury

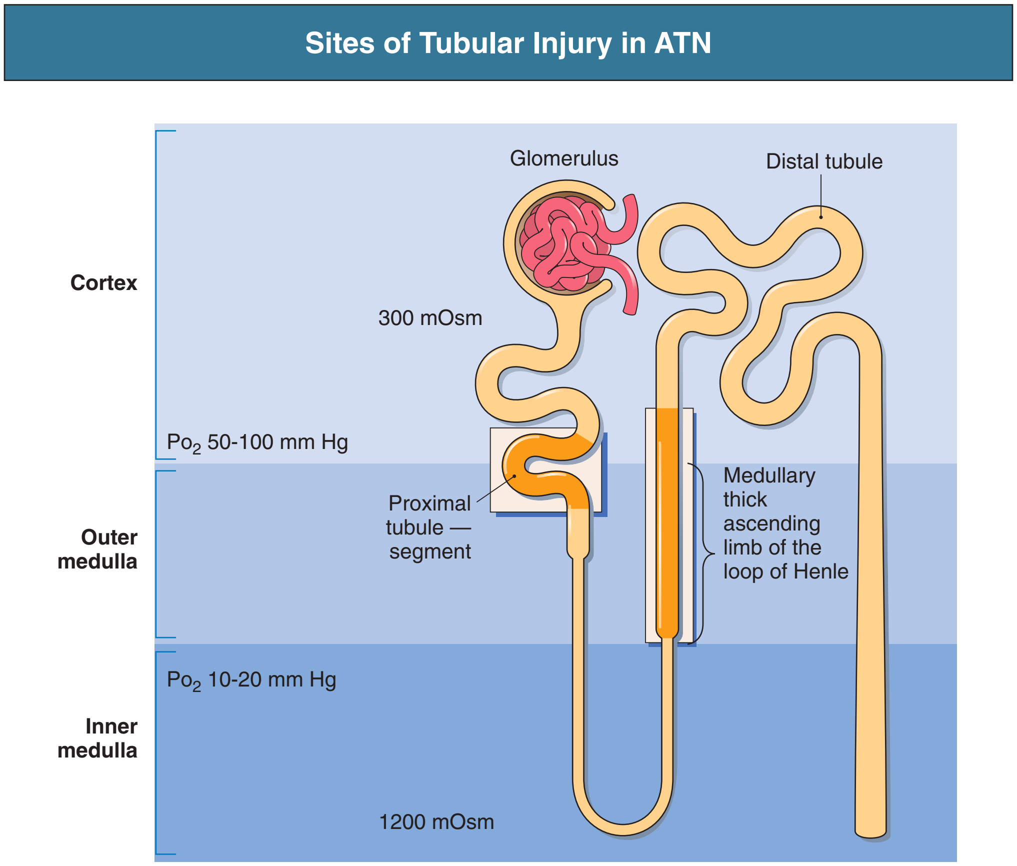

Fig. 66.4 **Sites of tubular injury in acute tubular necrosis (ATN).** The S3 segment of the proximal tubule and the medullary thick ascending limb are particularly vulnerable to ischemic injury because of the combination of borderline oxygen supply and high metabolic demands.

may result. In certain conditions, such as aging or CKD, autoregulation is impaired and ischemic injury may occur more easily with reductions in perfusion pressure. In settings of low renal perfusion (e.g., volume depletion, left ventricular failure, renal artery stenosis), GFR depend on autoregulation mediated by vasodilatory prostaglandins acting on the afferent arteriole Ang II-mediated efferent arteriolar vasoconstriction to maintain glomerular pressure. Any interference with these mechanisms (e.g., administration of ACE inhibitors or NSAIDs) may produce a precipitous fall in GFR.

Intrarenal Vasoconstriction

In established ATN, RBF is decreased by 30% to 50%. Indeed in AKI, rather than the normal autoregulatory renal vasodilation that occurs in response to decreased perfusion pressure, there is evidence of renal vasoconstriction. Vasoconstrictors implicated in this response include Ang II, endothelin-1, adenosine, thromboxane A_2, prostaglandin H_2, leukotrienes C_4 and D_4, sympathetic nerve stimulation (Fig. 66.5), and tubuloglomerular feedback (TGF). Some of these vascular abnormalities may be mediated by increased cytosolic calcium content in afferent arterioles as a result of ischemia.

Tubuloglomerular Feedback

The role of TGF (see Chapter 2) in the setting of AKI may be partly beneficial because the resultant decrease in GFR limits sodium delivery to damaged tubules. This in turn leads to reduced ATP-dependent tubular reabsorption of sodium, which protects against intracellular ATP depletion and thus renal injury. Adenosine A1 receptor knockout mice, with absent TGF, have augmented AKI after ischemia reperfusion.

Endothelial Cell Injury and the Development of Acute Tubular Necrosis

AKI is not limited to the tubular cell, and endothelial cell injury occurs partly as a result of acute renal ischemia and oxidant injury.[3] Endothelial injury is characterized by cell swelling, upregulation of adhesion molecules (with recruitment of inflammatory neutrophils and monocytes), and impaired vasodilation (decreased endothelial nitric oxide synthase and vasodilatory prostaglandins) and may mediate some of the impaired autoregulation and intrarenal vasoconstriction described earlier. Endothelial injury within the peritubular capillaries (vasa rectae) may produce congestion in the outer medulla, exacerbating interstitial edema and worsening hypoxic injury to the S3 segment of the proximal tubule and the TAL of Henle.

Tubular Epithelial Cell Injury and the Development of Acute Tubular Necrosis

The tubular cell may be injured because of ischemia (depletion of cellular energy stores [ATP]), or from direct cytotoxic injury. After acute renal ischemia, tubular cell injury also may result from the restoration of RBF (reperfusion injury). Mediators of tubular cell injury include reactive oxygen species (ROS), intracellular calcium influx, nitric oxide, phospholipase A2, complement, and cell-mediated cytotoxicity.[3] Mitochondrial injury can be caused by ROS, depletion of antioxidants, and increased intracellular calcium. Disruption of mitochondrial function exacerbates cellular injury as a result of disrupted energy metabolism and release of proapoptotic proteins. Autophagy is a mechanism by which cells degrade self-proteins and is a central part of the cellular

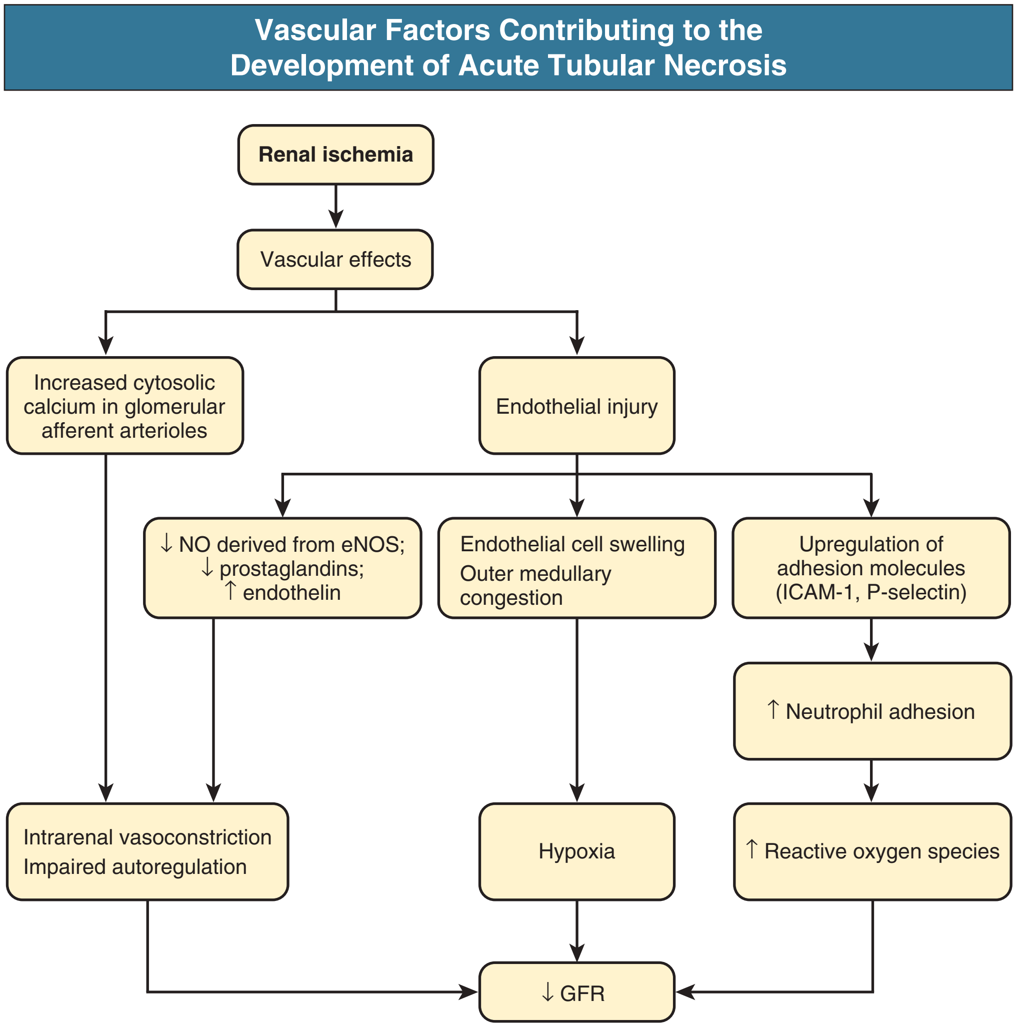
Vascular Factors Contributing to the Development of Acute Tubular Necrosis
Renal ischemia
Vascular effects
Increased cytosolic calcium in glomerular afferent arterioles
Endothelial injury
↓ NO derived from eNOS; ↓ prostaglandins; ↑ endothelin
Endothelial cell swelling
Outer medullary congestion
Upregulation of adhesion molecules (ICAM-1, P-selectin)
↑ Neutrophil adhesion
Intrarenal vasoconstriction
Impaired autoregulation
Hypoxia
↑ Reactive oxygen species
↓ GFR

Fig. 66.5 Vascular factors contributing to the development of acute tubular necrosis. Renal vasoconstriction and endothelial injury promote renal ischemia and tubular injury. *eNOS,* endothelial nitric oxide synthase; *GFR,* glomerular filtration rate; *ICAM-1,* intercellular adhesion molecule 1; *NO,* nitric oxide.

response to stress and injury. Experimental work has shown that autophagy is important for removal of damaged mitochondria and the recovery of tubular epithelial cells from ischemic injury. ROS may be derived from local sources (including xanthine oxidase and cyclooxygenases secondary to mitochondrial injury) or from infiltrating leukocytes. In models of ischemic ATN, a variety of methods that inhibit ROS protect against renal injury. Hypoxia inducible factor and downstream mediators such as heme oxygenase 1 may protect cells against ischemic injury.[4]

Factors that affect the integrity and function of the renal tubular epithelial cells and contribute to the reduction in GFR include the following (Fig. 66.6):

1. *Cell death:* Despite the term *acute tubular necrosis,* only few tubular cells undergo cell death and mostly by apoptosis rather than necrosis. Indeed, in animal models, renal injury is ameliorated using caspase inhibitors and p53 inhibitors that decrease apoptosis.[5]
2. *Disruption of actin cytoskeleton:* A characteristic feature of sublethally injured cells is the disruption of the actin cytoskeleton. Activation of the cysteine protease calpain (partly as a result of increased intracellular calcium) can degrade actin-binding proteins such as spectrin and ankyrin. This leads to abnormal translocation of Na^+,K^+-ATPase and other proteins from the basolateral membrane to the cytoplasm or apical membranes. In the proximal tubular cell, this loss of polarity results in impaired proximal reabsorption of filtrate with resultant increased distal sodium chloride delivery, which activates TGF.
3. *Cast obstruction:* Tubular cells are attached to the tubular basement membrane (TBM) by $\alpha3\beta1$ integrins, which recognize RGD (arginine-glycine-aspartate) sequences in matrix proteins. Disruption of the actin cytoskeleton results in movement of integrins from basolateral positions to the apical membrane, leading to impaired cell matrix adhesion and cell detachment. Many of these detached cells are still viable and can be cultured from urine of patients with ATN. Sloughed proximal tubular cells can bind to RGD sequences in Tamm-Horsfall protein, resulting in cast formation and intratubular obstruction. In models of ischemic AKI, the elevation in tubular pressures may be inhibited by synthetic RGD peptides mitigating the obstructive process.
4. *Backleak:* The loss of adhesion molecules (E-cadherin) and tight junction proteins (ZO-1, occludin) weakens junctions between cells, allowing filtrate to leak back into the renal interstitium. Although this does not alter the actual GFR at the level of the glomerulus, the net effect is a reduction in the measured GFR. Earlier dextran sieving experiments suggest only a modest effect of backleak on the decrement of GFR in AKI (about 10%); however, in the renal allograft

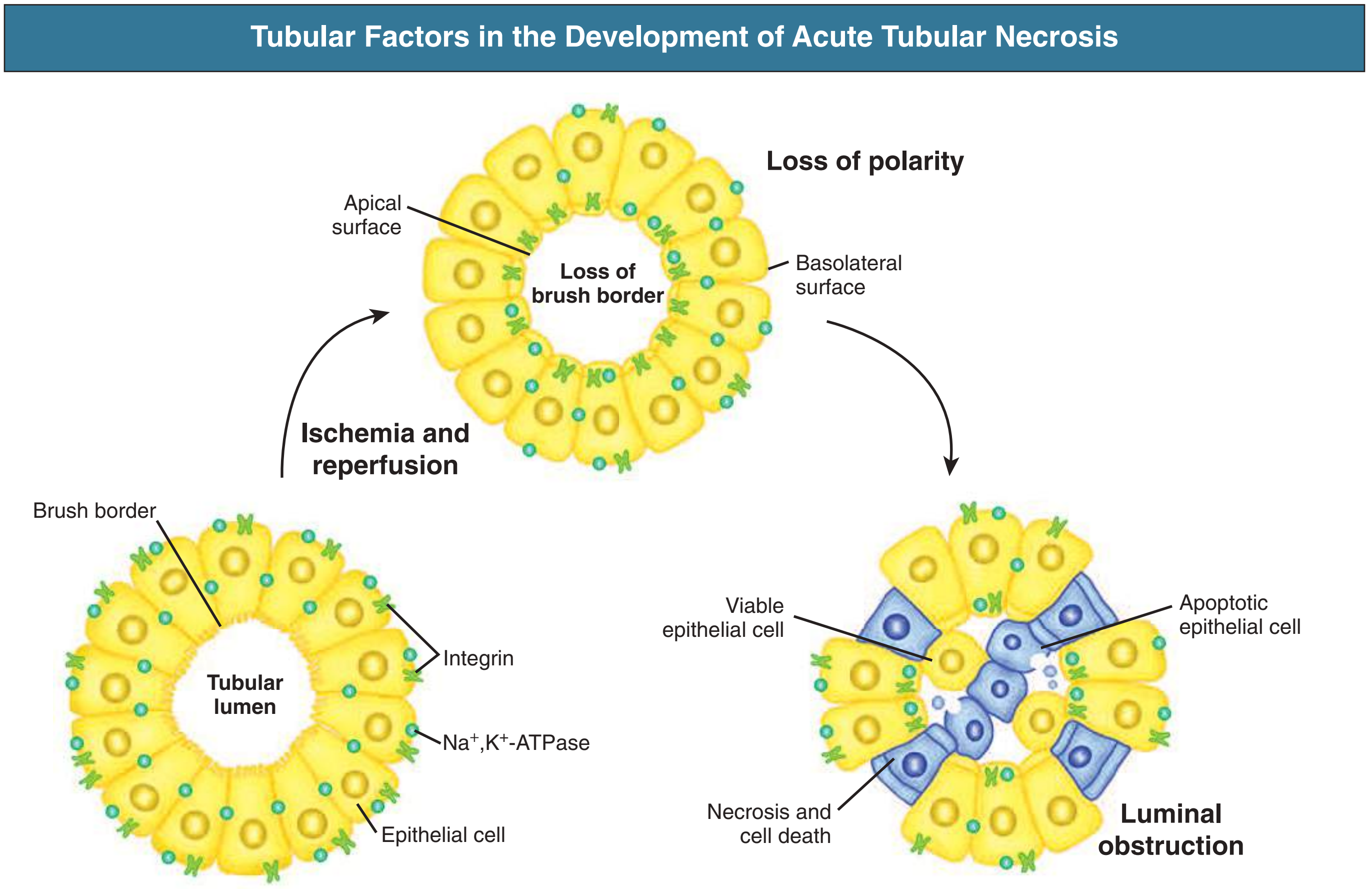

Fig. 66.6 **Tubular factors in the development of acute tubular necrosis.** Loss of cell polarity results in weakening of cell-to-cell and cell matrix adhesion resulting in cast obstruction and backleak of tubular fluid. (Modified from reference 40.)

with severe ATN, backleak has been calculated to account for up to 50% of the GFR reduction.

Inflammatory Factors in the Development of Acute Tubular Necrosis

Although ischemia causes direct renal cytotoxicity, tissue inflammation during reperfusion also contributes to renal injury and may cause some of the systemic effects of AKI. Components of both the innate and the adaptive immune systems contribute to the pathogenesis of ATN.[6] The innate immune system is activated by cellular injury and certain pattern recognition molecules. Toll-like receptor 2 (TLR2) and TLR4 are upregulated within the ischemic kidney, activated by molecules released from injured cells, and induce renal epithelial cells to produce chemokines. The complement system is also activated within the tubulointerstitium after ischemia/reperfusion, predominantly by the alternative pathway. It can directly induce nearby epithelial cells to produce proinflammatory cytokines (e.g., tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], IL-1β) and chemokines (such as MCP-1, IL-8, RANTES [regulated on activation, normal T cell expressed and secreted]) that promote the infiltration of leukocytes and are also directly vasoactive.

A network of dendritic cells extends throughout the renal interstitium, which help shape the inflammatory response within the kidney after ischemia/reperfusion, likely through their interactions with other inflammatory cell types. Neutrophils and mononuclear cells are seen in peritubular capillaries. Neutrophil activation and the release of proteases and ROS can exacerbate injury. By contrast, neutrophil depletion or the inhibition or genetic deletion of neutrophil adhesion molecules (ICAM-1) ameliorates injury in ischemic ATN. Monocytes infiltrate the kidney after reperfusion and differentiate into the M1 (proinflammatory) type, exacerbating renal injury after ischemia. These macrophages may later convert to an M2 (reparative) phenotype. Cells of the adaptive immune system, including T and B lymphocytes, also contribute to renal injury in models of ATN, and their depletion ameliorates injury. It is not known whether these responses are antigen specific. Furthermore, some B cell and T cell subsets, such as T regulatory cells, help limit renal injury.

AKI may have systemic effects on other organ systems.[7] The injured kidney may prime and activate leukocytes, which produce proinflammatory cytokines that can mediate remote organ injury (Fig. 66.7). The lungs may be particularly vulnerable from the combined effects of volume overload, increased vascular permeability, and proinflammatory environment. These distant organ effects may partly account for the increased mortality in patients with AKI (Chapter 69).

Recovery Phase

Recovery from ATN requires the restoration of tubular cell number and coverage of denuded TBM. A marked increase in cell proliferation occurs in recovering human ATN (see Fig. 66.3). The restoration of tubular cell number is due to the dedifferentiation and proliferation of surviving tubular cells rather than from a mesenchymal stem cell source.[8] After tubular epithelial cell proliferation, the dedifferentiated cells must migrate to areas of denuded TBM, attach to the basement

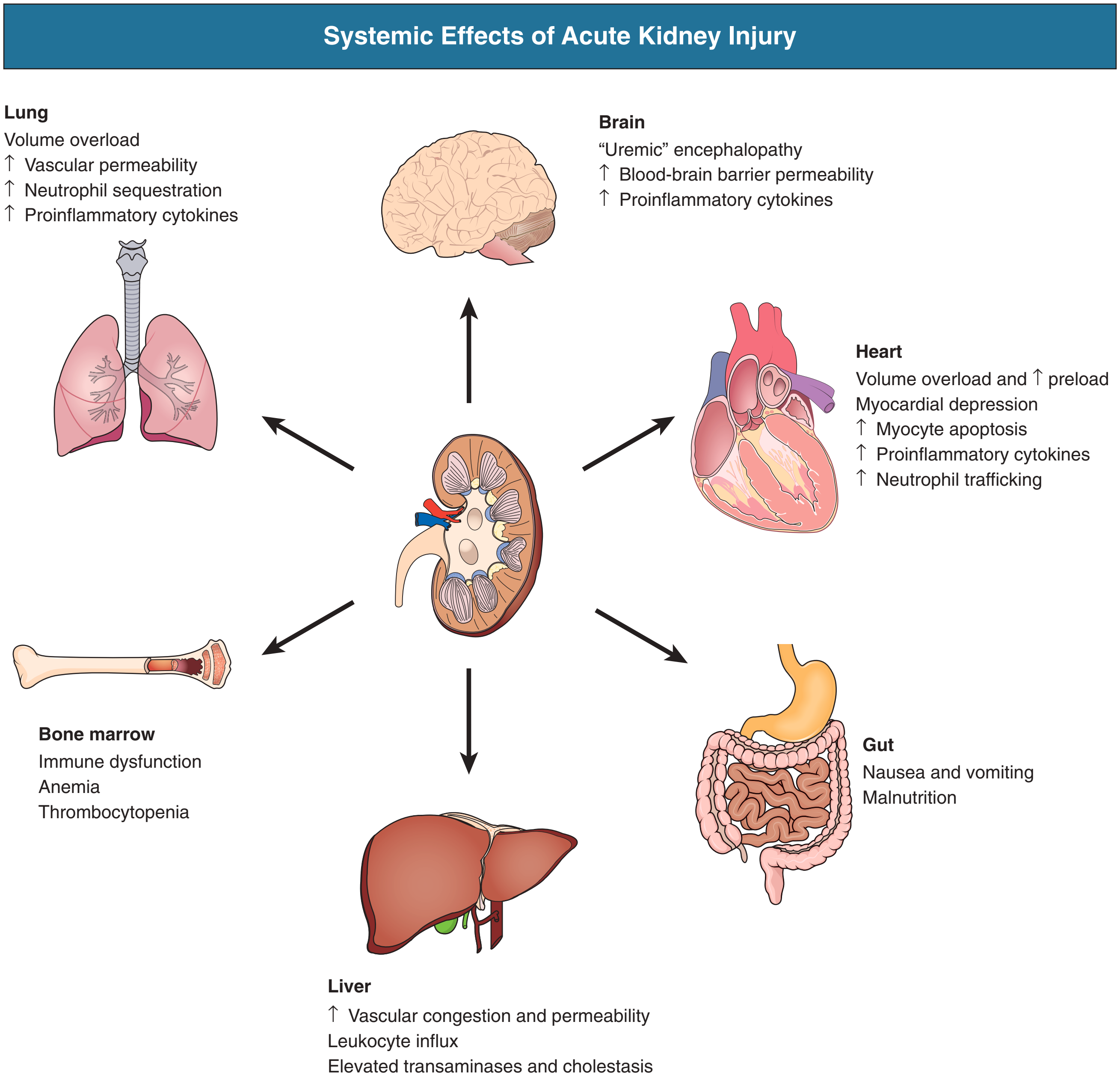
Systemic Effects of Acute Kidney Injury
Lung
Volume overload
↑ Vascular permeability
↑ Neutrophil sequestration
↑ Proinflammatory cytokines
Brain
"Uremic" encephalopathy
↑ Blood-brain barrier permeability
↑ Proinflammatory cytokines
Heart
Volume overload and ↑ preload
Myocardial depression
↑ Myocyte apoptosis
↑ Proinflammatory cytokines
↑ Neutrophil trafficking
Bone marrow
Immune dysfunction
Anemia
Thrombocytopenia
Gut
Nausea and vomiting
Malnutrition
Liver
↑ Vascular congestion and permeability
Leukocyte influx
Elevated transaminases and cholestasis

Fig. 66.7 Systemic effects of acute kidney injury (AKI). AKI may contribute to remote organ injury, partly because of abnormalities in inflammatory and immune function from renal tubular dysfunction. (Modified from reference 7.)

membrane, and differentiate into mature polar tubular epithelial cells. The early inflammatory infiltrates of neutrophils and M1 monocytes are replaced by M2 monocytes, which support epithelial cell repair, after which their numbers decline by migration or apoptosis. When the injury process is persistent or severe, maladaptive repair may occur leading to CKD.[9]

NEPHROTOXIC AGENTS AND MECHANISMS OF TOXICITY

The identification and avoidance of nephrotoxic agents in AKI is critical because AKI may be rapidly reversible on removal of the offending agent. The mechanisms of nephrotoxicity include alterations in renal hemodynamics, induction of direct tubular injury, generation of allergic reactions resulting in interstitial nephritis, and intratubular obstruction. The list is extensive, but the more common agents are presented in Fig. 66.8.

Nonsteroidal Antiinflammatory Drugs

NSAIDs commonly cause AKI in the community because of the large amounts of these drugs either prescribed or purchased over the counter. COX-2–specific NSAIDs have similar effects on renal function as the nonselective NSAIDs and thus are not safer with respect to AKI. NSAID-related AKI is most often due to a hemodynamically mediated reduction in GFR that occurs in patients who are particularly dependent on vasodilatory prostaglandins to maintain renal perfusion. These include elderly

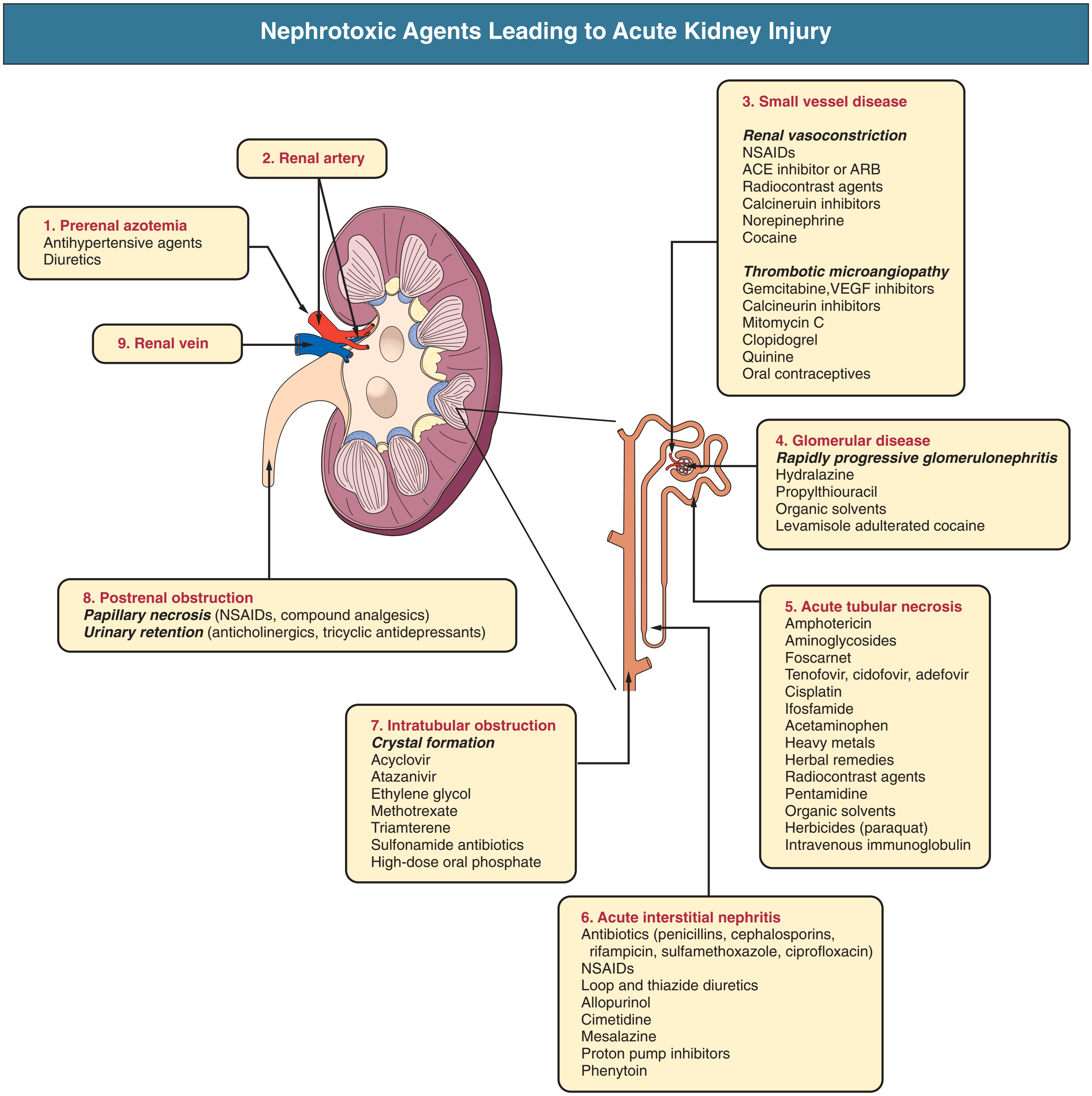
Nephrotoxic Agents Leading to Acute Kidney Injury
1. Prerenal azotemia
Antihypertensive agents
Diuretics
2. Renal artery
3. Small vessel disease
Renal vasoconstriction
NSAIDs
ACE inhibitor or ARB
Radiocontrast agents
Calcineruin inhibitors
Norepinephrine
Cocaine
Thrombotic microangiopathy
Gemcitabine,VEGF inhibitors
Calcineurin inhibitors
Mitomycin C
Clopidogrel
Quinine
Oral contraceptives
4. Glomerular disease
Rapidly progressive glomerulonephritis
Hydralazine
Propylthiouracil
Organic solvents
Levamisole adulterated cocaine
5. Acute tubular necrosis
Amphotericin
Aminoglycosides
Foscarnet
Tenofovir, cidofovir, adefovir
Cisplatin
Ifosfamide
Acetaminophen
Heavy metals
Herbal remedies
Radiocontrast agents
Pentamidine
Organic solvents
Herbicides (paraquat)
Intravenous immunoglobulin
6. Acute interstitial nephritis
Antibiotics (penicillins, cephalosporins, rifampicin, sulfamethoxazole, ciprofloxacin)
NSAIDs
Loop and thiazide diuretics
Allopurinol
Cimetidine
Mesalazine
Proton pump inhibitors
Phenytoin
7. Intratubular obstruction
Crystal formation
Acyclovir
Atazanivir
Ethylene glycol
Methotrexate
Triamterene
Sulfonamide antibiotics
High-dose oral phosphate
8. Postrenal obstruction
Papillary necrosis (NSAIDs, compound analgesics)
Urinary retention (anticholinergics, tricyclic antidepressants)
9. Renal vein

Fig. 66.8 Common nephrotoxic agents leading to acute kidney injury. *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *NSAIDs,* nonsteroidal antiinflammatory drugs.

patients with atherosclerotic disease, volume-depleted patients, and those in sodium-avid states such as cirrhosis, nephrotic syndrome, and congestive heart failure. This form of AKI is usually reversible in 2 to 7 days on discontinuation of the drug and rarely occurs in otherwise healthy individuals. Less frequently, NSAIDs induce ATN or even more rarely papillary necrosis. NSAIDs also may cause an acute interstitial nephritis, often with significant proteinuria (see Chapter 60). Other renal side effects of NSAIDs include fluid and electrolyte disturbances such as sodium retention exacerbating hypertension and congestive heart failure, hyponatremia, and hyperkalemia.

Acetaminophen (Paracetamol)

Isolated ATN with acetaminophen may occur in rare cases, but renal injury is more typically associated with acute hepatitis. Renal and liver toxicity usually occur when more than 15 g has been taken, but in alcoholics, normal doses may be toxic. Acetaminophen is conjugated in the liver and undergoes renal excretion. Less than 5% undergoes metabolism by cytochrome P-450 (CYP2E1) enzymes to form a toxic metabolite, *N*-acetyl imidoquinone, which is inactivated by the thiol group of glutathione. With high levels of acetaminophen, glutathione becomes depleted, and *N*-acetyl imidoquinone can bind to thiol groups on intracellular proteins, resulting in cell injury. Because glutathione is a major intracellular antioxidant, its loss may predispose to oxidative injury of the tubular cells.

Clinically, acute hepatitis and ATN only begin once glutathione levels are depleted, and clinical manifestations usually present 3 to 4 days after ingestion. *N*-Acetylcysteine, which substitutes for glutathione by providing a free thiol group, can be protective if administered early.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors and ARBs may cause hemodynamically induced AKI in the setting of reduced renal perfusion by impairing compensatory vasoconstriction of the efferent arteriole. These drugs may directly impair renal perfusion by their antihypertensive effects. Patients in whom renal perfusion is compromised because of dehydration, renovascular disease, or functionally impaired autoregulation are at particular risk for developing AKI after initiation of therapy. Patients chronically treated with ACE inhibitors or ARBs have an increased risk for postoperative renal dysfunction, probably as a consequence of intraoperative hypotensive episodes.

Aminoglycosides

Aminoglycosides are excreted by glomerular filtration. Toxicity may occur if the dose is not adjusted to the GFR. Cationic amino groups (NH_3^+) on the drugs bind to anionic megalin on the brush border of proximal tubular epithelial cells, and the drugs are then internalized by endocytosis. Aminoglycosides accumulate in proximal tubular cell lysosomes and can reach 100 to 1000 times their serum concentration. The drug interferes with cellular energetics, impairs intracellular phospholipases, and induces oxidative stress.[10]

Nonoliguric AKI usually occurs after 5 to 10 days of treatment with gentamicin. Involvement of distal tubular segments may produce polyuria, potassium, and magnesium wasting. The risk for AKI correlates with the accumulation of gentamicin in proximal tubular cells and is related to the daily dose and duration of therapy. Prolonged accumulation in proximal tubular cells may allow development of AKI even after the drug has been discontinued. Additional risk factors for gentamicin toxicity include increasing age, preexisting renal disease, hypotension, concurrent liver disease, sepsis, and concurrent nephrotoxins. Simultaneous treatment with vancomycin can potentiate aminoglycoside nephrotoxicity. Aminoglycoside serum levels should be monitored to minimize nephrotoxicity. When possible, the drug should be administered in a single daily total dose, which leads to lower renal proximal tubular cell accumulation. Gentamicin, tobramycin, and netilmicin appear to have similar nephrotoxic effects. Amikacin, which has fewer amino groups per molecule, may be less nephrotoxic.

Vancomycin

Whether vancomycin is nephrotoxic is controversial.[11] Early formulations of the drug contained impurities that were thought to account for the renal injury. More recently, the recommendation for higher vancomycin trough levels to target resistant methicillin-resistant *Staphylococcus aureus* has led to recognition that vancomycin monotherapy can be nephrotoxic. Vancomycin is excreted primarily by glomerular filtration, but accumulation in proximal tubule cells via basolateral secretion is thought to underlie nephrotoxicity. Experimentally, high-dose vancomycin causes oxidative stress and triggers intrarenal apoptotic pathways. In humans, high trough levels of vancomycin have been associated with nephrotoxicity in a graded fashion, with an initial trough greater than 20 mcg/ml significantly increasing the odds of AKI. Additional risk factors for vancomycin nephrotoxicity include total dose greater than 4 g/day, long duration of therapy, concurrent nephrotoxin exposure, and critical illness. ATN is the predominant lesion seen in experimental models, but case reports of human biopsies have shown both interstitial nephritis and ATN. Vancomycin can cause a drug reaction with eosinophilia and systemic symptoms (drug-related eosinophilia with systemic symptoms [DRESS] syndrome) with inflammatory renal injury. Treatment is generally conservative. High-flux hemodialysis can be used for drug removal when levels are very high. Renal injury from vancomycin is generally reversible.

Amphotericin B

This polyene macrolide antibiotic binds to sterols in the cell membranes of both fungal walls (ergosterol) and mammalian (cholesterol) cell membranes, resulting in the formation of aqueous pores that increase membrane permeability. Within the renal tubular cell, the subsequent sodium influx leads to increased Na^+,K^+-ATPase activity and depletion of cellular energy stores.[12] Additionally, the standard amphotericin B formulation is suspended in the bile salt deoxycholate, which has a detergent effect on cell membranes. Nephrotoxicity relates to cumulative dosage, usually occurring after administration of 2 to 3 g.

Early signs of nephrotoxicity include a loss of urine-concentrating ability, followed by a decrease in GFR. Hypokalemia and hypomagnesemia secondary to distal tubular wasting are common. A distal renal tubular acidosis may be present as a result of proton backleak in the cortical collecting duct.

Prevention of nephrotoxicity requires the maintenance of high urine flow rates by saline loading during amphotericin administration. The more expensive liposomal amphotericin B preparations reduce the incidence of AKI by approximately 50%. Because amphotericin B binds more avidly to fungal ergosterol than to cholesterol, delivering the drug as a cholesterol liposome diminishes binding to tubular epithelial cell membranes without altering fungicidal activity. Additionally, liposomal preparations do not contain deoxycholate. Amphotericin B–induced AKI is usually reversible with discontinuation of the drug, although distal tubular injury as manifested by magnesium wasting may persist.

Antiviral Therapy

Acyclovir

Nephrotoxicity is typically seen after intravenous acyclovir administration and may be due to direct tubular cell toxicity and the formation of intratubular acyclovir crystals. The latter appear as birefringent needle-shaped crystals on urine microscopy. However, crystals also may be seen in non-AKI patients, and renal biopsy data suggest that acute interstitial nephritis may be the predominant mechanism of toxicity.

Oliguric AKI typically occurs within a few days of treatment and may be associated with abdominal or loin pain. High serum levels of acyclovir as a result of decreased renal clearance may produce neurologic toxicity. The AKI is usually mild and recovers on stopping the drug. Maintaining a high urine flow rate and avoiding intravenous bolus administration of acyclovir may be preventive.

Tenofovir

Tenofovir is a nucleoside reverse transcriptase inhibitor used to treat both HIV and hepatitis B infection. The prodrug, tenofovir disoproxil fumarate (TDF), is the most widely used therapy for HIV in the world. Tenofovir is secreted into proximal tubule cells via organic anion transporters, where it can interfere with mitochondrial DNA synthesis and upset the energy supply, resulting in characteristic enlarged, dysmorphic mitochondria. Manifestations of tenofovir nephrotoxicity include subclinical tubular defects (e.g., normoglycemic glycosuria), Fanconi syndrome, ATN, and CKD.[13] Renal manifestations can develop within weeks of drug initiation or can occur after years, but reversibility is common. Risk factors include preexisting CKD, advanced age, low CD4 count, and total dose and duration of TDF use. Patients with HIV infection are at increased risk for a variety of renal diseases (see Chapter 56), and biopsy should be strongly considered when renal dysfunction does not improve after drug cessation or resistance patterns make tenofovir critical for patient care. Tenofovir alafenamide, a new formulation, concentrates in mononuclear cells, resulting in reduced drug delivery to the kidney. Early reports suggest a lower risk for nephrotoxicity with this agent.[14]

Atazanivir

Atazanvir is a protease inhibitor used in many HIV regimens. Atazanivir can cause urolithiasis and crystalline-induced renal injury, although at a much lower frequency than its predecessor indinavir. Risk factors for atazanivir stones include duration of therapy, history of nephrolithiasis, and hyperbilirubinemia. Renal biopsies have shown acute interstitial nephritis or a granulomatous interstitial nephritis in which atazanivir crystals were detectable in a giant cell reaction. Acute manifestations are largely reversible, but long-term use can lead to CKD.[15]

Other Antiviral Agents

Among antivirals used to treat HIV infection, both cobicistat and dolutegravir inhibit proximal tubular secretion of creatinine, causing a false elevation in serum creatinine that does not reflect an actual drop in GFR. A small rise in creatinine is considered acceptable and generally occurs within 2 weeks of starting these drugs. New direct-acting antivirals used to treat hepatitis C (e.g., ledipasvir, sofosbuvir) do not have significant nephrotoxicity. Adefovir, a second-line drug used to treat hepatitis B, was frequently nephrotoxic when prescribed at high doses, but current low-dose regimens appear safe for most patients. Foscarnet and cidofovir are well-recognized nephrotoxic antivirals.

Hypoglycemic Therapy: SGLT2 Inhibitors

Sodium glucose cotransporter type 2 (SGLT2) inhibitors have shown promise for reducing cardiovascular events and CKD in patients with diabetes, but may also predispose to AKI. There have been numerous recent reports of AKI associated with use of SGLT2 inhibitors, including canagliflozin, dapagliflozin, and empagliflozin. Most patients developed AKI within the first month of therapy, and it was not always reversible. Risk factors may include dehydration and use of NSAIDs. However, in a recent randomized controlled trial, the use of empagliflozin was associated with a lower incidence of AKI than placebo.[16]

Immunosuppressive Agents

Calcineurin Inhibitors

Cyclosporine and tacrolimus may cause AKI because of afferent arteriolar vasoconstriction, partly mediated by endothelin. This is usually reversible on dose reduction. Persistent injury may lead to chronic interstitial fibrosis in a striped pattern along medullary rays reflecting both the ischemic nature of the insult and the development of arteriolar hyalinosis. Associated clinical features include hypertension, hyperkalemia, hyperuricemia, and wasting of phosphorus and magnesium from tubular injury. Calcineurin inhibitors also cause reversible tubular dysfunction and are associated with the development of thrombotic microangiopathy, likely because of their effects on the endothelium (see Chapter 29).

Other Immunosuppressive Agents

The monoclonal anti-CD3 antibody (OKT3) or polyclonal antilymphocyte and antithymocyte preparations (ALG, ATG) may cause first-dose cytokine release syndrome and prerenal azotemia secondary to capillary leak. Intravenous immunoglobulin can cause AKI, which may be partly mediated by the high sucrose concentration in these products. Tubular uptake of sucrose may result in osmotic cell swelling and injury. Although it does not typically cause AKI, sirolimus delays the recovery from AKI in animal models and in kidney transplant patients with delayed graft function.

Ethylene Glycol

Ethylene glycol, found in antifreeze, is a cause of both deliberate and accidental overdose. It is rapidly metabolized by alcohol dehydrogenase to glycoaldehyde and glyoxylate, which are toxic to tubular cells. Further metabolism generates oxalic acid, which can precipitate, leading to intratubular obstruction.

The diagnosis is suggested by the presence of severe anion gap metabolic acidosis and elevated serum osmolal gap. Calcium oxalate crystals are often seen on urine microscopy (see Chapter 4, Fig. 4.7). Management includes inhibition of alcohol dehydrogenase with fomepizole or intravenous ethanol if this agent is not available. Although there is no specific ethylene glycol level above which extracorporeal removal is mandated, hemodialysis is the quickest way to remove both parent alcohol and toxic metabolites. Methanol intoxication may manifest with similar metabolic abnormalities, but rarely causes AKI (see Chapter 12).

Anticoagulation-Related Nephropathy

AKI has been described in patients taking warfarin who develop an acute rise in the international normalized ratio, usually to greater than 3. This occurs predominantly in patients with underlying CKD. AKI results from glomerular hematuria with obstruction of renal tubules by red blood cell casts. The direct thrombin inhibitor dabigatran can cause similar glomerular lesions when administered to rats, but human studies are lacking.[17]

Acute Phosphate Nephropathy

Oral sodium phosphate has been widely used as a bowel preparation for colonoscopy procedures, but recent cases of AKI have limited the use of this purgative.[18] AKI associated with oral sodium phosphate is believed to be caused by phosphaturia and acute calcium-phosphate deposition within the renal tubules. Risk factors for this condition include older age, volume depletion, and underlying CKD.

Drugs of Abuse

AKI is a common condition in those who abuse drugs and may be due to nephrotoxicity of the drug, coexistent viral infection (HIV, hepatitis C), sepsis, infective endocarditis, or rhabdomyolysis.[19]

Cocaine induces intense vasoconstriction, which may lead to AKI secondary to severe hypertension or rhabdomyolysis. Mechanisms for rhabdomyolysis include coma and pressure necrosis, vasospasm leading to ischemic muscle injury, and adrenergic stimulation with hyperpyrexia leading to increased cellular metabolism. Cocaine also may exert direct toxic effects on the myocyte.[20] The majority of cocaine entering the United States is contaminated by levamisole, an immunomodulator and antihelminthic agent. In humans, levamisole has been reported to cause an antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis with a necrotizing crescentic GN and prominent skin lesions.

Other illicit drugs associated with AKI include opiates (coma-associated, pressure-induced rhabdomyolysis), phencyclidine (rhabdomyolysis secondary to hyperpyrexia and vasoconstriction), and methamphetamines (AKI secondary to rhabdomyolysis, acute interstitial nephritis, or acute necrotizing angiitis). Synthetic cannabinoids have been implicated as a cause of AKI, although the culprit component is unclear. When available, renal biopsy has shown ATN and more rarely AIN. In the majority of cases no other cause for AKI could be identified.[19]

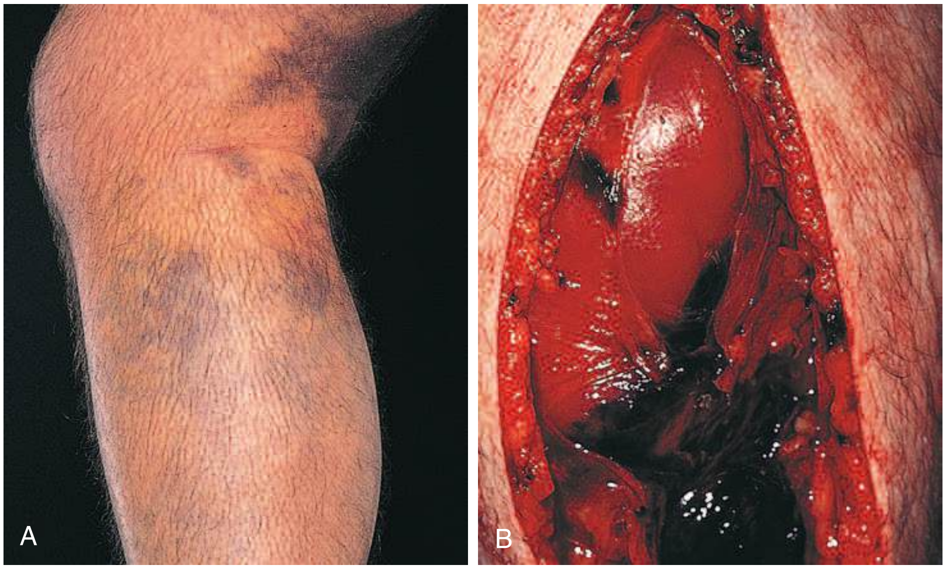

Fig. 66.9 **Compartment syndrome.** (A) Severe calf swelling secondary to anterior and posterior compartment syndromes after ischemia-reperfusion. (B) Appearance after emergency fasciotomy. Note edematous muscle and hematoma. (Courtesy M. J. Allen, FRCS.)

Occupational Toxins

Heavy Metals

Lead intoxication usually causes chronic nephropathy (see Chapter 62). Rarely, acute tubular injury occurs that may be associated with Fanconi syndrome. ATN also may occur in cadmium and mercury poisoning.

Organic Solvents

Organic solvents may cause acute tubular injury as a result of peroxidation of membrane lipids. Subacute renal failure secondary to anti–glomerular basement membrane (anti-GBM) antibody disease has been reported with exposure to halogenated hydrocarbons.

Herbal Remedies

Specific herbs used in traditional African medicine (e.g., Cape aloes, *Callilepis laureola*) are common causes of AKI in parts of Africa. Aristolochic acid (found in certain traditional Chinese medicines) can cause subacute renal failure (see Chapters 62 and 76).

Radiocontrast-Induced Nephropathy

AKI secondary to contrast nephrotoxicity typically occurs in patients with underlying renal impairment and is rarely seen in patients with preserved renal function. In hospitalized patients, it is often difficult to determine whether contrast computed tomography (CT) is the primary cause of AKI because imaging is often obtained in the setting of other potential renal insults (infection, antibiotics, etc.). Recent studies have questioned the link of intravenous contrast CT with nephrotoxicity, suggesting minimal risk for AKI when low or isoosmolar contrast is administered intravenously to patients with an eGFR greater than 30 ml/min.[21-23] Indeed, in these studies, the rates of AKI were similar among well-matched hospitalized patients who received noncontrast CT scans.

Intraarterial contrast administration, required for cardiac catheterization or renal angiography, is felt to pose a greater risk for AKI because these procedures often require larger doses of iodinated material that is then delivered to the renal arteries in a concentrated manner. Risk factors for the development of AKI from radiocontrast nephropathy include diabetic nephropathy, advanced age (>75 years), congestive heart failure, volume depletion, hyperuricemia, and high or repetitive doses of radiocontrast agents. Concurrent use of NSAIDs, ACE inhibitors, or diuretics may increase the risk.

Both renal ischemia and direct tubular epithelial cell toxicity are implicated in the pathogenesis of contrast nephrotoxicity. Typically, a biphasic hemodynamic response is seen. Initial vasodilation (lasting a few seconds to minutes) is followed by more prolonged renal vasoconstriction. The resultant medullary hypoxia may be exacerbated by low flow in the vasa recta as a result of a contrast-induced rise in blood viscosity. An osmotic diuresis, leading to increased sodium delivery to the mTAL, may result in increased oxygen consumption for sodium reabsorption. Uricosuria, as well as a hyperosmolar activation of the aldose reductase-fructokinase system in the kidney, has been proposed to play a role. Radiocontrast agents also cause direct tubular epithelial cell injury. Human studies have demonstrated low-molecular-weight proteinuria, suggestive of proximal tubular injury, partly mediated by ROS. The administration of antioxidants ameliorates contrast nephrotoxicity in animals.

OTHER SPECIFIC ETIOLOGIES OF ACUTE KIDNEY INJURY

Heme Pigment Nephropathy

Heme pigment nephropathy is a common cause of AKI and is usually secondary to the breakdown of muscle fibers (rhabdomyolysis), which release potentially nephrotoxic intracellular contents (particularly myoglobin) into the systemic circulation. Less commonly, heme pigment nephropathy may occur secondary to massive intravascular hemolysis. Prevention and therapy of heme pigment nephropathy are discussed in Chapter 70.

Causes of Rhabdomyolysis

Muscle trauma is the most common cause of rhabdomyolysis. The initial description was by Beall and colleagues[24] during the bombing of London in World War II. Other common causes of muscle injury include marked exercise, seizures, pressure necrosis secondary to coma, substance abuse, and limb ischemia (Fig. 66.9). In skeletal muscles confined to rigid compartments, cell swelling after injury may result in increased intracompartmental pressures that can impair local

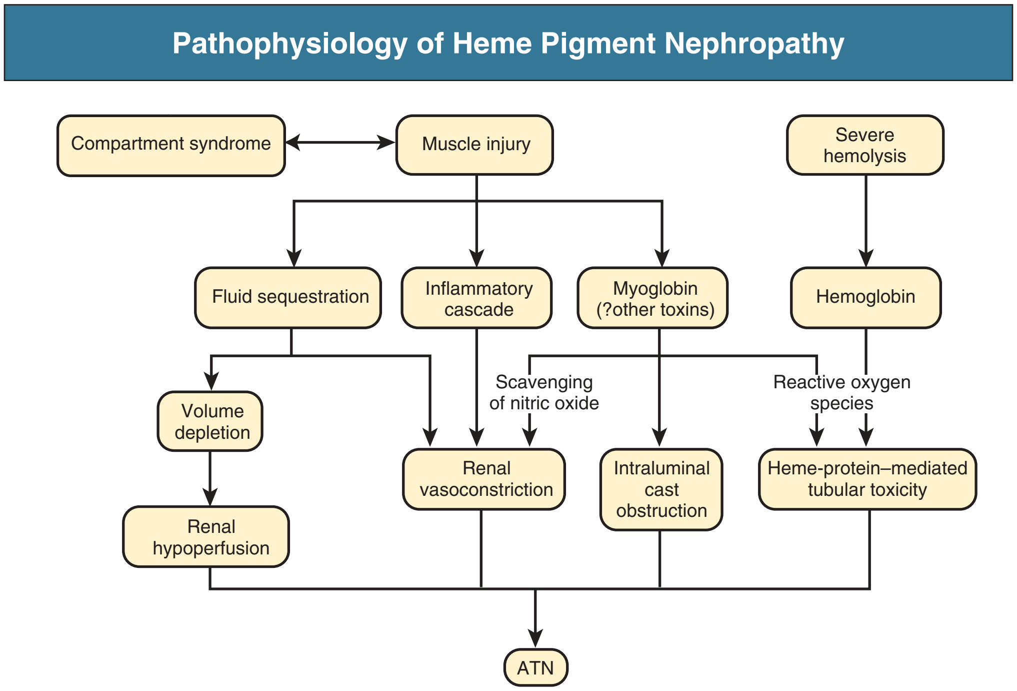

Fig. 66.10 Pathophysiology of heme pigment nephropathy. *ATN,* Acute tubular necrosis.

microvascular circulation and lead to compartment syndrome (Fig. 66.10). In the patient with alcohol abuse, rhabdomyolysis is often multifactorial. Contributing causes include pressure necrosis from coma ("found down"), direct myotoxicity from ethanol, seizures, and electrolyte abnormalities (hypokalemia and hypophosphatemia). Therapy with statins may be associated with rhabdomyolysis, especially when fibrates, cyclosporine, or erythromycin are used concurrently. Familial myopathies such as McArdle syndrome and carnitine palmitoyl transferase deficiency should be suspected in patients with recurrent episodes of rhabdomyolysis associated with muscle pain, positive family history, onset in childhood, and the absence of other identifiable causes. In developing countries, ingestion of hair dye containing paraphenylene diamine as a means of self-harm may cause AKI secondary to rhabdomyolysis. Snake and spider bites, bee stings, and venomous caterpillar bites may cause rhabdomyolysis (see Chapter 67).

Causes of Hemoglobinuria

Intravascular hemolysis results in circulating free hemoglobin. If the hemolysis is mild, the released hemoglobin is bound by circulating haptoglobin. With massive hemolysis, however, haptoglobin stores become exhausted. Hemoglobin (69 kDa) then dissociates into α-β dimers (34 kDa) that are small enough to be filtered, resulting in hemoglobinuria, hemoglobin cast formation, heme uptake by proximal tubular cells, ATN, and filtration failure. Causes of hemoglobinuric AKI include incompatible blood transfusion, autoimmune hemolytic anemia, malaria (blackwater fever), glucose-6-phosphate dehydrogenase deficiency, paroxysmal nocturnal hemoglobinuria, march hemoglobinuria, and toxins (dapsone, venoms).

Pathogenesis of Heme Pigment Nephropathy

The renal injury is due to a combination of factors, including volume depletion, renal vasoconstriction, direct heme-protein–mediated cytotoxicity, and intraluminal cast formation (Table 66.1).[25] Volume depletion is often prominent in patients with rhabdomyolysis owing to the sequestration of large amounts of fluid (up to 15 to 20 liters) in injured muscle. Volume depletion activates the sympathetic nervous system and renin-angiotensin system, resulting in renal vasoconstriction. This may be exacerbated by the scavenging of nitric oxide by circulating heme proteins.

Myoglobin (17 kDa) is freely filtered at the glomerulus and is toxic to tubular epithelial cells. The heme center of myoglobin may directly induce lipid peroxidation and renal injury, and liberated free iron catalyzes the formation of hydroxyl radical through the Fenton reaction, inducing free radical–mediated injury. Renoprotection has been demonstrated in animal models with free iron scavengers and various antioxidants. Finally, the precipitation of myoglobin with Tamm-Horsfall protein and sloughed proximal tubular cells may result in obstructing casts in the distal nephron, especially when tubular flow rates are low because of volume depletion. The binding of myoglobin to Tamm-Horsfall protein is enhanced in acidic urine.

TABLE 66.1 Causes of Rhabdomyolysis

Muscle injury/ ischemia	Trauma; pressure necrosis, electric shock, burns, acute vascular disease
Myofiber exhaustion	Seizures, excessive exercise, heat exhaustion
Toxins	Alcohol, cocaine, heroin, amphetamines, ecstasy, phencyclidine, snake bite
Drugs	Statins, fibrates, zidovudine, neuroleptic malignant syndrome, azathioprine, theophylline, lithium, diuretics
Electrolyte disorders	Hypophosphatemia, hypokalemia, hyperosmolar states
Infections	Viral: Influenza, HIV, coxsackievirus, Epstein-Barr virus Bacterial: *Legionella, Francisella, Streptococcus pneumoniae, Salmonella, Staphylococcus aureus*
Familial	McArdle disease, carnitine palmitoyl transferase deficiency, malignant hyperthermia
Other	Hypothyroidism, polymyositis, dermatomyositis

Atheroembolic Renal Disease

This underrecognized condition occurs predominantly in older patients with atherosclerotic vascular disease (see also Chapter 38). It can occur spontaneously, but is most commonly precipitated by arteriography, vascular surgery, thrombolysis (streptokinase and tissue plasminogen activator), or anticoagulation. Destabilization of atherosclerotic plaques primarily in the aorta above the level of the renal arteries results in showers of cholesterol that lodge in small arteries in the kidneys (see Fig. 41.13) and the lower extremities (see Fig. 41.11). Characteristic needle-shaped clefts may be seen on renal or skin biopsy, denoting the localization of cholesterol plaques before dissolution with tissue fixation (Fig. 41.13). The cholesterol emboli produce a marked and progressive inflammatory reaction, resulting in occlusion of the involved vasculature.

Renal Artery or Vein Occlusion

AKI can be caused by bilateral renal artery occlusion or unilateral occlusion in the setting of a single functioning kidney (see also Chapter 38). Thrombosis or embolization (noncholesterol) of the renal artery or its intrarenal branches are more common in elderly patients. Atrial fibrillation is an important risk factor for renal emboli. Aortic dissection may progress to occlude the renal arteries. Renal vein thrombosis most commonly occurs in the setting of nephrotic syndrome and rarely may cause AKI if bilateral.

Acute Interstitial Nephritis

This is most commonly a drug-induced phenomenon and is an important differential diagnosis in AKI because removal of the offending agent can result in reversal of the condition. Less commonly, interstitial nephritis may be due to infection or immune-mediated diseases. Acute interstitial nephritis is discussed further in Chapter 60.

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) constitutes a wide range of conditions that should be considered when a patient presents with AKI and thrombocytopenia, although the condition may occur in the absence of a low platelet count. All forms of TMA can manifest with AKI (see also Chapter 29).

Glomerular Disease

All types of glomerular disease may present with AKI, but it is more commonly seen with forms of acute GN such as postinfectious GN, ANCA-associated small-vessel vasculitis, anti-GBM disease, lupus nephritis, and IgA nephropathy. The term *rapidly progressive GN* has been used in this setting and is often associated with glomerular crescents on renal biopsy. Glomerular disease associated with the nephrotic syndrome is less likely to manifest as AKI, but AKI may occur secondary to volume depletion from diuretic use, superimposed ATN, renal vein thrombosis, or, rarely, from superimposed acute GN (e.g., anti-GBM disease in membranous nephropathy). Minimal change disease in adults is the most common nephrotic disorder associated with AKI. Glomerular disease is discussed further in Section IV.

SPECIFIC CLINICAL SITUATIONS

Determining the cause of AKI is often aided by recognizing common patterns of manifestation and determining the likely causes arising in each of these situations.

Acute Kidney Injury in the Patient With Sepsis

Sepsis accounts for up to 50% of cases of AKI in intensive care unit patients, and the presence of septic AKI is associated with mortality rates as high as 50% to 60% in those requiring renal replacement therapy.[26] In recent years, the traditional model of hypotension and vasoconstriction leading to ischemic ATN has been challenged by the finding that in early sepsis, RBF is often normal or even increased. Moreover, the severe drop in GFR observed with sepsis is out of proportion to the relatively mild degree of histologic injury seen on renal biopsies, and on autopsy only 22% of patients with sepsis-associated AKI had histologic features of ATN.[27]

The pathogenesis of sepsis-associated AKI is mediated by molecules released from pathogens (lipopolysaccharide, flagellin, lipoteichoic acid, DNA), or injured cells, which activate the innate immune system by binding to TLRs and other receptors on immune cells.[28,29] This leads to the activation of a wide range of cellular and humoral mediator systems, including the cytokine cascade (TNF-α, IL-1β, IL-6); the complement, coagulation, and fibrinolytic systems, increased oxidative stress, and the release of mediators such as eicosanoids, platelet-activating factor, endothelin-1, and nitric oxide. Renal endothelial cells can be damaged in the procoagulant milieu and upregulate their expression of adhesion molecules, further amplifying the immune response. Disruption of the renal microcirculation ensues, with local areas of cortical ischemia despite maintenance of normal renal arterial blood flow. Ligation of TLRs on tubular cells (TLR-4) leads to mitochondrial dysfunction, oxidative stress, and severe apoptosis, rather than necrosis. The mechanism for the abrupt GFR decline in early sepsis likely involves *efferent* arteriolar vasodilation. Therapies that promote efferent arteriolar vasoconstriction may be beneficial. In a sheep model of sepsis, infusion of Ang II improved mean arterial pressure and GFR despite a decrement in RBF. In human studies, treatment with arginine vasopressin, which constricts the efferent more than the afferent arteriole, was associated with reduced progression to the most severe category of AKI in patients with septic shock.[30] Sepsis may lead to multiorgan failure, and affected patients may have repeated episodes of AKI as a result of nephrotoxic drug exposure or hospital-acquired infections. Finally, maladaptive repair processes can lead to CKD after AKI in sepsis.

Acute Kidney Injury in the Trauma Patient

AKI significantly increases mortality among those with severe trauma.[31] Mechanisms for renal injury include rhabdomyolysis (earthquake victims, crush injuries, burns), ATN from hypovolemic shock, or abdominal compartment syndrome secondary to massive hemorrhage or aggressive hydration. Direct kidney injury may result from penetrating (gunshot, stab wound) or more commonly blunt trauma (fall, motor vehicle collision, assault, sports injury). Proper diagnosis of these injuries requires a contrast-enhanced CT with delayed imaging; otherwise, late extravasation from the renal pelvis or ureters may be missed. Management is generally conservative, but emergent nephrectomy may be required.

Acute Kidney Injury in the Postoperative Patient

Postoperative AKI is commonly due to perioperative hemodynamic instability, volume depletion, and/or nephrotoxin exposure.

After Cardiac Surgery

Risk factors for postoperative AKI include duration of cardiac bypass, preoperative renal function, hyperuricemia, age, diabetes, valvular surgery, blood transfusions, and poor cardiac function.[32] The surgery is often performed with the patient cooled to less than 30°C to protect cells against ischemic injury; however, systemic hypothermia may cause intravascular coagulation. Aortic instrumentation and cross-clamping may lead to renal atheroembolism. Cardiac bypass causes exposure of blood to a nonendothelialized surface, resulting in activation of neutrophils, platelets, complement, and fibrinolytic systems. Significant hemolysis may occur, potentially resulting in hemoglobinuria. Perioperative myocardial infarction or left ventricular dysfunction may impair renal perfusion postoperatively, although the low cardiac output is often transient (myocardial stunning) and recovers within 24 to 48 hours. Atrial fibrillation is a common complication and may be associated with peripheral embolization. Off-pump coronary artery bypass operations may have a lower risk for AKI than surgeries involving cardiopulmonary bypass.

After Vascular Surgery

AKI is common after abdominal aortic aneurysm repair, but the risk appears to be lower in those undergoing endovascular versus open repair.[33] Mechanisms for AKI include ischemic ATN as a result of prolonged aortic cross-clamping, renal artery thromboembolism or dissection, and cholesterol atheroemboli. Additional complications specific to endovascular repair include contrast nephropathy and renal ischemia secondary to endograft malpositioning or migration. In patients with peripheral vascular disease, there is often ischemic renal disease, and preoperative reduction in eGFR is the strongest predictor of the risk for postoperative AKI.

Abdominal Compartment Syndrome

Markedly raised intraabdominal pressures (>20 mm Hg) may occur after trauma, after abdominal surgery, or secondary to massive fluid resuscitation and can cause AKI.[34] The mechanism remains unclear, but may be due to increased renal venous pressure and vascular resistance. Intraabdominal pressures are best estimated by measurement of intravesical (bladder) pressures. Efforts to reduce intraabdominal pressures, including paracentesis, nasogastric suction, ultrafiltration, or surgical decompression, may improve renal function.

Pulmonary-Renal Syndrome

The term *pulmonary-renal syndrome* usually describes the presence of pulmonary hemorrhage in a patient with acute GN. It can be caused by anti-GBM disease (Goodpasture syndrome), systemic vasculitis, or systemic lupus erythematosus (see Chapters 24 to 26). Given the fulminant course of the previously mentioned diseases, patients with pulmonary-renal syndrome require urgent evaluation, and specific testing for these diseases should be pursued. A similar clinical presentation may occur in patients with pulmonary infection and AKI or in the setting of pulmonary edema secondary to volume overload from AKI. Other conditions that may masquerade as a pulmonary renal syndrome are outlined in Table 66.2.

Acute Kidney Injury and Liver Disease

AKI is common in patients with cirrhosis. The differential diagnosis is typically among prerenal AKI, ATN, and hepatorenal syndrome. The pathophysiology of hepatorenal syndrome is discussed in Chapter 73. Assessment of intravascular volume status can be difficult, and a therapeutic trial of volume replacement is typically undertaken. Risk factors for AKI in this population include hypovolemia, gastrointestinal bleeding, and infection (particularly spontaneous bacterial peritonitis). It is important to note that severe malnutrition and decreased muscle mass may be masked by the presence of edema. In these settings, a "normal" creatinine can be deceptive and represent a significant loss of GFR. Rarely, the same etiologic agent may be responsible for both the liver and renal injury. This occurs with certain infections (e.g., leptospirosis, hantavirus) and nephrotoxic agents (Table 66.3). AKI secondary to bile cast nephropathy has been described in obstructive jaundice.

TABLE 66.2 **Causes of Pulmonary-Renal Syndrome**

Immunologic and drug induced	Anti–glomerular basement membrane disease (Goodpasture) Antineutrophil cytoplasmic antibody associated: Granulomatosis with polyangiitis Microscopic polyangiitis Churg-Strauss syndrome Immune complex disease: Lupus IgA-vasculitis Mixed cryoglobulinemia Rheumatoid vasculitis Drugs: Penicillamine Hydralazine Propylthiouracil
Infection	Severe bacterial pneumonia, postinfectious glomerulonephritis, *Legionella,* leptospirosis, hantavirus, infective endocarditis
Pulmonary edema and acute kidney injury	Volume overload in severe left ventricular failure
Multiorgan failure	Acute respiratory distress syndrome and acute kidney injury
Other	Paraquat poisoning; renal vein or inferior vena cava thrombosis with pulmonary emboli

TABLE 66.3 **Causes of Acute Kidney Injury and Liver Disease**

Prerenal azotemia	Diuretic use, gastrointestinal loss, large volume paracentesis, hypoalbuminemia
Hepatorenal syndrome	
Acute tubular necrosis	Hyperbilirubinemia (bile cast nephropathy), sepsis, gastrointestinal hemorrhage
Drugs	Acetaminophen (paracetamol), NSAIDs, tetracycline, rifampicin, isoniazid, anesthetic agents, sulfonamides, anticonvulsants (DRESS syndrome), allopurinol, methotrexate, aspirin (Reyes syndrome)
Infections	Hepatitis C and cryoglobulinemia, hepatitis B and polyarteritis nodosa, leptospirosis, hantavirus, Epstein-Barr virus, gram-negative sepsis, spontaneous bacterial peritonitis
Other	Papillary necrosis, inhalation of chlorinated hydrocarbons, mushroom poisoning *(Amanita phalloides),* carbon tetrachloride

DRESS, Drug rash with eosinophilia and systemic symptoms; *NSAIDs,* nonsteroidal antiinflammatory drugs.

Acute Kidney Injury in Heart Failure (Cardiorenal Syndrome)

The development of AKI in patients with decompensated heart failure is common and is associated with poor prognosis (see also Chapter 72). Reduced renal perfusion secondary to decreased cardiac output has long been considered the primary cause; however, there are

TABLE 66.4 Causes of Acute Kidney Injury in Patients With Cancer

Prerenal	Nausea and vomiting, hypercalcemia, cardiomyopathy secondary to chemotherapy
Vascular	Thrombotic microangiopathy (adenocarcinoma of stomach; cancer of the breast, prostate, lung, or pancreas; radiation nephropathy), renal vein thrombosis secondary to hypercoagulability, disseminated intravascular coagulation (acute promyelocytic leukemia)
Glomerular	Rapidly progressive glomerulonephritis
Acute tubular necrosis	Sepsis and antibiotic nephrotoxicity
Malignant infiltration	Lymphoma, acute lymphoblastic leukemia
Intraluminal obstruction	Tumor lysis syndrome, myeloma cast nephropathy
Postrenal obstruction	Transitional cell carcinoma ureters and bladder, prostatic obstruction, extrinsic ureteral compression (tumor, nodes, retroperitoneal fibrosis)
Chemotherapeutic agents	
Tubular toxicity	Cisplatin, ifosfamide, plicamycin (mithramycin), imatinib, pemetrexed, pentostatin, high-dose bisphosphonates
Thrombotic microangiopathy	Mitomycin C, gemcitabine, cisplatin, calcineurin inhibitors, anti-VEGF therapies
Other mechanisms	Capillary leak syndrome (IL-2 therapy), acute interstitial nephritis (interferon-α, checkpoint inhibitors), intraluminal obstruction (methotrexate)

IL-2, Interleukin-2; *VEGF,* vascular endothelial growth factor.

important contributions from right ventricular dysfunction leading to renal venous hypertension and activation of renin angiotensin and sympathetic nervous systems.[35]

Acute Kidney Injury in the Cancer Patient

Patients with cancer are prone to AKI because of the underlying malignancy and its treatment (see Chapter 65). In a large European population, the incidence of AKI was 18% in the year after cancer diagnosis, and AKI occurs commonly in critically ill cancer patients.[36] Prerenal azotemia is common in cancer patients because of the high frequency of vomiting and diarrhea, and urinary tract obstruction must always be ruled out (Table 66.4). More specific causes of intrarenal AKI are noted in the following sections.

Tumor Lysis Syndrome

Necrosis of tumor cells may release large amounts of nephrotoxic intracellular contents (uric acid, phosphate, xanthine) into the circulation. This usually occurs after treatment of lymphoma (particularly Burkitt) and leukemia, but may occur with solid tumors. Rarely, a spontaneous form of tumor lysis syndrome (TLS) occurs in patients with rapidly growing tumors that have outstripped their blood supply. AKI occurs when crystals of uric acid, calcium phosphate, and xanthine precipitate in the renal tubules causing obstruction and inflammation. Hyperuricemia may contribute to AKI by crystal-independent mechanisms, including renal vasoconstriction, and oxidative injury.[37] Risk factors for TLS include preexisting CKD, bulky and rapidly proliferating tumors, volume depletion, and acidic urine. The AKI is typically oligoanuric, and the condition should be suspected in patients with high lactate dehydrogenase levels suggestive of massive cell lysis. Markedly elevated phosphate and urate levels may be found. Hyperkalemia may be prominent and life threatening. Prevention and therapy of TLS are discussed in Chapter 70.

Hypercalcemia

Hypercalcemia is common in advanced cancer and may result from lytic bone metastases, overproduction of 1,25 dihydroxyvitamin D (predominantly lymphomas), or the production of parathyroid hormone–related peptide. Hypercalcemia causes nausea, vomiting, and polyuria, and AKI in this setting is often driven by volume depletion. Additional mechanisms for hypercalcemia-induced AKI include direct intrarenal vasoconstriction and intratubular obstruction.

Chemotherapeutic Agents

Cisplatin is commonly associated with nonoliguric AKI, and nephrotoxicity is the most common dose-limiting side effect of this drug.[38] Cisplatin accumulates in mitochondria, inhibiting oxidative phosphorylation and resulting in excessive reactive oxygen formation and impairment in ATP generation, leading to cell death. Tubular injury affects both the proximal and distal nephron and clinically may be associated with magnesium wasting, impaired urinary concentration, and, rarely, salt wasting with volume depletion. Prophylaxis against nephrotoxicity includes volume loading and reducing the dose when possible. Although renal impairment may persist after treatment, progressive decline in GFR is unusual. When combined with bleomycin and vinca alkaloids, cisplatin has been associated with thrombotic microangiopathy. The alternative agent carboplatin appears to be less nephrotoxic.

Ifosfamide is a cyclophosphamide analogue with a nephrotoxic metabolite, chloroacetaldehyde. AKI is usually mild, although proximal tubular dysfunction (Fanconi syndrome) and hypokalemia may be prominent and sometimes persistent.

High-dose methotrexate and its metabolites can precipitate within the tubular lumen and cause AKI. Risk factors for drug crystallization include acid urine, volume depletion, impaired GFR, and concurrent nephrotoxin exposure. Aggressive hydration and urinary alkalinization (pH >7.0) can reduce the risk for nephrotoxicity.

Gemcitabine is a nucleoside analogue that causes AKI primarily by damaging the renal endothelium. The most common manifestation is a thrombotic microangiopathy that develops 1 to 2 months after drug completion. AKI is often accompanied by new-onset hypertension or worsening of existing hypertension. Laboratory evidence of systemic hemolysis is common. AKI secondary to thrombotic microangiopathy may be caused by mitomycin and by drugs that inhibit VEGF pathways (e.g., bevacizumab, tyrosine kinase inhibitors).[39]

PD-1 (programmed cell death 1) receptor inhibitors, such as ipilimumab, nivolumab, and pembrolizumab have recently emerged as agents with an increased risk for AKI. Additional chemotherapeutic agents that may cause AKI are listed in Table 66.4.

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SELF-ASSESSMENT QUESTIONS

1. Acute tubular injury predominantly affects which segments of the nephron?
   A. Proximal convoluted tubule and loop of Henle
   B. Proximal tubule and distal convoluted tubule
   C. Loop of Henle and distal convoluted tubule
   D. Distal convoluted tubule and collecting ducts
   E. All tubular segments of the nephron equally
2. What is the most likely mechanism by which nonsteroidal antiinflammatory drugs (NSAIDs) cause acute kidney injury (AKI) in a patient with systolic heart failure?
   A. Impaired efferent arteriole vasodilation
   B. Impaired efferent arteriole vasoconstriction
   C. Impaired tubuloglomerular feedback
   D. Impaired afferent arteriole vasodilation
   E. Impaired afferent arteriole vasoconstriction
3. Which of the following nephrotoxic agents causes AKI predominantly by the formation of intratubular crystals?
   A. Cisplatin
   B. Methotrexate
   C. Gentamicin
   D. Amphotericin
   E. Tacrolimus
4. How does tubular injury (acute tubular necrosis) cause a drop in glomerular filtration rate?

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Acute Kidney Injury in the Tropics

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The tropics span the area on either side of the equator (approximately 23 degrees north to 23 degrees south). Approximately 40% of the world population lives in the tropics, and this proportion is expected to rise to 60% by 2060.[1] Tropical countries have high sociopolitical and economic heterogeneity. The same country may have poor underdeveloped areas that lack basic public health infrastructure and also wealthy regions with sophisticated health facilities.

Acute kidney injury (AKI) epidemiology in the tropics is heavily influenced by these dissimilarities. In large cities and tertiary hospitals, AKI patient characteristics are similar to those found in high-income countries in nontropical areas and the principal causes of AKI are ischemia, principally secondary to sepsis, and drug nephrotoxicity. In contrast, in remote small urban areas, in poor and vulnerable neighborhoods of large cities, and in rural zones, AKI is frequently community-acquired and affects previously healthy young individuals. Poverty, malnutrition, lack of sanitary infrastructure, deficient public health system, and uncontrolled urbanization are frequent problems that add significantly to the disease burden. In those settings, infectious diarrhea linked to unsafe drinking water and poor hygiene, tropical infectious diseases, envenomation by snakes or arthropods, use of natural medicines, and poor obstetric care are common causes of AKI. A strong seasonal variation in the incidence of AKI occurs in the tropics, with a spike during and immediately after the rainy seasons. Heavy precipitation leads to conditions favorable for survival of organisms causing or transmitting infectious diseases and forces venomous snakes out of their flooded burrows, making accidents more likely.[1,2] Although epidemiologic data for community-acquired AKI in tropical countries are limited, some authors showed a high frequency and high early mortality for these patients.[3,4] Access to renal replacement therapy (RRT) is frequently limited because of nonavailability or high costs.[3-5]

There is regional variability in the cause of AKI in the tropics. Malaria, leptospirosis, diarrheal diseases, and venomous snakebite are common causes in South Asia. Malaria, diarrheal diseases, obstetric accidents, and indigenous herbal remedies are frequent causes in Africa. Malaria, leptospirosis, dengue fever, animal envenomation, and obstetric complications are important causes in Latin America.[1-5] AKI associated with rhabdomyolysis and dehydration secondary to heat stroke and/or prolonged strenuous work in an unhealthy environment may occur.[6] The long-term morbidity, mortality, and economic weight of tropical disease–associated AKI are nearly unknown.

SNAKEBITE

Snakebite is a neglected public health occupational hazard. Economically deprived populations living in rural communities are affected disproportionately.[7] It has been suggested that there are 0.5 to 2 million cases of envenomation from snakebite (20,000 to 94,000 deaths) annually, with the highest burden in South and Southeast Asia, Latin America, and sub-Saharan Africa.[8] This is likely an underestimate because the data are based on hospital admissions.

Kidney injury may develop after bites by hematoxic or myotoxic snakes belonging to Viperidae and Elapidae families, such as Russell viper, saw-scaled viper, puff adder, rattlesnake, tiger snake, green pit viper, *Bothrops, Lachesis, Crotalus,* boomslang, gwardar, dugite, *Hypnale, Cryptophis,* and sea snakes. AKI is more frequent after Russell viper bites (Fig. 67.1) in Asia and *Bothrops* or *Crotalus* bites in Latin America.[1,2,9-11] The prevalence is higher in children, probably because of the higher venom dose in relation to the body size.[1,2]

Clinical and Laboratory Features

Clinical manifestations depend on the nature and injected dose of venom. Local pain, swelling, blistering, ecchymosis and tissue necrosis at the bite site, and coagulation abnormalities leading to bleeding diathesis are frequent in Russell viper and *Bothrops* bites (Figs. 67.2 and 67.3). Neurotoxicity (manifested by paralysis) and rhabdomyolysis (manifested by myalgia and cola-colored urine) may occur after sea snake and *Crotalus* bites.[1,2,9-12] Other uncommon clinical manifestations include myocardial injury and hypopituitarism.[13,14]

AKI develops within a few hours (snake venom concentrates in kidney minutes after the bite) to as late as 96 hours after the accident.[1,2,9-11] The AKI is usually oliguric and catabolic; rapid increases in serum creatinine and potassium are usual. Oliguria generally lasts for 1 to 2 weeks, and its persistence suggests the likelihood of acute cortical necrosis, which can be confirmed by renal biopsy or a contrast-enhanced computed tomography scan.[1,2,9-11] Proteinuria and hematuria have been described and may reflect differences in venom composition.[10] Although kidney function usually recovers, AKI-associated snakebite has been associated with chronic kidney disease (CKD) in both adults and children on long-term follow-up.[15,16] AKI after snakebite may aggravate renal dysfunction in agrochemical nephropathy.[17]

Laboratory investigation may disclose hemolysis (elevated free serum hemoglobin and lactate dehydrogenase and reduced haptoglobin), along with hypofibrinogenemia; reduced factors V, X, and XIIIA; protein C and antithrombin C; and elevated fibrin degradation products. Rhabdomyolysis may be indicated by raised creatinine phosphokinase, hyperphosphatemia, and hyperuricemia. Other findings include leukocytosis and elevated hematocrit as a result of hemoconcentration.[1,2,9-11]

Pathology

Grossly, the kidneys may have petechial hemorrhages. Acute tubular cell injury ranging from mild changes to overt tubular necrosis, with hyaline or pigment casts, variable degree of interstitial edema and

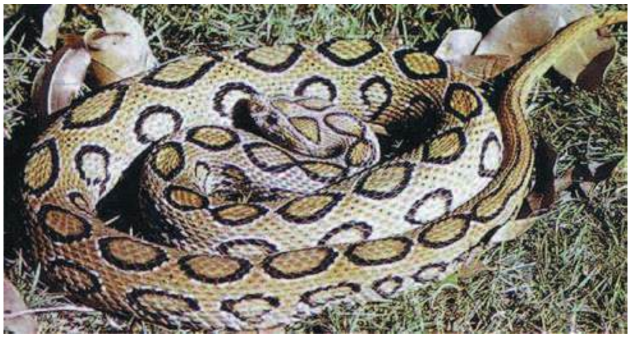

Fig. 67.1 Russell viper. This large snake is an important cause of venomous snakebite–induced acute kidney injury in Asia.

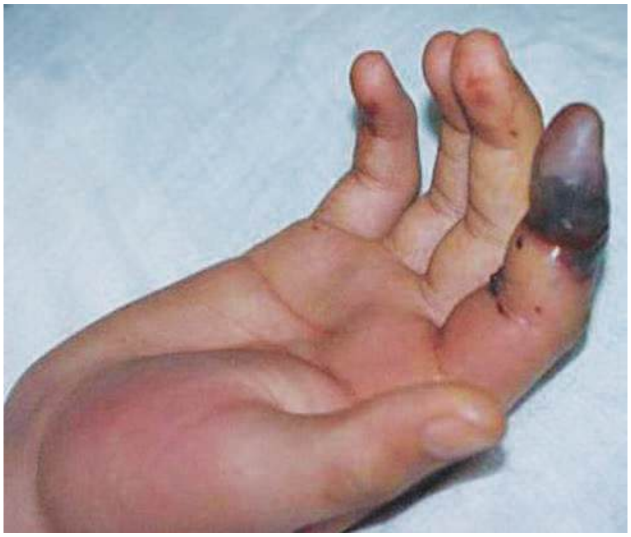

Fig. 67.2 Necrotic finger injury after *Bothrops* snakebite. (Courtesy Carlos A. C. Mendes, São José do Rio Preto, Brazil.)

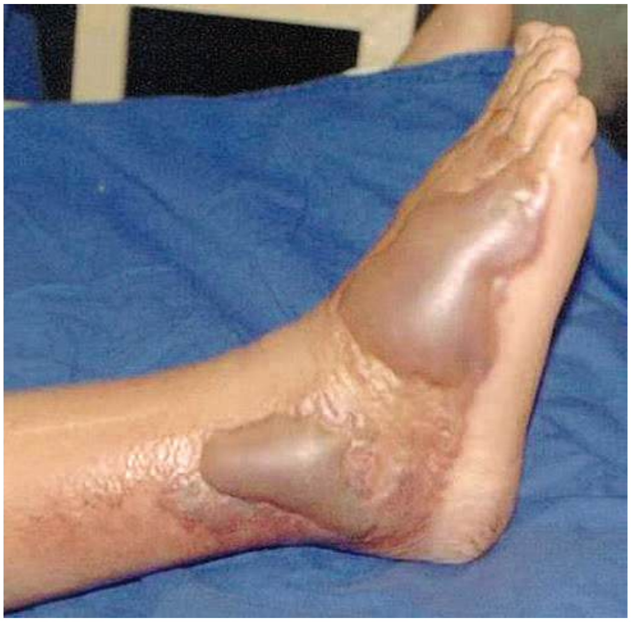

Fig. 67.3 Hemorrhagic blister developing a few hours after *Bothrops* snakebite. (Courtesy Carlos A. C. Mendes, São José do Rio Preto, Brazil.)

infiltration, and scattered hemorrhages, which usually are found on light microscopy. Mesangiolysis may occur (especially with *Crotalid* envenomation), and blood vessels may show fibrin thrombi. Electron microscopic findings include dense intracytoplasmic bodies representing degenerated organelles in the proximal tubules and electron-dense mesangial deposits. Less common findings are acute interstitial nephritis, necrotizing vasculitis, and proliferative and crescentic immune-complex glomerulonephritis (GN). Acute cortical necrosis is seen in about 20% to 25% of cases after Russell viper and *Echis carinatus* bites and has been described after *Bothrops* bites.[1,2,9-11]

Pathogenesis

Snake venom is a mixture of enzymes, toxins, peptides, carbohydrates, lipids, metals, biogenic amines, and nucleotides. Several factors are potentially involved in kidney injury, including direct tubular toxicity, hemodynamic instability, hemolysis, rhabdomyolysis, systemic inflammation, coagulation abnormalities causing glomerular deposition of microthrombi, oxidative stress, hyperuricemia, release of cytochrome c, and apoptosis of tubular epithelial cells.[1,2,9-11,18-21]

Management

The basic therapeutic approach is the same as that for AKI related to any cause (see Chapters 70 and 71). Key steps for reducing morbidity and mortality include early administration of specific monovalent antivenom, appropriate volume replacement, maintenance of adequate urine output, correction of electrolyte imbalance, administration of tetanus immunoglobulin, and treatment of infections.[1,2,9-11,18] Locally available polyvalent antivenom is effective against envenoming by multiple snakes or unknown snakes.[22] Nonavailability of antivenom in rural hospitals and poor infrastructure that hampers transportation to health centers delay administration of antivenom and contribute to high mortality.[1,2,9-11,23] Limited availability and the risk for side effects have encouraged the exploration of alternatives for antivenom therapies, but to date none have shown efficacy.[24]

ARTHROPODS

Bees

Hundreds of simultaneous bee stings causes a multifaceted clinical picture, comprising intravascular hemolysis; rhabdomyolysis; low platelet count; coagulation disorders and bleeding; cardiovascular, hepatic, and pulmonary injury; and severe AKI, with mortality up to 16%.[1,25,26] Similarly, AKI can follow multiple stings from wasps, yellow-jackets, or hornets.[26] The potential mechanisms include direct venom nephrotoxicity, intrarenal vasoconstriction, hemoglobinuria, myoglobinuria, hypotension, thrombotic microangiopathy,[27] and inflammatory and oxidative stress pathways activation.[28] Renal histologic examination usually shows acute tubular necrosis (ATN).[1,25,27] The high morbidity and lethality of massive bee attacks has prompted the development of equine serum antivenom, which was effective in protecting against rhabdomyolysis and hemolysis in mice.[29]

Caterpillars

Accidents with caterpillars of the genus *Lonomia* produce severe hemorrhagic disorders, characterized by both fibrinolytic and disseminated intravascular coagulation–like activity.[25] Severe and prolonged AKI, with some patients evolving to CKD, has been reported after *Lonomia obliqua* (Fig. 67.4) bites.[25,30,31] Availability of *Lonomia* antivenom has led to an apparent decrease in the number of severe cases in Brazil.[30] Early antivenom administration in rats prevented *Lonomia* venom–induced hemorrhagic manifestations and renal dysfunction.[32] The AKI involves glomerular deposition of fibrin, intravascular hemolysis, direct venom

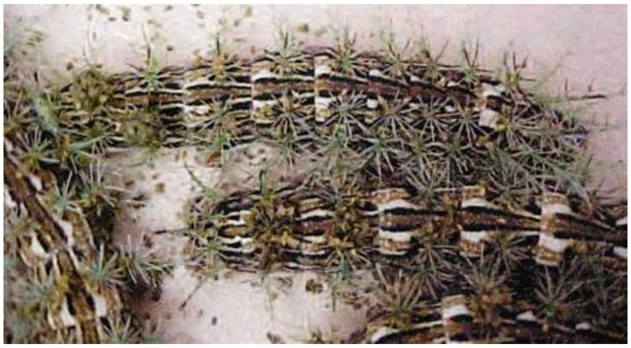

Fig. 67.4 ***Lonomia obliqua*** **caterpillars.** Each hair works as a miniature hypodermic needle to inject the hemolymph, which contains powerful venom that is able to induce severe coagulation system changes. (Courtesy Elvino J. G. Barros, Porto Alegre, Brazil.)

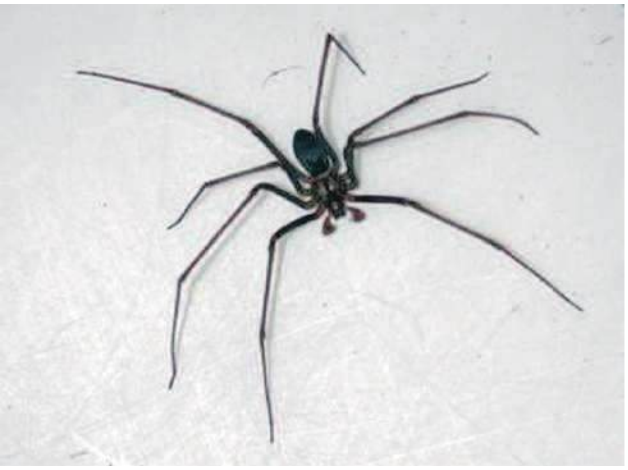

Fig. 67.5 ***Loxosceles*** **spp. (brown recluse spider).** (Courtesy Katia C. Barbaro, São Paulo, Brazil.)

nephrotoxicity, activation of the endothelial cell inflammatory pathway, increased renal expression of proteins involved in cell stress, heme-induced oxidative stress, coagulation, and complement system activation.[33] Kidney histologic findings include ATN, ischemia, and tubular atrophy.[31,33]

Loxosceles

Spiders of the genus *Loxosceles* (Fig. 67.5) can cause local necrosis at the bite site (Fig. 67.6), intravascular hemolysis, rhabdomyolysis, coagulation abnormalities, and AKI.[25] Even patients with mild cutaneous lesions may develop severe hemolysis and AKI, which is the main cause of death after these accidents. AKI pathogenesis has been related to massive intravascular hemolysis, renal vasoconstriction, direct nephrotoxicity, and rhabdomyolysis.[25,34] Renal histologic examination shows pigment-induced ATN.[34] Antivenom is likely the most effective therapy against AKI, but its use is frequently delayed because the bite goes unnoticed.

Scorpions

Scorpion venom causes autonomic overactivity and massive discharge of vasoactive substances and inflammatory cytokines.[35] The venom concentrates rapidly in kidney tissue. Scorpion venom–associated AKI is rare.[36,37] Mechanisms causing AKI are probably renal vasoconstriction, hemodynamic instability, rhabdomyolysis, systemic inflammation, and direct venom nephrotoxicity.[35-39] Renal histologic abnormalities include ATN, glomerular changes, interstitial infiltrates, thrombotic microangiopathy, and cortical necrosis.[35,36,38,39] A Mexican study suggests that scorpion envenomation can lead to CKD in children.[40]

NATURAL MEDICINE

Herbs and indigenous remedies are widely used in poor societies living in the tropics, and are an important cause of AKI, especially in sub-Saharan Africa. This is discussed in Chapter 76.

MALARIA

Five species of *Plasmodium* parasites (*falciparum, vivax, malariae, ovale,* and *knowlesi*) cause malaria. Globally, malaria afflicts over 200 million people annually, causing nearly 500,000 deaths, mostly in children with *P. falciparum.* The incidence of *P. knowlesi* infection is increasing in Southeast Asia, predominantly in Sarawak, Malaysia. The contribution of malaria as the cause of AKI among different geographical areas ranges from 2% to 39%. The frequency of AKI in *P. falciparum* malaria might reach 60%, and in *P. vivax* malaria varies from 10% to 19%.[41] Using Kidney Disease: Improving Global Outcomes (KDIGO) criteria, the frequency of malaria-associated AKI is higher than using the World Health Organization (WHO) criteria.[42] *P. malariae, P. knowlesi,* and *P. ovale*–induced AKI are less common. In this chapter, we focus on *P. falciparum* malaria–associated AKI.

Pathophysiology

The characteristics of the different species of parasite influence the pathogenesis and clinical manifestations of malaria. *P. vivax, P. ovale,* and *P. knowlesi* infect young erythrocytes, and *P. malariae* infects aging cells. *P. falciparum* infects erythrocytes of all ages, producing a higher number of merozoites (Fig. 67.7). Heavy parasitemia is therefore commonly observed in *P. falciparum* malaria, creating adverse effects on the microcirculation. *Plasmodium* parasites primarily infect erythrocytes, with secondary effects on the microcirculation and immune system. Parasitized erythrocytes play a major role in the pathophysiologic process of the disease through decreased erythrocyte deformability and sequestration, knobs and rosette formation, cytoadherence, and changes in membrane transport and permeability (Fig. 67.8). The presence of knobs on parasitized erythrocyte membranes and cytoadherence between parasitized erythrocytes and vascular endothelial cells are characteristic of *P. falciparum* malaria. Cytoadherence of mature *P. vivax* parasitized erythrocytes to vascular endothelial cells involves intercellular adhesion molecule-1, CD36, endothelial protein C receptor, platelet endothelial cell adhesion molecule, and chondroitin sulfate A receptors.[43] *P. vivax*–caused cytoadherence is lower than that of *P. falciparum*–infected erythrocytes. As in other infectious diseases, several proinflammatory cytokines (tumor necrosis factor, interleukins 1, 6, and 8, interferon-γ) and vasoactive mediators are released. The renin-angiotensin-aldosterone-system is also stimulated. Hemodynamic changes in malaria are similar to those of bacterial sepsis, including decreased systemic vascular resistance, hypervolemia, increased cardiac output, and increased renal vascular resistance. Because of increased vascular permeability, the initial hypervolemia is followed by hypovolemia and decreased cardiac output, with decreased renal blood flow and glomerular filtration rate (GFR). Increased blood viscosity, intravascular coagulation, hemolysis, rhabdomyolysis, jaundice, fever, lactic acidosis, complement activation, and reactive oxygen species further compromise renal blood flow. Activation of poly (ADP-ribose) polymerase by peroxynitrite and free radicals decreases oxygen utilization.

AKI in malaria is ischemic and hypoxic in origin and usually occurs with heavy parasitemia, intravascular coagulation, intravascular hemolysis,

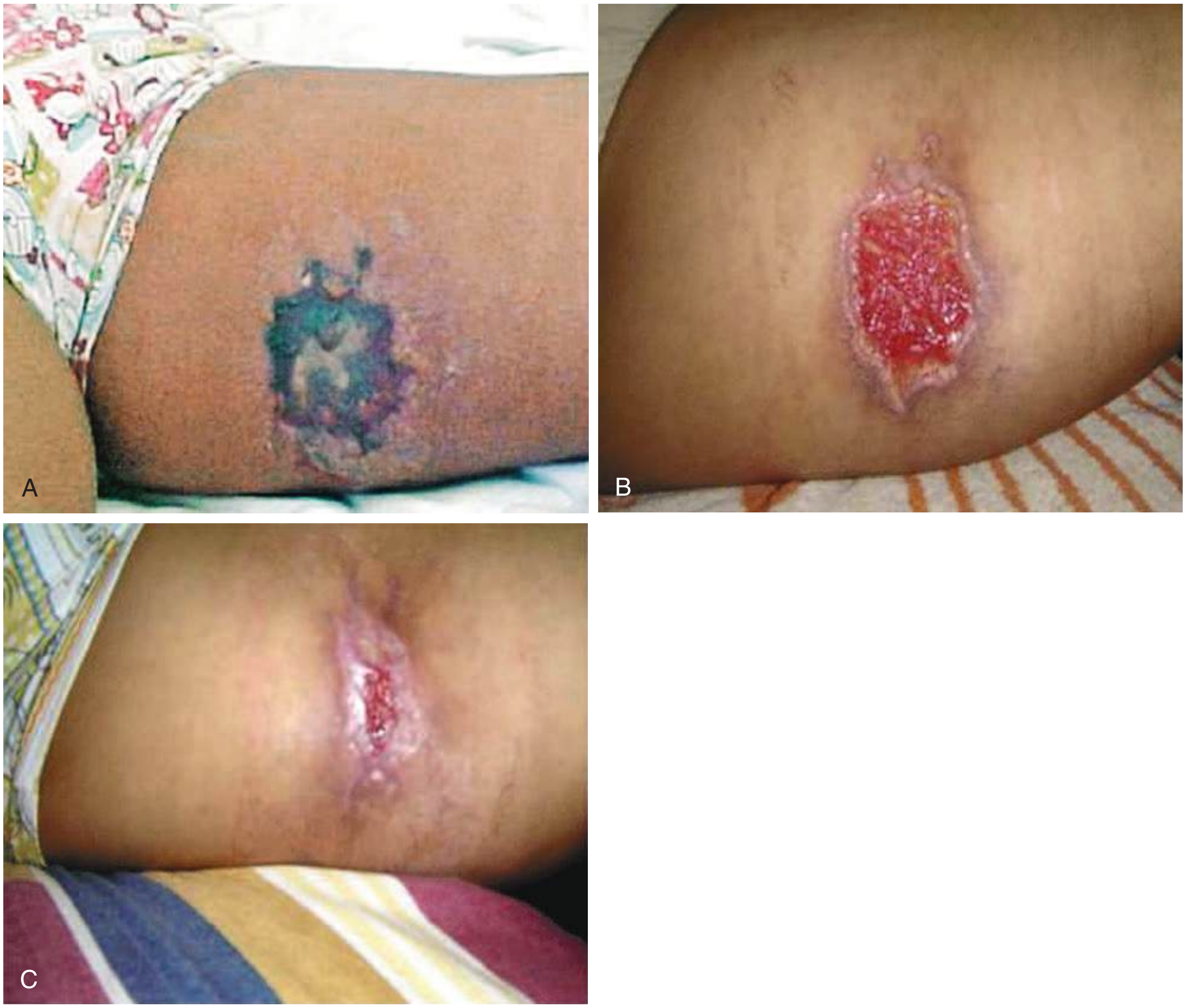

Fig. 67.6 Local necrotic injury in the left leg of a female patient after *Loxosceles* bite. (A) At 4 days after the bite. (B) At 60 days after the bite. (C) At 3 months after the bite. (Courtesy Carlos A. C. Mendes, São José do Rio Preto, Brazil.)

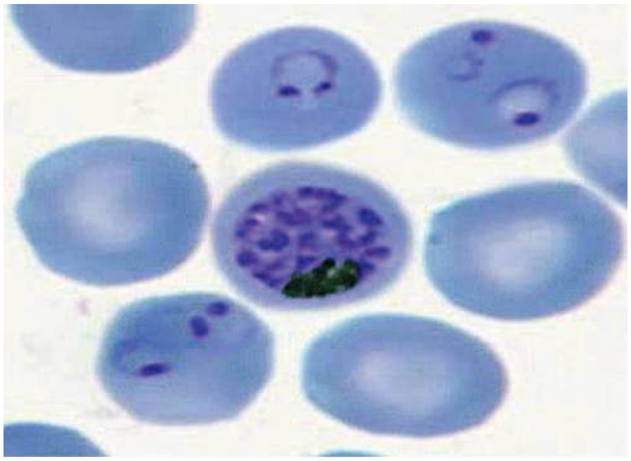

Fig. 67.7 Ring form and merozoites of *Plasmodium falciparum* in infected erythrocytes.

or rhabdomyolysis.[41] Immune responses in malaria involve Th1 and Th2 activation. Immune complex GN can occur (see Chapter 55). Tubular changes vary from cloudy swelling to tubular degeneration with tubulorrhexis in the patient with AKI (Fig. 67.9). Bile and hemoglobin casts and Tamm-Horsfall protein are present in the tubular lumen. Interstitial mononuclear infiltration and edema can occur. Thrombotic microangiopathy and cortical necrosis have been reported.[44,45] Malarial antigens are occasionally seen along the glomerular endothelium and medullary capillaries. Adhesion molecules and proinflammatory cytokines are overexpressed in the vascular endothelium and proximal tubules.[41]

Clinical Manifestations

Malarial AKI affects predominantly nonimmune adults, mostly infected by *P. falciparum*. Reports link *P. vivax* infection with acute respiratory distress syndrome (ARDS), severe AKI, and thrombotic microangiopathy.[44] Mixed *Plasmodium* infections and comorbidities related to sepsis are likely important contributing factors to AKI. Constitutional symptoms include fever, chills, headache, prostration, and occasionally jaundice. The urinalysis usually shows few erythrocytes, leukocytes, and granular casts and proteinuria, often less than 1 g/24 hours.

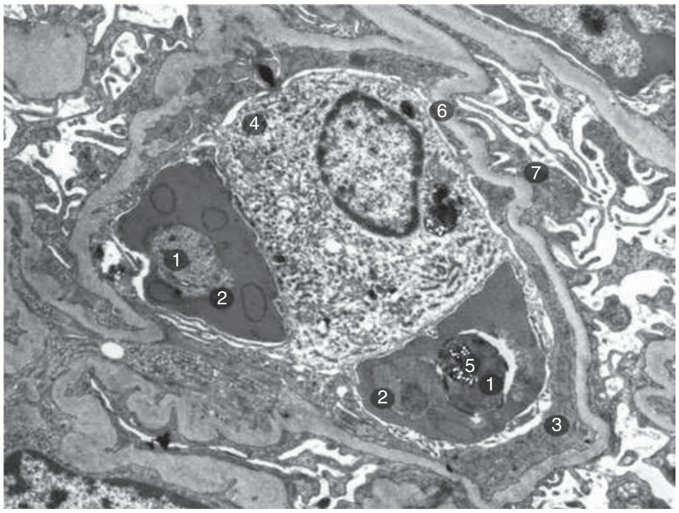

Fig. 67.8 A transmission electron micrograph from the kidney of *P. falciparum* malaria showing sequestration of two parasitized red blood cells *(2)* within a glomerular capillary. Malarial pigment *(5)* is seen in a phagocyte *(4)*. *(1) P. falciparum. (3)* Glomerular endothelial cell. *(6)* Glomerular basement membrane. *(7)* Podocyte. (Courtesy Dr. Emsri Pongponratn, Faculty of Tropical Medicine, Mahidol University.)

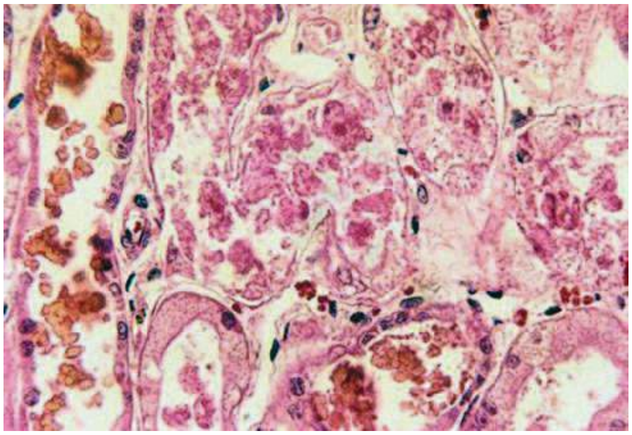

Fig. 67.9 Acute tubular necrosis in *Plasmodium falciparum* malaria.

Hemoglobinuria happens in the patient with intravascular hemolysis, frequently associated with glucose-6 phosphate dehydrogenase deficiency. Rhabdomyolysis with myoglobinuria can be observed. Fluid and electrolyte changes are common in malaria.[41,46] Hyponatremia, usually asymptomatic, is observed in 67% of patients, is related to the severity of malaria, and resolves within a few days after antimalarial treatment. The causes of hyponatremia are multiple, including increased antidiuretic hormone with water retention, intracellular shift of sodium as a result of decreased Na^+,K^+-ATPase activity, and sodium depletion. Hypernatremia is uncommon, indicates hypothalamic lesions with diabetes insipidus, and is associated with unfavorable prognosis. Hypokalemia secondary to respiratory alkalosis occurs in 20% to 40% of patients with uncomplicated cases. Hyperkalemia is observed in patients with intravascular hemolysis, rhabdomyolysis, and/or AKI. Hypocalcemia with prolonged QTc interval occurs in 45% of severe malaria cases and resolves when infection is controlled.[46] Decreased activities of Na^+,K^+-ATPase, Ca^{2+}-ATPase, and parathyroid hormone are considered the main causes for hypocalcemia. Hypophosphatemia secondary to respiratory alkalosis is observed in 6% to 30% of the patients. Hypomagnesemia is seen in 30% of patients.[46] Downregulation of sodium channels on the apical membrane of alveolar epithelial cells and increased vascular permeability account for the development of pulmonary edema and ARDS.[47]

Malarial AKI is characterized by a rapid increase in SCr and is often associated with cholestatic jaundice. Risk factors for AKI include high parasitemia, deep jaundice, high liver enzyme values, thrombocytopenia, decreased diastolic blood pressure, retinopathy, and ARDS. Hemolytic uremic syndrome has been described. Severe acidosis-associated lactic acidemia, hypoglycemia, and central nervous system symptoms are observed in severe malaria. Malarial AKI with multiple organ involvement and papilledema carries an unfavorable prognosis. AKI duration ranges from 1 to several weeks and is oliguric in 60% of the patients. Quinine and artesunate are the antimalarial agents most commonly used. The first choice in malarial AKI is artesunate, because it has high efficacy and does not need adjustment for renal function. Early and frequent RRT (hemodialysis or peritoneal dialysis) is lifesaving.[41] Continuous venovenous hemofiltration yields good results in patients with multiorgan involvement, especially those with pulmonary edema or ARDS.[41] Exchange blood transfusion and erythrocytapheresis are adjunctive for the patient with heavy parasitemia.[48] The mortality rate of malarial AKI ranges from 10% to 50%. Kidney function may not recover completely in severe AKI, evolving to CKD in 7% of malaria-induced AKI.

LEPTOSPIROSIS

Leptospirosis, the world's most common zoonosis, is caused by *Leptospira* genus spirochetes. The WHO included leptospirosis as a reemerging infectious disease in both developed and developing areas, and cases have been increasingly reported in developed countries.[49] Wild and domestic mammals (rodents, dogs, pigs, cattle, horses) are the disease vectors. The infection is transmitted accidentally to humans through broken skin or mucosal membranes exposed to water or soil contaminated with organisms shed in the urine from the natural vectors.[1,2,50] Leptospirosis is a job-related threat for rodent exterminators, slaughterhouse workers, farmers, pet traders, veterinarians, garbage collectors, and sewer workers.[50]

Human leptospirosis is endemic in many tropical countries and usually reaches epidemic levels after heavy rainfall and flooding, or natural disasters, such as hurricanes or earthquakes. There is an annual global estimate of 1 million cases, with 58,900 fatalities, about half among young adult males.[51] A high seroprevalence of anti-*Leptospira* antibodies has been found in the general asymptomatic population in tropical countries, ranging from 18% to 33%. As many as 29% of wild small animals in the Peruvian Amazon were found to be infected by leptospiras.[1,2,50]

L. interrogans, the only parasitic species, is mobile, aerobic, and unstained by the Gram method. Its endotoxins primarily affect tubulointerstitial cells. The bacterial outer membrane contains lipopolysaccharide, cytotoxic glycolipoprotein (GLP), and lipoproteins (LipL), especially LipL 32, which is immunogenic. Because leptospiras have special tropism for the kidneys, the effect of GLPs on tubular Na^+,K^+-ATPase activity is potentially involved in the AKI cellular pathophysiology,[52] in the urinary concentrating defects, and in the paradoxical hypokalemia frequently seen in these patients.[1,2,50,52] Glycocalyx and endothelial injury caused by spirochete membrane proteins also may contribute to AKI.[53]

Kidney involvement is almost universal in leptospirosis, but becomes relevant in Weil disease, the most severe form of leptospirosis, which is characterized by multiorgan involvement, with diffuse alveolar hemorrhage, pulmonary edema, ARDS, or a combination of these features, accompanied by AKI and a high mortality rate.[50] Leptospirosis-associated AKI incidence of varies from less than 10% to more than 80%, and its severity is associated with increasing mortality.[54,55] Oliguria, jaundice, arrhythmias, thrombocytopenia, elevated baseline SCr, and urinary neutrophil gelatinase–associated lipocalin (NGAL) levels have been associated with AKI development.[54,56] AKI is typically nonoliguric and associated with hypokalemia.[1,2,50] Tubular changes characterized by high urinary fractional excretion of sodium and potassium precede reduced GFR, which could explain the high frequency of hypokalemia.[50] Long-term follow-up of leptospirosis-associated AKI found late development of CKD and presence of tubular function abnormalities.[57-59]

Antibiotics of the penicillin group are considered the basis of treatment, but their efficacy remains unproven.[50,60] Treatment recommendations include a high RRT dose, conservative fluid intake, and approaches to minimize lung injury.[50]

HEMORRHAGIC FEVERS

Viral hemorrhagic fevers (VHFs) are caused by RNA viruses of four different families *(Flaviridiae, Arenaviridae, Bunyaviridae, Filoviridae).* Dengue, Rift Valley fever, yellow fever, and Crimean-Congo virus can be acquired by bites from infected arthropods, by inhalation of infected rodent excreta particles (Lassa, Junin, Machupo, Hantaan virus), or through contact with contaminated material (Ebola virus). The clinical picture includes fever, malaise, increased vascular permeability, and coagulation abnormalities that may lead to bleeding. Dengue and yellow fever are the most prevalent forms of VHF in the tropical regions.[1,2,61]

Dengue Fever

Dengue is an acute febrile disease caused by an arbovirus transmitted primarily by mosquitoes, with usually a benign evolution. The main dengue vector is the female *Aedes aegypti* mosquito. Dengue is currently the most important urban arboviral disease. The number of yearly infections is estimated at 390 million.[62]

Several factors account for the rising incidence and widespread occurrence of dengue such as climate changes (global warming, intensity and duration of rain season, hurricanes), ecosystem modifications, demographic increases, uncontrolled urbanization, and human migration. There are four serotypes of antigenically related dengue *flavivirus* (DEN 1 to DEN4), but immunity to one does not confer enduring immunity to another. The introduction of a new serotype in a determinate area accounts for the occurrence of epidemics and the hemorrhagic fever dengue form, which is a more severe form of the disease that may be lethal.[63] A new serotype of dengue virus was recently discovered in Malaysia.[64]

Dengue virus infection may manifest as undifferentiated fever, dengue fever, dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Common clinical manifestations of dengue fever are high fever, myalgia, arthralgia, retroocular pain, headache, anorexia, nausea, vomiting, and a cutaneous rash similar to measles or rubella. DHF and DSS are severe forms of the disease, characterized by fever, hemorrhage, thrombocytopenia, and evidence of plasma leakage (increased hematocrit, pleural effusion, ascites, and hypoalbuminemia), mental disorientation, breath shortness, tachycardia, shock, and death.[63]

Kidney involvement in dengue includes AKI, proteinuria (sometimes nephrotic), GN (see Chapter 55), hemolytic uremic syndrome, and electrolyte abnormalities.[63,65] The frequency of dengue-associated AKI varies from 1% to approximately 30%, and its development and severity are related to poor prognosis.[63,66,67] Dengue-induced AKI is usually associated with shock, hemolysis, and/or rhabdomyolysis,[63,68] but may occur without any of these triggers, and is described in all forms of dengue.[63] Risk factors for AKI comprise increased hepatic enzymes, hypoalbuminemia, reduced serum bicarbonate, other simultaneous viral or bacterial infection, multiple organ dysfunction, use of inotropic or nephrotoxic drugs, increased age, obesity, dengue severity, rhabdomyolysis, presence of diabetes mellitus, and delayed hospitalization.[63,69]

There is no specific treatment for dengue fever. Therapy is mostly supportive, avoiding the use of aspirin and nonsteroidal antiinflammatory drugs.

Yellow Fever

Yellow fever is a noncontagious infectious disease that is endemic in tropical Africa, South America, and Panama. The yellow fever virus is part of the *Flavivirus* genus (Flaviviridae family).[61] Yellow fever is transmitted to humans by blood-eating insect bites, especially by the *Aedes* and *Haemagogus* genera. There are two cycles, termed *sylvatic* and *urban*. The sylvatic cycle affects sporadic individuals who get in contact with the vectors when performing economic or recreational activities in infested forests. The urban cycle is characterized by virus transmission through *A. aegypti* to individuals living in urban areas. The urban cycle was eliminated in the Americas from the 1940s to 1950s, but its resurgence was recently documented in Bolivia. The movement of viremic individuals to cities with high vector populations can potentially generate explosive urban epidemics affecting thousands of nonvaccinated people.[61] There is no evidence of yellow fever in Asia, despite an extensive presence of vectors.[70] It is possible that the hyperendemicity of dengue in Southwest Asia has afforded protection because of cross-reactive antibodies.

Yellow fever infection might be asymptomatic, cause moderate febrile disease, or be severe, causing hemorrhagic fever, liver failure, AKI, and death. Most patients (85%) fully recover after 3 to 4 days and become permanently immunized against the disease. About 20% develop the severe form, with mortality of up to 50%.[61] After 3 to 6 days of incubation, the clinical picture of yellow fever starts abruptly with high fever, chills, anorexia, myalgia, headache, vomiting, and bradycardia. Hemorrhagic manifestations may occur. There is then a remission period with symptom improvement, and mild cases do not have any further manifestation. In the severe forms fever recurs, followed by vomiting, epigastric pain, and jaundice, the so-called intoxication phase. There are large increases in transaminases and bilirubin, and leukopenia and ST segment abnormalities may develop. Hemorrhagic events associated with hepatic damage and consumptive coagulopathy can occur, such as hematemesis, melena, petechiae, bruises, mucosal bleeding, and metrorrhagia in women. Microcirculatory thrombosis, disseminated intravascular coagulation, tissue anoxia, oliguria, and shock may follow.[61]

Yellow fever–associated AKI occurs usually after 5 days of disease in the severe forms and may evolve to anuria and ATN, with increased mortality. In Africa, AKI is observed earlier, without jaundice or liver abnormalities, with higher mortality. AKI mechanisms are poorly understood. Renal ischemia, intravascular coagulation, shock, bilirubin-induced renal tubule cell toxicity, virus direct effect on renal tissue, and intense inflammatory cytokine discharge are likely mechanisms of AKI.[71,72]

Ebola Virus Disease

Ebola virus belongs to the Filoviridae family and has caused several outbreaks of Ebola virus disease (EVD) in Central and West Africa in the last several years, with high morbidity and mortality. The virus is transmitted from individual to individual through mucous membrane contact with contaminated body fluids or tissue. Like other VHFs, the initial clinical picture of EVD is unspecific (fever, weakness, arthralgias, muscle pain, headache). The disease evolves to anorexia, nausea and vomiting, abdominal pain, intense diarrhea, electrolyte unbalance, hemodynamic instability, and multisystem organ failure, including ARDS and AKI. In the most recent outbreak, critically ill patients treated early and adequately by experienced teams in well-provided tertiary health care settings experienced strikingly lower mortality. Some of them developed anuric AKI and needed RRT. Because there is no effective Ebola virus–specific therapy, the big challenge is how to prevent and treat the complications of EVD, including AKI, in low-resources settings.[73-76]

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68

Diagnosis and Clinical Evaluation of Acute Kidney Injury

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The term *acute renal failure* (ARF) describes the clinical syndrome in which an abrupt (hours to days) decrease in renal function leads to the accumulation of nitrogenous waste products and, commonly, a reduction in urine output. *Acute kidney injury* (AKI) has become the consensus term for ARF.[1-3] This change in terminology served to standardize a definition for the syndrome as well as incorporate knowledge that increases in serum creatinine as small as 0.3 mg/dl (27 µmol/l) are associated with increased morbidity and mortality.[4]

In 2012 the Kidney Disease: Improving Global Outcomes (KDIGO) guideline unified the definition of AKI and included stages of severity (Table 68.1). AKI has since been defined as an increase in serum creatinine of 0.3 mg/dl or more within 48 hours of observation or 1.5 times baseline or greater, which is known or presumed to have occurred within 7 days, or a reduction in urine volume below 0.5 ml/kg/h for 6 hours.[1] Subclassification of AKI based on disease severity as indicated by the level of increase in serum creatinine and reduction in urine output has been adopted as a three-stage classification by KDIGO. Increasing severity of AKI based on creatinine and urine output associates with increased risk for death.[1]

Mortality rates for patients with AKI in the intensive care unit (ICU) remain high, 17% in stage 1 and 28% in stage 2 to 3.[5,6] Even after adjusting for risk factors, odds ratios for mortality of such patients were: stage 1, 1.68 (0.89-3.17, confidence interval [CI] 95%); stage 2, 2.95 (1.38-6.88, CI 95%); and stage 3, 6.88 (3.88-12.23, CI 95%).[7] In a large population of hospitalized adults, AKI severity was directly associated with increased hospital mortality, lengthened hospital stay, and higher overall cost. The associations were present for changes in serum creatinine as low as 0.3 mg/dl.[4] Patients with AKI who survive hospitalization also have an increase in long-term mortality, with an adjusted relative risk for mortality of 1.4, which is amplified with increasing AKI stage.[8] Furthermore, AKI survivors are at increased risk for developing comorbidities, including chronic kidney disease (CKD).[9]

There are many different causes of AKI, and most are identified through clinical investigation. Globally, hypotension and volume contraction or dehydration accounted for 40% of AKI cases in both the hospital and nonhospital setting.[10] In higher income countries, hypotension and shock was the most common cause of AKI, whereas volume contraction or dehydration predominated in lower income countries. Nephrotoxic agents were implicated in up to a quarter of AKI events across all countries.[10] However, nephrotoxin administration may account for a larger proportion of hospital-acquired AKIs in older patients.[11,12] Kidney biopsy is rarely performed to establish the cause of AKI. In an observational study of 745 patients with AKI in the ICU, 3% (22 patients) underwent kidney biopsy, and, as expected, glomerulonephritis (GN) and acute interstitial nephritis (AIN) were each diagnosed in about a third of the biopsy specimens and about 23% showed only acute tubular necrosis (ATN).[6]

EARLY DETECTION OF ACUTE KIDNEY INJURY

The definition of AKI is based on increases in serum creatinine, yet when used as a marker of renal function, serum creatinine concentrations have multiple limitations. In addition to a steady-state balance of creatinine production and excretion being required for appropriate estimation of glomerular filtration rate (GFR), serum creatinine concentrations may not rise for subtle declines in GFR and are slow to rise for rapid falls in GFR. Furthermore, the generation of creatinine from muscle is reduced in sepsis-induced AKI, and serum creatinine concentrations may not increase proportionally to GFR decline.[13] A window of time exists in which kidney injury goes undetected until serum creatinine concentrations rise (8 to 48 hours) (Fig. 68.1).[14] Novel serum and urine biomarkers with potential as early indicators of AKI include tissue inhibitor of metalloproteinase 2 (TIMP-2), insulin-like growth factor–binding protein 7 (IGFBP7), hepcidin, kidney injury molecule 1 (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL), cystatin C, interleukin-18 (IL-8), and others. They also may allow for improved prognostication and insight into the specific cause of AKI.

Fig. 68.2 depicts the continuum of kidney injury severity and a number of biomarkers. Serum cystatin C, a cysteine protease inhibitor that is freely filtered at the glomerulus and normally reabsorbed by proximal tubule cells, may be more sensitive than serum creatinine concentrations at detecting small reductions in GFR.[15] Urinary cystatin c has been shown to detect AKI in multiple clinical settings.[14]

The combination of urinary levels or IGFBP7 and TIMP-outperforms all other biomarkers in the early detection of AKI in critically ill patients.[16] Both proteins are expressed in tubular cells and have autocrine and paracrine effects that lead to G1 cell cycle arrest for short periods. In AKI, preventing or delaying tubular cell division may be a protective response to injury. The risk for stage 2 or 3 AKI correlated well with logarithmic values of [IGFBP7]*[TIMP-2] measured from a urine sample obtained within 12 hours of the diagnosis of AKI,[16] and their combined urinary levels correlated to clinician-adjudicated AKI better than KDIGO criteria.[17]

Assessing kidney function with a loop diuretic challenge (furosemide stress test) improves prediction of kidney outcomes compared with biomarker measurement. In patients with early AKI in the ICU, urinary responses to intravenous furosemide predicted the need for dialysis better than biomarker measurement alone.[18] Failure to produce more than 200 ml of urine within 2 hours of intravenous furosemide dosed

TABLE 68.1 **Kidney Disease: Improving Global Outcomes Composite Staging of Acute Kidney Injury**

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 × baseline *Or* ≥0.3 mg/dl (≥26 μmol/l) increase	<0.5 ml/kg/h for 6-12 h
2	2.0-2.9 × baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 × baseline *Or* Increase in serum creatinine to ≥4.0 mg/dl (≥352 μmol/l) *Or* Initiation of renal replacement therapy *Or* In patients younger than 18 yr, decrease in estimated glomerular filtration rate <35 ml/min/1.73 m^2	<0.3 ml/kg/h for ≥24 h *Or* Anuria for ≥12 h

From The Kidney Disease Improving Global Outcomes (KDIGO) Working Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl.* 2012;2(1):1-138.

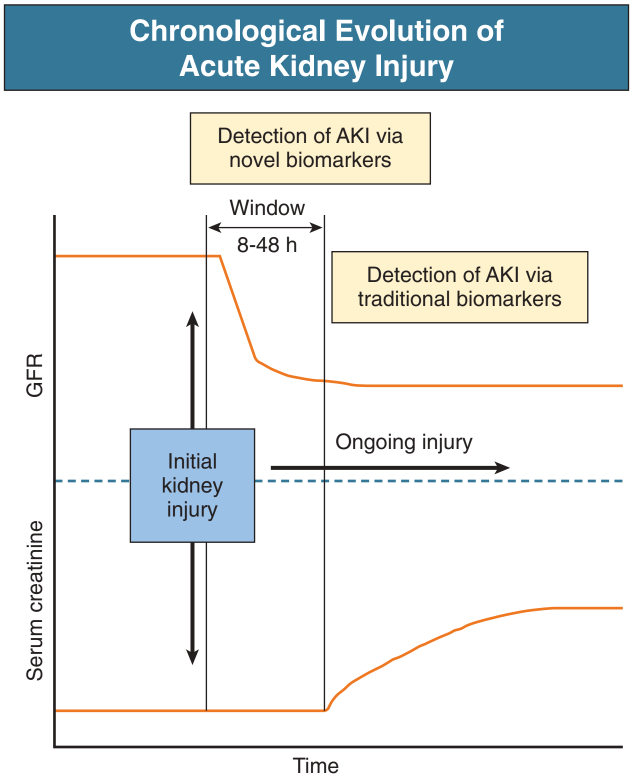
Chronological Evolution of Acute Kidney Injury
Detection of AKI via novel biomarkers
Window
8-48 h
Detection of AKI via traditional biomarkers
GFR
Initial kidney injury
Ongoing injury
Serum creatinine
Time

Fig. 68.1 Chronological evolution of acute kidney injury *(AKI). GFR,* Glomerular filtration rate. (Modified from reference 14.)

at 1 to 1.5 mg/kg strongly predicted both the need for dialysis and progression to AKI stage 3.[18]

KIM-1, a cell membrane glycoprotein upregulated in injured proximal tubular cells, can act as a nonmyeloid phosphatidylserine receptor that transforms epithelial cells into semiprofessional phagocytes.[19] The ectodomain of this membrane-associated molecule is shed into the urine of injured but not healthy kidneys. KIM-1 messenger ribonucleic acid (mRNA) levels may rise more than any other gene after kidney injury, and urinary levels are increased specifically with AKI resulting from ischemia or toxin exposure.[20,21]

NGAL, a protein produced by neutrophils, binds and traffics free iron.[20] It also mediates the tubular response to epidermal growth factor and is thereby involved in the progression of kidney disease.[22] Urinary NGAL levels are increased in the setting of tubular stress or injury, but not in prerenal disease.[23,24] A large number of studies correlated urinary NGAL levels to early detection of AKI.[14]

IL-18 is an inflammatory cytokine found in macrophages, monocytes, and proximal tubule cells. Urinary levels are upregulated in renal ischemic injury in multiple clinical settings.[14]

Biomarkers have the potential for detecting AKI early, identifying minor kidney injuries that do not raise serum creatinine concentrations, monitoring therapeutic benefits of novel treatment interventions, and specifying the cause of AKI. However, AKI frequently occurs unobserved in the community or is present at the time of recognition. Approximately 50% of patients admitted from the emergency department with septic shock have AKI on arrival to the ICU.[5] Even with early recognition of AKI, health care providers have not been able to alter its trajectory. The composite outcome of maximum change in serum creatinine level, need for dialysis, or death at 7 days did not change when primary providers were notified of AKI by an electronic alert system.[25] Nevertheless, biomarkers have potential to further understanding of AKI and remain an exciting tool on the horizon of clinical use for diagnosing, identifying a cause of, and predicting outcomes of AKI.

DIAGNOSTIC APPROACH TO ACUTE KIDNEY INJURY

The basic diagnostic approach to patients with AKI is to determine the cause (see Chapter 66). This process should start by excluding or correcting both prerenal and postrenal causes (Fig. 68.3). In hospitalized patients, determining the causative diagnosis often involves selecting the most probable cause among many choices.[26] Assessing daily urine volume can narrow the differential diagnosis, dividing AKI into oliguric (<500 ml) and nonoliguric causes. A careful history and physical examination and basic laboratory tests often suffice for diagnosis (Table 68.2).[26]

Acute Kidney Injury Versus Chronic Kidney Disease

On occasion, it can be difficult to determine whether a patient with renal failure has AKI or AKI superimposed on CKD. Knowledge of prior serum creatinine concentrations is required to determine the degree of potentially reversible AKI. Ultrasound evidence of small, scarred kidneys is consistent with CKD, but even advanced diabetic nephropathy, amyloidosis, HIV infection–related nephropathy, or polycystic kidney disease can present with normal or increased kidney size. The findings on presentation of normocytic anemia, hyperparathyroidism, peripheral neuropathy, and broad waxy casts in the urinary sediment suggest CKD. Patients with CKD are at high risk for the development of AKI.[27]

CLINICAL ASSESSMENT

The evaluation of a hospitalized patient with AKI should begin with a complete medical history and review of the hospital records. Once the prior serum creatinine concentration or other evidence of underlying kidney disease is established, the history should be directed toward the events preceding the AKI (see Fig. 68.3). These events may be part of a systemic disease process (e.g., sepsis, rhabdomyolysis), an inpatient event (e.g., surgery, nephrotoxic agent exposure), or an outpatient event

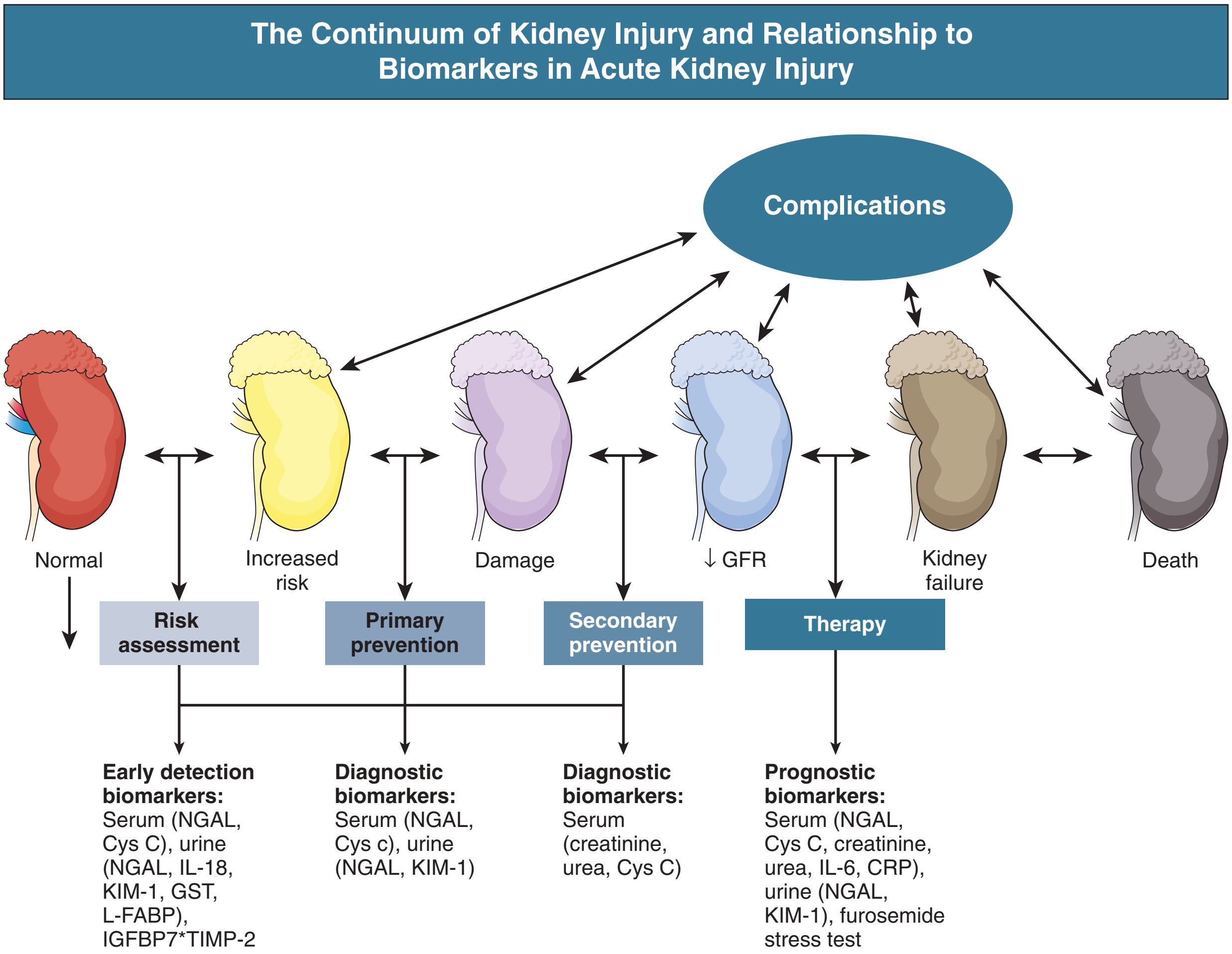
The Continuum of Kidney Injury and Relationship to Biomarkers in Acute Kidney Injury
Complications
Normal
Increased risk
Damage
↓ GFR
Kidney failure
Death
Risk assessment
Primary prevention
Secondary prevention
Therapy
Early detection biomarkers:
Serum (NGAL, Cys C), urine (NGAL, IL-18, KIM-1, GST, L-FABP), IGFBP7*TIMP-2
Diagnostic biomarkers:
Serum (NGAL, Cys c), urine (NGAL, KIM-1)
Diagnostic biomarkers:
Serum (creatinine, urea, Cys C)
Prognostic biomarkers:
Serum (NGAL, Cys C, creatinine, urea, IL-6, CRP), urine (NGAL, KIM-1), furosemide stress test

Fig. 68.2 Continuum of kidney injury and biomarkers of acute kidney injury (AKI). Injury begins before excretory function is lost (i.e., decreased glomerular filtration rate *[GFR]*) and can potentially be detected by the measurements of biomarkers. *CRP,* C-reactive protein; *Cys C,* cystatin c; *GFR,* glomerular filtration rate; *GST,* glutathione-*S*-transferase; TIMP-2, tissue inhibitor of metalloproteinase 2; IGFBP7, insulin-like growth factor-binding protein 7; *IL-6,* interleukin-6; *IL-18,* interleukin-18; *KIM-1,* kidney injury molecule 1; *L-FABP,* liver fatty acid–binding protein; *NGAL,* neutrophil gelatinase-associated lipocalin. (Modified from reference 23.)

(e.g., medication or drugs, volume contraction from diarrhea or vomiting). Particular attention should be paid to the medication record, looking for use of nonsteroidal antiinflammatory drugs (NSAIDs), renin-angiotensin-aldosterone antagonists, diuretics, antibiotics, proton pump inhibitors, Chinese herbs that contain aristolochic acid (see Chapter 62), or the use of a synthetic cannabinoid, a newly identified nephrotoxin.[28] In Africa and India the ingestion of hair dyes containing paraphenylenediamine may result in AKI. Clues to a postrenal cause (e.g., urinary hesitancy, frequent nocturia, pelvic or flank pain, overflow urinary incontinence, metastatic cancer) should be assessed early.

Physical examination may reveal reduced body weight, marked orthostatic decrease in blood pressure, an increase in pulse rate, and lack of jugular venous distention, all suggesting a reduction in extracellular fluid volume. Patients with prerenal AKI can appear volume overloaded in heart failure, cirrhosis, and nephrotic syndrome when effective arterial blood volume is reduced. In critically ill patients, hemodynamic measurement by right heart catheterization may be necessary to differentiate volume overload from noncardiogenic pulmonary infiltrates. Trends in daily intake and output volumes also assist in determining the extracellular fluid volume of the critically ill patient.

Examination of the abdomen may reveal a tender, distended bladder in a lower urinary tract obstruction, and, when this is present, sterile postvoid bladder catheterization should be performed. A distended, tense abdominal wall may represent ascites, aggressive intravenous fluid resuscitation, or recent abdominal surgery. Intraabdominal pressure can be measured in the ICU to distinguish AKI from abdominal compartment syndrome, defined as an intraabdominal pressure exceeding 20 mm Hg.[29]

Fever, skin rash, and arthralgias may be signs of systemic lupus erythematosus, vasculitis, endocarditis, or drug allergy with AIN. A history of recent aortic catheterization (e.g., cardiac catheterization) and the findings of livedo reticularis or a discolored toe are diagnostic clues for cholesterol or atheromatous emboli. Painless hematuria suggests acute GN or genitourinary malignancy, whereas painful hematuria is more consistent with obstruction.[26]

Electronic Health Record to Predict Acute Kidney Injury

Computer-based models have been used to develop AKI electronic alerts.[30, 31] In one study, real-time alert of worsening of AKI by an AKI "sniffer" increased the timeliness of early therapeutic intervention.[32]

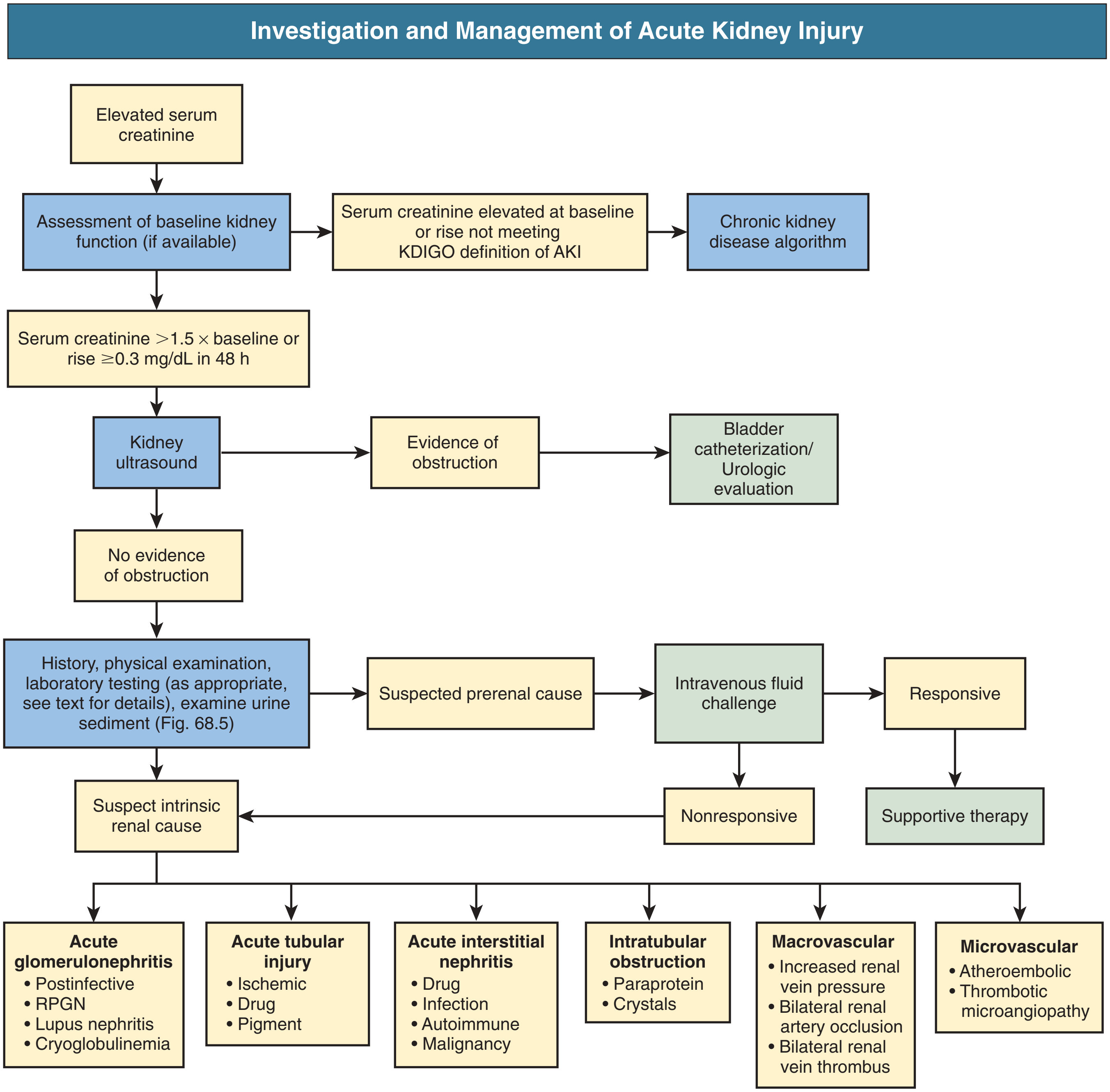
Investigation and Management of Acute Kidney Injury
Elevated serum creatinine
Assessment of baseline kidney function (if available)
Serum creatinine elevated at baseline or rise not meeting KDIGO definition of AKI
Chronic kidney disease algorithm
Serum creatinine >1.5 × baseline or rise ≥0.3 mg/dL in 48 h
Kidney ultrasound
Evidence of obstruction
Bladder catheterization/ Urologic evaluation
No evidence of obstruction
History, physical examination, laboratory testing (as appropriate, see text for details), examine urine sediment (Fig. 68.5)
Suspected prerenal cause
Intravenous fluid challenge
Responsive
Supportive therapy
Nonresponsive
Suspect intrinsic renal cause
Acute glomerulonephritis
• Postinfective
• RPGN
• Lupus nephritis
• Cryoglobulinemia
Acute tubular injury
• Ischemic
• Drug
• Pigment
Acute interstitial nephritis
• Drug
• Infection
• Autoimmune
• Malignancy
Intratubular obstruction
• Paraprotein
• Crystals
Macrovascular
• Increased renal vein pressure
• Bilateral renal artery occlusion
• Bilateral renal vein thrombus
Microvascular
• Atheroembolic
• Thrombotic microangiopathy

Fig. 68.3 Investigation and management of suspected acute kidney injury (AKI). The majority of AKI causes can be identified by reviewing the events that preceded the AKI. Evaluating for urinary obstruction early prevents the delay of urologic therapy, if needed; however, not all patients require a kidney ultrasound. If prerenal and postrenal causes have been excluded, the kidneys are normal size, and the diagnosis remains unclear, a kidney biopsy may be indicated. *AKI,* Acute kidney injury; *KDIGO,* Kidney Disease: Improving Global Outcomes; *RPGN,* rapidly progressive glomerulonephritis.

However, in a large randomized controlled study, an electronic alert system for AKI in hospitalized patients did not demonstrate any improvements in clinical outcomes and rather increased the use of health care resources.[25] Further studies are needed to further define the utility of such AKI alerts.

DIAGNOSTIC EVALUATION

Differentiating the two most common causes of AKI in hospitalized patients, prerenal AKI and ATN, may be difficult when both the effective arterial blood volume and the time course of the kidney injury are unknown.[33] Here the term *acute tubular injury* may more accurately describe the pathology involved in intrinsic AKI from ischemic or toxic insults.[34] Evaluation of urine volume, urinary sediment, and urinary indices (the last is useful only in patients with oliguria) is helpful in making the correct diagnosis (Table 68.3 and Fig. 68.3). Initial laboratory tests include a urinalysis, blood urea nitrogen (BUN), serum sodium, potassium, bicarbonate, and creatinine levels not only for the diagnosis but also for assessment of complications of AKI.[26]

TABLE 68.2 Differential Diagnosis by Pathophysiologic Classification of Acute Kidney Injury

Cause	Comments
Prerenal	**30%-60% of AKI**
Volume depletion	Renal losses, GI losses, hemorrhage
Decreased cardiac output	Right- or left-sided heart failure, cardiac tamponade
Systemic vasodilation	Sepsis, anaphylaxis, anesthetics
Afferent arteriolar vasoconstriction	NSAIDs, calcineurin inhibitors, radiocontrast, hepatorenal syndrome, hypercalcemia
Efferent arteriolar vasodilation	ACE inhibitors, ARBs
Intrinsic	**~40% of AKI**
Acute tubular injury	
Ischemic	
Nephrotoxic (drug)	Aminoglycosides, lithium, amphotericin, pentamidine, cisplatin, ifosfamide, radiocontrast
Nephrotoxic (pigment)	Rhabdomyolysis, intravascular hemolysis
Acute interstitial nephritis (AIN)	
Drug induced	Penicillins, cephalosporins, NSAIDs, PPIs, allopurinol, rifampin, sulfonamides
Infection related	Pyelonephritis, viral nephritides
Autoimmune diseases	Sjögren syndrome, sarcoidosis, SLE
Malignancy	Lymphoma, leukemia
Intratubular obstruction	
Paraprotein	Immunoglobulin light chains
Crystals	Acute phosphate nephropathy, tumor lysis syndrome, ethylene glycol, acyclovir, indinavir, methotrexate
Acute glomerulonephritis	Postinfectious, cryoglobulinemia, RPGN, SLE
Macrovascular	Increased renal vein pressure from increased intraabdominal pressure, bilateral renal vein thrombosis, bilateral renal artery emboli
Microvascular	Atheroembolic disease, HUS, TTP, scleroderma renal crisis, malignant hypertension
Postrenal (Obstruction)	**Approximately 10% of AKI**
Intrinsic	Bilateral ureteral stones, bladder outlet obstruction (prostatic enlargement or blood clot), neurogenic bladder
Extrinsic	Retroperitoneal fibrosis, metastatic cancer

ACE, Angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *GI,* gastrointestinal; *HUS,* hemolytic uremic syndrome; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PPIs,* proton-pump inhibitors; *RPGN,* rapidly progressive glomerulonephritis; *SLE,* systemic lupus erythematosus; *TTP,* thrombotic thrombocytopenic purpura.

Results from initial laboratory testing may prompt further evaluation. For example, glycosuria occurring with a normal plasma glucose level offers evidence for proximal tubular dysfunction. The presence of amino acids and bicarbonate in the urine along with elevated urinary fractional excretion of phosphate and uric acid confirm Fanconi syndrome (see Chapter 48).

Ratio of Blood Urea Nitrogen to Creatinine

The ratio of BUN to creatinine in healthy individuals is 10 to 15 : 1 (when both are expressed in mg/dl or 40 to 60 when expressed in mmol/l). In prerenal AKI the ratio may be greater than 20 : 1 because of a disproportionate increase in urea reabsorption resulting from elevated serum vasopressin levels. However, upper gastrointestinal tract bleeding, impaired protein anabolism (e.g., systemic corticosteroid administration), increased catabolism (e.g., sepsis), and increased protein intake also can raise BUN levels. Furthermore, diminished urea production from decreased protein intake or underlying liver disease can prevent the expected rise in BUN by increased tubular reabsorption. Also, elevations in creatinine levels may exceed BUN levels in patients with creatinine release from muscle breakdown, as in rhabdomyolysis.

Urine Volume

In AKI, urine volume directly correlates with residual GFR.[35] Urine volume can indicate the severity of AKI and also provide important diagnostic information. Oliguric AKI (<500 ml/day) is typically associated with worse outcomes than AKI with preserved urine volume, especially with a positive fluid balance in the critical care setting.[36-39] Oliguria commonly occurs in AKI caused by ATN, although it can be seen in early prerenal AKI or AIN. Wide variations in daily urine output suggest obstruction. Anuria (urine output <100 ml/day) suggests obstruction or a bilateral acute vascular catastrophe (renal vein or renal artery occlusion), shock or rarely renal cortical necrosis, hemolytic uremic syndrome, or anti–glomerular basement membrane (GBM) antibody disease.[26]

Urinalysis and Urine Microscopy

In the setting of AKI, a dipstick urinalysis may reveal microhematuria or proteinuria but must be interpreted in conjunction with more specific tests such as a ratio of spot urinary protein or albumin to creatinine and urine microscopy. Dipstick urinalysis may not detect immunoglobulin free light chains (FLCs) or may be falsely positive for protein in the setting of radiographic contrast or alkaline urine. In conjunction with urine microscopy, the presence of urinary hemoglobin or myoglobin by dipstick can be further differentiated. Urine microscopy has been validated as a diagnostic and prognostic tool in hospitalized patients with AKI.[33] A fresh urine sample is centrifuged, and the sediment is examined for the presence of cells, casts, and crystals (Figs. 68.4 and 68.5) (see also Chapter 4). Urine microscopy in early prerenal AKI is typically normal with occasional hyaline casts. "Muddy brown" granular casts and renal tubular epithelial cells in the urine support ATN-related

TABLE 68.3 Clinical and Laboratory Variables in the Differential Diagnosis Between Prerenal and Renal Acute Kidney Injury

	Prerenal	Renal
History	Volume loss from GI, urinary, skin, or blood or reduced EABV (e.g., heart failure, pancreatitis)	Drugs or toxin exposure, hemodynamic change
Clinical presentation	Hypotension or volume depletion	No specific symptoms or signs
Laboratory studies		
BUN/S_{Cr}	>20	<20
Sediment	Normal to few hyaline casts	Muddy brown casts
U_{osm} (mmol/kg)	>500	<350
Proteinuria	None to trace	Mild to moderate
U_{Na} (mmol/l)	<20	>40
FE_{Na} (%)	<1	>1
FE_{Urea} (%)	<35	>35
Novel biomarkers	None	IGFBP7*TIMP-2, KIM-1, cystatin C, NGAL, CYR61, others

BUN, Blood urea nitrogen; *CYR61,* cysteine-rich protein 61; FE_{Na}, fractional excretion of sodium; FE_{Urea}, fractional excretion of urea; *GI,* gastrointestinal; EABV, effective arterial blood volume; IGFBP7*TIMP-2, insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinase 2; *KIM-1,* kidney injury molecule 1; *NGAL,* neutrophil gelatinase–associated lipocalin; S_{Cr}, serum creatinine; U_{Na}, urinary sodium; U_{osm}, urinary osmolality.

AKI. In hospitalized patients with AKI, the presence of more than 10 granular casts per low-power field had a positive predictive value of 100% for a final diagnosis of ATN and a urine sediment score based on granular casts and renal tubular epithelial cells was directly associated with worsening AKI. Thus urine microscopy is useful both in distinguishing ATN-related AKI from prerenal AKI and in predicting the severity of AKI.[33]

Findings on urinalysis and urine microscopy (see Chapter 4) may suggest CKD (broad, waxy casts) but, more important, may be diagnostic clues to a rare cause of AKI. Proliferative GN may be characterized by considerable microhematuria and proteinuria by dipstick and an active urinary sediment consisting of red blood cells (RBCs) and RBC casts. In this setting the history and physical examination findings should be supported by serologic testing and a kidney biopsy, if the kidneys are normal in size. The presence of white blood cells (WBCs) in clumps and casts, in the absence of bacteria, suggests AIN.[26] Renal tubular epithelial cells, granular casts, RBCs, and, rarely, even RBC casts can occur in patients with AIN, whereas urinary eosinophils are no longer considered helpful in diagnosing AIN (see Chapter 60).[40] A urine sediment with abundant uric acid crystals accompanying high serum phosphorus levels in a patient undergoing chemotherapy may indicate tumor lysis syndrome (TLS).

Fractional Excretion of Sodium and Urea

The urine-serum concentrations of sodium in relation to the urine-serum concentrations of creatinine (fractional excretion of sodium [FE_{Na}]) has been used to approximate renal tubular function:

$$FE_{Na} = \frac{[U/S]_{Na}}{[U/S]_{Cr}} \times 100\%$$

where U = urine, S = serum, Na = sodium, and Cr = creatinine.

The basic premise is that renal tubular cells will reabsorb sodium in the prerenal setting, whereas tubules damaged by ATN will not.[41] FE_{Na} less than 1% is consistent with prerenal AKI, and FE_{Na} above 3% is typical of ATN. However, FE_{Na} may be less than 1% despite the presence of ATN in the setting of sepsis, hemoglobinuria or myoglobinuria, radiocontrast exposure, nonoliguria, heart failure, and advanced cirrhosis. Underlying CKD, diuretic use, recent intravenous fluid administration, glycosuria, bicarbonaturia, and salt-wasting disorders may be associated with elevated FE_{Na} despite the presence of prerenal AKI.[41] Therefore FE_{Na} has significant limitations in the setting of hospital-acquired AKI, yet may be helpful in differentiating prerenal AKI from ATN in specific patient populations with oliguria.

Urea reabsorption, primarily occurring in proximal tubules, is less affected by loop and thiazide diuretics, and the fractional excretion of urea (FE_{Urea}) may be an alternative to FE_{Na} in patients receiving diuretics. FE_{Urea} calculation is identical to that of FE_{Na}, and values less than 35% favor prerenal AKI over ATN.

Laboratory Evaluation of Acute Kidney Injury in Systemic Illnesses

In the presence of a systemic illness, additional laboratory evaluation may narrow the differential diagnosis of AKI. Serum complement levels of C3 and C4 are useful in differentiating causes of GN, particularly when a kidney biopsy is not feasible. Postinfectious GN, infective endocarditis, lupus nephritis, mixed cryoglobulinemia, and membranoproliferative GN are typically associated with low levels of serum C3 and/or C4 (see Chapter 21). Whereas, serum complement levels are normal in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti–glomerular basement antibody disease, and Henoch-Schönlein purpura (immunoglobulin A [IgA] vasculitis). Despite activation of the complement system in thrombotic microangiopathy (see Chapter 29), serum C3 and C4 can be maintained at normal levels through increased hepatic production.[42] Alternatively, when liver synthesis is impaired, low serum levels of C3 and/or C4 are less reliable in differentiating the type of acute GN.

In the right clinical setting, laboratory studies may support a specific cause of AKI. For example, AKI with thrombocytopenia, schistocytes on peripheral blood smear, and an elevated blood lactate dehydrogenase level would be consistent with thrombotic microangiopathy. However, these laboratory findings may be present in sepsis with disseminated intravascular coagulation (DIC). AKI in sepsis with DIC typically results from ATN or antibiotic-related AIN and not thrombotic microangiopathy.

In the appropriate clinical setting the following laboratory tests can help identify a cause: complete blood count, hemoglobin, serum albumin, creatine kinase, uric acid, phosphorus, urine myoglobin, HIV antibody, hepatitis C antibody, cryoglobulins, rheumatoid factor, hepatitis B virus studies, antinuclear antibody, anti–double-stranded DNA antibody, ANCA, anti-GBM antibody, and serum FLC.

Imaging Studies

Kidney imaging may not be necessary if a clear diagnosis of AKI exists (e.g., prerenal AKI or ATN). However, when the diagnosis is uncertain, and especially if urinary obstruction or renal vascular occlusion are suspected, imaging is indicated.[26] Renal ultrasound can identify urinary obstruction, polycystic kidney disease, and the size and number of kidneys. When Doppler flow is used, renal artery and veins can be assessed. High-resolution, noncontrast computed tomographic imaging

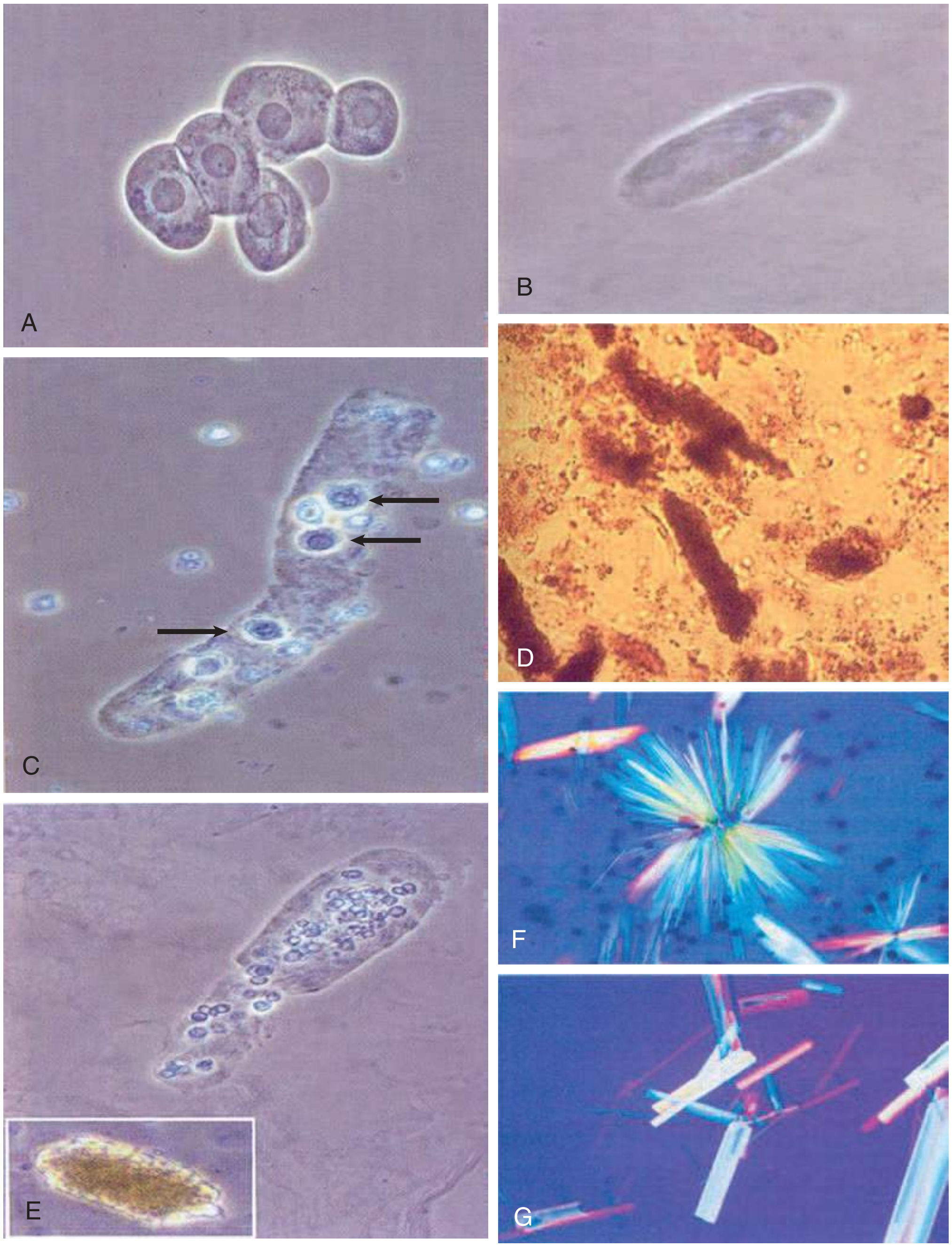

Fig. 68.4 Examples of urinary sediments seen in acute kidney injury (AKI). (A) Epithelial cell aggregate. (B) Hyaline cast as can be seen in prerenal AKI. (C) Epithelial cast as can be seen in early acute tubular necrosis (ATN, *arrows* indicate epithelial cells). (D) Muddy brown cast, typical of established ATN. (E) Erythrocyte cast as seen in glomerulonephritis and vasculitis. *Inset:* Hemoglobin cast. (F and G) Two forms of indinavir crystals.

is the preferred test for the detection of urinary tract calculi. Radionuclide renography may be used to estimate the renal plasma flow in a transplanted kidney with AKI but is increasingly replaced by Doppler ultrasound. Other radionuclide methods are less useful in AKI (e.g., tagged WBC scan for AIN). Magnetic resonance imaging without contrast is now recommended to evaluate renal arterial or venous thrombosis.[26]

Kidney Biopsy

Kidney biopsy is reserved for patients in whom prerenal and postrenal AKI have been excluded and the cause of intrinsic renal AKI remains unclear (see Fig. 68.3). Kidney biopsy is particularly useful when clinical assessment and laboratory investigations suggest diagnoses other than ischemic or nephrotoxic injury that may respond to disease-specific therapy (e.g., vasculitis, systemic lupus erythematosus, and AIN).

ACUTE KIDNEY INJURY IN SPECIFIC SETTINGS

Acute Tubular Necrosis

ATN is a clinical syndrome of abrupt and sustained decline in GFR that is triggered by an acute ischemic or nephrotoxic event and develops

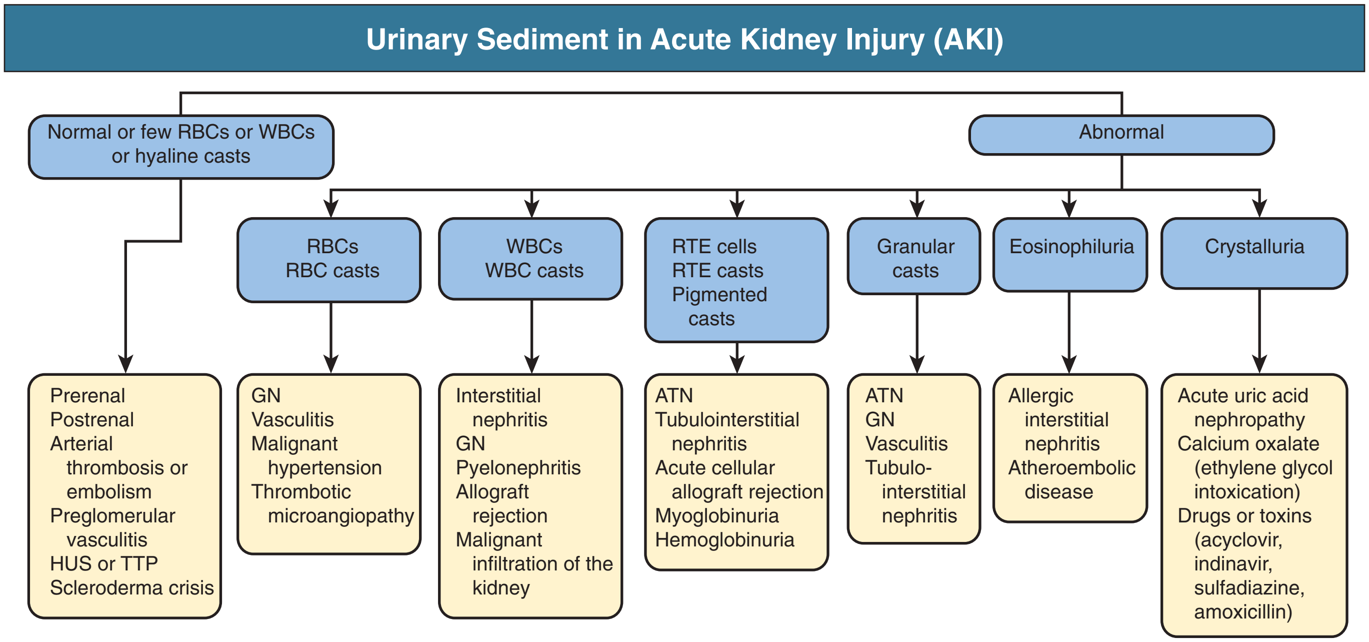
Urinary Sediment in Acute Kidney Injury (AKI)
Normal or few RBCs or WBCs or hyaline casts
Abnormal
RBCs RBC casts
WBCs WBC casts
RTE cells RTE casts Pigmented casts
Granular casts
Eosinophiluria
Crystalluria
Prerenal Postrenal Arterial thrombosis or embolism Preglomerular vasculitis HUS or TTP Scleroderma crisis
GN Vasculitis Malignant hypertension Thrombotic microangiopathy
Interstitial nephritis GN Pyelonephritis Allograft rejection Malignant infiltration of the kidney
ATN Tubulointerstitial nephritis Acute cellular allograft rejection Myoglobinuria Hemoglobinuria
ATN GN Vasculitis Tubulo-interstitial nephritis
Allergic interstitial nephritis Atheroembolic disease
Acute uric acid nephropathy Calcium oxalate (ethylene glycol intoxication) Drugs or toxins (acyclovir, indinavir, sulfadiazine, amoxicillin)

Fig. 68.5 **Urinary sediment in acute kidney injury (AKI).** *ATN,* Acute tubular necrosis; *GN,* glomerulonephritis; *HUS,* hemolytic uremic syndrome; *RBC,* red blood cell; *RTE,* renal tubular epithelial; *TTP,* thrombotic thrombocytopenic purpura; *WBC,* white blood cell.

within minutes to days after the insult.[26] Apart from kidney biopsy, no definitive test can diagnose ATN. The diagnosis is suggested by a history of recent hypotension, volume depletion, sepsis, or nephrotoxic exposure. Muddy brown, coarse, granular casts are present on urine microscopy in the majority of patients with ATN, particularly those who are oliguric.[26] Other laboratory findings consistent with the diagnosis of ATN are shown in Table 68.3.

The pathophysiology of ATN involves multiple pathways (see Chapter 66). Obstruction of flow within the tubule by cellular debris, disruptions of tubular cell polarity and cytoskeleton, loss of the lining epithelium with resulting backleak of glomerular filtrate into the renal interstitium, and afferent arteriolar constriction all may play pathophysiologic roles in ATN. ATN has been described as a (mal)adaptive response of the kidney—"trading away" GFR for the preservation of medullary oxygenation and tubular integrity.[34]

ATN after ischemia/reperfusion injury is usually most severe within the outer medulla of the kidney (see Chapter 66).[43] The typical histologic features of human proximal tubular injury include vacuolation, loss of brush border, disruption of the epithelial cells lining the tubule, and presence of intratubular casts. Necrosis of tubular cells is typically focal and may be missed in a biopsy specimen because most biopsies contain cortex and the outer medulla is not sampled adequately. Apoptosis of tubular cells is present in kidney biopsy specimens from humans with ATN, and evidence of cellular regeneration is often seen, most commonly in areas of greatest tubular cell loss. Regenerative changes and fresh epithelial injury are often observed in the same biopsy specimen, suggesting that recurrent episodes of tubular ischemia continue to occur during the maintenance phase of ATN. The morphologic appearance of the common forms of nephrotoxin-induced ATN is similar to that of ischemic ATN, with loss of microvasculature and immune cell infiltration. Correlations of morphologic findings to functional end-points have been difficult.

Acute Interstitial Nephritis

AIN is characterized by the presence of inflammatory infiltrates and edema within the interstitium, with an acute deterioration in GFR (see Chapter 60).[44] It is not an uncommon cause of AKI, accounting for 15% to 27% of renal biopsies performed because of AKI, yet AIN may be overlooked as a cause of AKI in settings in which ATN is common (e.g., sepsis). Drug use, in particular antimicrobials and NSAIDs, are the most common cause of AIN (see Table 68.2).[44]

The diagnosis of AIN generally requires kidney biopsy. The clinical presentation of drug-induced AIN is variable, with a mean delay between drug exposure and the appearance of renal manifestations of 10 days, although the latent period can be as short as 1 day with some antibiotics or as long as several months with NSAIDs.[44] In AIN the reported frequency of symptoms included arthralgias (45%), fever (36%), and skin rash (22%). In the same analysis, urinary findings included non-nephrotic proteinuria (93%), leukocyturia (82%), and microscopic hematuria (67%).[44] The classic clinical presentation of maculopapular rash, peripheral eosinophilia, and arthralgias may not be present in drug-induced AIN and is uncommon in infection-related or idiopathic AIN (see Table 68.2).

Acute Kidney Injury from Intratubular Obstruction

Several endogenous and exogenous molecules can precipitate in the tubular lumen to produce AKI, including uric acid, calcium phosphate, calcium oxalate, immunoglobulin FLCs, myoglobin, and medications (e.g., acyclovir, indinavir, methotrexate, sodium phosphate–containing cathartics, and sulfadiazine).[26] Medication-induced crystal nephropathy occurs more commonly when high doses of medication are combined with low tubular flow rates from volume contraction or underlying CKD.

Ethylene glycol ingestion from solvents and antifreeze may result in AKI from calcium oxalate crystal deposition. Patients with ethylene glycol poisoning typically have high anion gap metabolic acidosis because the ethylene glycol is metabolized into glycolic acid. The glycolic acid is converted to oxalic acid, which binds free calcium to form calcium oxalate crystals. Crystal deposition resulting in AKI typically manifests 48 to 72 hours after ingestion; oxalate crystals can be readily identified in the urine soon after exposure.

Intratubular obstruction from calcium phosphate and urate crystals contribute to AKI in TLS, which is characterized by a constellation of metabolic derangements caused by massive and abrupt release of intracellular components in the blood after rapid lysis of malignant cells. It is typically seen after initiation of cytotoxic therapy for hematologic malignancies with large tumor burden or cell counts.[45] Clinical features of TLS result from the effects of the metabolic derangements. Nucleic acids released during cell lysis are metabolized to hypoxanthine and then xanthine, which is converted by xanthine oxidase to uric acid. With significant tumor lysis, severe hyperuricemia and intratubular obstruction from urate crystals may result. Hyperkalemia may induce cardiac arrhythmias, weakness, and paresthesias. Hyperphosphatemia initially produces muscle cramps and lethargy but also can promote nausea, vomiting, diarrhea, and seizure. Hypocalcemia, primarily caused by phosphorus binding, causes similar symptoms with muscle cramps, tetany, cardiac arrhythmias, and seizures.[45] Hyperkalemia and hypocalcemia associated with AKI in a patient receiving cytotoxic chemotherapy may be the only initial clues to the syndrome because blood uric acid and phosphate levels are not routinely monitored. Urine microscopy can assist in the diagnosis by revealing the presence of many urate crystals.

Rhabdomyolysis

Rhabdomyolysis is characterized by the leakage of muscle-cell contents, including myoglobin, electrolytes, creatine kinase, aldolase, lactate dehydrogenase, nucleic acids, and aspartate aminotransferase into the circulation.[46] AKI, occurring primarily in severe rhabdomyolysis, results from renal vasoconstriction, proximal tubular cell injury from oxidant stress, and intranephronal obstruction. Both myoglobin, a heme pigment protein that contains iron in the ferrous (Fe^{2+}) state, and uric acid have less nephrotoxicity in alkaline urine. Intravascular volume contraction and acidic urine promote distal tubule obstruction from myoglobin and uric acid precipitation.

Muscle injury leading to rhabdomyolysis frequently follows trauma (e.g., crush syndrome or prolonged immobilization), increased exertion (e.g., seizure, alcohol withdraw, strenuous exercise), genetic defects (e.g., disorders of glycolysis or gluconeogenesis, disorders of lipid metabolism, mitochondrial disorders), infections (e.g., influenza A and B), body temperature changes (e.g., heat stroke, neuroleptic malignant syndrome, hypothermia), and drug or toxin exposure (e.g., lipid-lowering drugs, alcohol, quetiapine, cocaine, heroin).[46]

Patients with acute rhabdomyolysis often present with muscle pain and reddish-brown urine. The presence of pigmented granular casts and the lack of RBCs on urine microscopy coupled with a blood-positive urinary dipstick are important diagnostic clues for rhabdomyolysis-related AKI. However, the diagnosis must be confirmed by elevated serum creatine kinase levels and the presence of urinary myoglobin.[26] A weak correlation exists between creatine kinase values and the incidence of AKI. The risk for AKI is lower when creatine kinase levels are less than 20,000 U/l. Rhabdomyolysis may contribute to AKI with creatinine kinase levels as low as 5000 U/l when coexisting conditions such as sepsis, intravascular volume contraction, and acidosis are present.[46]

Acute Kidney Injury in Myeloma

Monoclonal immunoglobulin FLCs are responsible for the majority of severe AKI in patients with myeloma. In such patients, monoclonal FLCs are overproduced, often with circulating levels hundreds times higher than normal.[47] Unlike most endogenously produced proteins, monoclonal FLCs have a strong propensity to cause tubular damage (see Chapter 27).[47] Some kappa monoclonal FLCs are cytotoxic and promote proximal tubular cell injury, with one mechanism resulting in a defect in sodium-coupled cotransport processes producing type II renal tubular acidosis, aminoaciduria, phosphaturia, and glycosuria (i.e., Fanconi syndrome).[48] A separate mechanism of FLC-mediated AKI is intratubular obstruction from precipitation of monoclonal FLCs in the distal nephron, that is, cast nephropathy.[26] Cast formation occurs under specific conditions mediated by the ionic composition of tubule fluid, tubule fluid flow rates, the concentration of Tamm-Horsfall glycoprotein and FLCs, the strength of the binding interaction between Tamm-Horsfall glycoprotein and FLC, and the presence of furosemide.[47] AKI attributed to cast nephropathy occurs in approximately one third of patients with multiple myeloma and AKI. Other causes of AKI include extrarenal obstruction (e.g., nephrolithiasis, amyloid deposition in the ureters), hypercalcemia, hyperviscosity syndrome, and non–myeloma-related causes (e.g., AIN or contrast-induced nephropathy [CIN]).[26]

Cast nephropathy should be considered, particularly in older patients with unexplained AKI. Predisposing conditions may include hypercalcemia, intravascular volume contraction, furosemide use, exposure to radiocontrast, and/or NSAID use. AKI may be the presenting event in patients with an undiagnosed plasma cell dyscrasia. Because FLC may not be detected on dipstick analysis, urinalysis in cast nephropathy will often show no or trace protein and the urinary sediment is typically bland. Assay of serum FLC levels is critical in assisting in the differential diagnosis of unexplained AKI (Chapter 64), but kidney biopsy may be needed to diagnose cast nephropathy. A low urinary albumin excretion (<10%) assessed with 24-hour urine electrophoresis was found useful in distinguishing cast nephropathy from ATN and less acute causes of kidney injury in multiple myeloma (e.g., amyloid light-chain [AL] amyloidosis and monoclonal immunoglobulin deposition disease).[49]

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN), defined as AKI occurring shortly after exposure to intravenous radiocontrast, is an established cause of AKI. However, the incidence of CIN is low (<1%) in patients with normal renal function and no other risk factors for AKI.[26] Risk factors for CIN include CKD, diabetic nephropathy, advanced heart failure, states of reduced renal perfusion, high total dose of contrast, and concomitant exposure to other nephrotoxins. Data from animal models suggest that both renal vasoconstriction from direct effects of the contrast media and toxic injury of tubular cells (likely from activation of osmolality-sensitive aldose reductase in the proximal tubule) are the main factors in the pathophysiology of CIN.[50] Emerging data suggest a role for contrast-induced uricosuria in the pathogenesis of CIN.[51] The kidney injury likely occurs within minutes of contrast exposure; however, the detection of AKI is typically delayed by 24 to 48 hours after contrast exposure. The timing of AKI in relation to contrast exposure and the exclusion of other causes of AKI generally suffice for diagnosis. Urinalysis and urine sediment findings are typically consistent with ATN. Renal biopsy is generally not helpful in the setting of CIN because the expected findings of ATN are nonspecific, no CIN-specific treatment exists, and the renal injury is typically short lived.

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SELF-ASSESSMENT QUESTIONS

1. A 20-year-old man with Marfan syndrome is admitted to the hospital for elective aortic valve replacement and endovascular repair of a distal (type B) thoracic aortic dissection. On postoperative day 4, his urine output decreases to 420 ml over a 24-hour period and the urine appears dark in his Foley catheter collection bag. He requires mechanical ventilation and pressor support, with a mean arterial blood pressure of 70 mm Hg. There is no rash visible on examination. Available laboratory data follow.

Preoperation Blood	
Sodium	140 mEq/l
Potassium	4.0 mEq/l
Chloride	108 mEq/l
Bicarbonate	24 mEq/l
Blood urea nitrogen (BUN)	12 mg/dl
Creatinine	0.6 mg/dl
Glucose	100 mg/dl

Postoperation Day 4 Blood	
Sodium	141 mEq/l
Potassium	6.1 mEq/l
Chloride	106 mEq/l
Bicarbonate	14 mEq/l
BUN	24 mg/dl
Creatinine	4.4 mg/dl
Glucose	98 mg/dl
Calcium	5 mg/dl
Phosphate	10.2 mg/dl
Albumin	3.8 g/dl
Osmolality	294 mOsm/kg
Lactate	Normal

Postoperation Day 4 Blood	
Arterial Blood Gas	
pH	7.27
P_{CO_2}	31 mm Hg
P_{O_2}	97 mm Hg
HCO_3^-	14 mEq/l
Urinalysis	
Specific gravity	1.028
pH	6.0
Protein	Negative
Blood	Positive
Ketones	Negative
Red blood cells	none

What is the most appropriate next diagnostic test?

A. Serum creatine kinase level
B. Kidney ultrasound with Doppler
C. Kidney biopsy
D. Serum antineutrophil cytoplasmic antibody
E. Fractional excretion of urea

2. Which test result is most consistent with preserved renal tubular function in a person who is volume contracted and has healthy kidneys?

A. Urine osmolality of 300 mOsm/kg
B. Fractional excretion of urea of 45%
C. Blood urea nitrogen of 34 mg/dl
D. Spot urine sodium of 40 mEq/l
E. None of the above

3. A 72-year-old man is brought to the emergency department by his family because of worsening confusion throughout the day. One week ago the patient fell and fractured his distal radius, necessitating splinting and pain medication. His medical history was pertinent with chronic kidney disease stage 3 (baseline serum creatinine 1.4 mg/dl), long-standing hypertension, chronic obstructive pulmonary disease, osteopenia, and benign prostatic hypertrophy. Current medications included lisinopril 20 mg/day, amlodipine 5 mg/day, hydrochlorothiazide 25 mg/day, doxazosin 4 mg nightly, oxycodone 5 mg every 8 hours as needed for arm pain, vitamin D 2000 international units/day, and ipratropium bromide–albuterol inhaled 4 times per day. Arrival vital signs include blood pressure 176/92 mm Hg, pulse 114/min, respirations 18/min, weight 55 kg, and temperature 98.5° F. Physical examination revealed an agitated older man with flat neck veins, reduced air movement on chest auscultation, a large and tender abdomen, a right forearm cast, and trace lower extremity edema. No skin lesions were seen or palpated. Initial laboratory test results were as follows:

Blood tests: Sodium 138 mEq/l, potassium 5.2 mEq/l, chloride 110 mEq/l, bicarbonate 20 mEq/l, BUN 54 mg/dl, serum creatinine 2.6 mg/dl, leukocyte count 7500 cells/ml, hemoglobin 11.2 g/dl, platelet count 150,000 cells/μmol, alanine aminotransferase 28 U/l (normal 15-58 U/l), aspartate aminotransferase 36 U/l (normal 15-40 U/l), and prothrombin time 14 seconds. Urinalysis with microscopy: Specific gravity 1.010, no blood or protein, and a bland sediment with no casts and few cells. What is the most appropriate next diagnostic test?

A. Kidney ultrasound with Doppler
B. Peripheral blood smear
C. Renal biopsy
D. Postvoid bladder catheterization
E. None of the above

69

Epidemiology and Prognostic Impact of Acute Kidney Injury

Neesh Pannu, Marcello Tonelli

INCIDENCE OF ACUTE KIDNEY INJURY

The incidence of acute kidney injury (AKI) in unselected hospitalized patients is between 0.4% and 18%, depending on the definition used, and accounts for 1% to 4% of all hospital admissions.[2] Several large studies suggest that the incidence of AKI in hospitalized patients has increased by approximately 13% per year over the last three decades.[3] In these studies, incidence was identified by diagnostic codes that are highly specific for AKI (97%) but are relatively insensitive (35% sensitivity),[4] and thus these studies likely underestimate the true incidence. Less is known about community-acquired AKI; there is significant etiologic and geographical variation in the reported incidence and risk factors for AKI in the community settings. A recent study from Taiwan reports an incidence of 17.25 in 1000 admissions using serum creatinine–based criteria for AKI.[5] Similar increases have been observed in the incidence of severe AKI (requiring renal replacement therapy [RRT]) between 2000 and 2009 and a doubling in the number of deaths attributable to AKI (Fig. 69.1).[6] The increased incidence is likely related to increasing patient age and a higher burden of comorbidity, including a higher prevalence of chronic kidney disease (CKD). AKI survivors had prolonged hospital length of stay and a greater requirement for posthospitalization care,[7] thus incurring significantly higher health care costs.[8]

The incidence of AKI using consensus definitions based on serum creatinine and urine output (Table 69.1) has been best characterized in critically ill populations. Despite using standardized definitions for AKI, multicenter studies of critically ill patients have reported the incidence of AKI to be between 10% and 67%, likely reflecting differences in case-mix between health care systems and countries.[9]

RISK FACTORS FOR ACUTE KIDNEY INJURY

Risk factors for AKI have been determined in a variety of clinical settings including cardiac surgery, contrast-induced AKI, and critically ill populations; however, risk prediction models that accurately predict the occurrence of AKI have been elusive. Nonmodifiable risk factors common to all populations are presented in Box 69.1.

Age

Multiple studies have shown that AKI is more common in older individuals, and many have shown an independent association between AKI and older age.[10] In a community-based prospective study, the patients aged 80 to 89 years were 55 times more likely to develop AKI than adults younger than 50 years.[11] Possible explanations for this association include (1) structural and functional changes associated with age that lead to diminished nephron reserve and reduced capacity for renal autoregulation, (2) accumulation of comorbidity that increases susceptibility to AKI (vascular disease, diabetes, hypertension, CKD), and (3) increased exposure among older persons to medications and procedures that predispose to AKI.[10]

Reduced Estimated Glomerular Filtration Rate

Preexisting reduction in estimated glomerular filtration rate (eGFR) is a potent risk factor for AKI after exposure to radiocontrast,[12] major surgery, and medical illness,[13] although the pathophysiology underlying this association is poorly understood. It has been reported that the odds of developing dialysis requiring AKI are increased at lower baseline eGFR; the excess risk compared with normal eGFR was approximately twofold in patients with baseline eGFR 45 to 60 ml/min/1.73 m^2, but more than 40-fold for patients with baseline eGFR less than 15 ml/min/1.73 m^2.[14] These associations were confirmed in several recent systematic reviews that demonstrate strong independent associations between risk for AKI and lower baseline eGFR[15-17] (see Fig. 69.2). Although these analyses support a causal association between CKD and in-hospital AKI, little is known about how this association may be modified by the presence of one or more comorbidities such as heart failure or whether all causes of CKD confer similar risk for AKI.

Proteinuria

Proteinuria is also strongly associated with AKI risk. A case-control study of over 600,000 patients identified proteinuria as an independent predictor for AKI,[14] which was replicated in multiple settings, including after cardiac surgery in Taiwan and in general population studies from the United States and Canada[18-20] (Fig. 69.3).

Hyperuricemia

Two prospective randomized trials[20a,20b] also found allopurinol plus hydration to be superior to hydration alone in preventing AKI following radiocontrast administration. Nevertheless, uric acid can also be a biomarker for other risk factors (e.g. mild CKD, cancer) and while the two studies are interesting, more data is needed before this intervention is recommended. Several retrospective studies have observed a graded association between uric acid levels and AKI after cardiac revascularization, as well as in unselected hospitalized patients. A recent systematic review and meta-analysis (n = 13,084) of 18 studies evaluating the association between uric acid and risk for contrast-associated AKI also found that that the presence of hyperuricemia was independently associated with an increased risk for AKI (adjusted odds ratio [OR] 1.68, confidence interval [CI] 95% 1.38-2.04).[21,22]

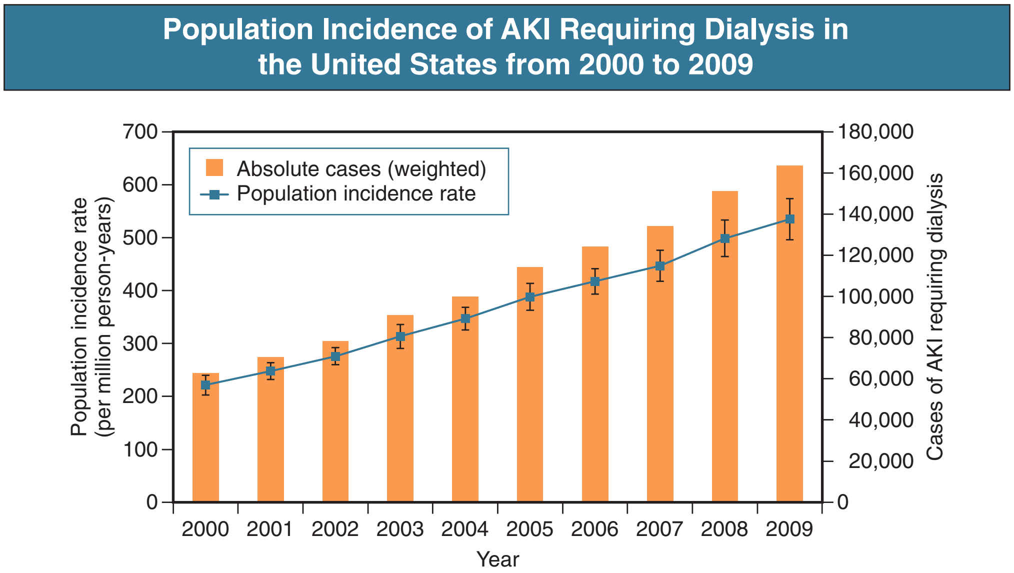

Fig. 69.1 **Population incidence of patients with acute kidney injury *(AKI)* who require dialysis in the United States from 2000 to 2009 (absolute count and incidence rate per million person-years).** Whiskers represent 95% confidence interval for incidence rates. The number of cases of AKI in which patients required dialysis increased from 63,000 in 2000 to almost 164,000 in 2009; the population incidence increased at 10% per year from 222 to 533 cases per million person-years. (From reference 6.)

BOX 69.1 Patient-Specific Risk Factors for Acute Kidney Injury

- Age
- Gender (male)
- Chronic kidney disease
- Proteinuria
- Diabetes
- Congestive heart failure
- Sepsis
- Volume depletion
- Chronic liver disease
- Hyperuricemia

TABLE 69.1 Recent Consensus Definitions of Acute Kidney Injury

Definitions	Serum Creatinine Criteria	Urine Output Criteria
RIFLE (2003)	Increase in serum creatinine × 1.5 or decrease in GFR by 25% within 48 h	Urine volume <0.5 ml/kg/h × 6 h
AKIN (2007)	Increase in serum creatinine × 1.5 or by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 h	Urine volume <0.5 ml/kg/h for 6 h
KDIGO (2012)	Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 h Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days Severity staging after initial criteria met	Urine volume <0.5 ml/kg/h for 6 h

BOX 69.2 Risk Factors for Chronic Kidney Disease After Acute Kidney Injury

- Age
- Baseline eGFR
- Congestive heart failure
- Hypertension
- Recurrent AKI
- Serum albumin during hospitalization
- Severity of AKI (AKI stage, requirement for dialysis)
- eGFR at hospital discharge

AKI, Acute kidney injury; *eGFR,* estimated glomerular filtration rate.

ASSOCIATION BETWEEN ACUTE KIDNEY INJURY AND ADVERSE OUTCOMES

AKI is associated with high costs and adverse clinical outcomes, including excess mortality, increased length of hospital stay, development and/or progression of CKD, and requirement for chronic dialysis in survivors (Box 69.2).

Mortality

Multiple observational studies demonstrate increased mortality among patients who develop AKI in hospital. In its most severe form (requirement for acute dialysis) AKI is associated with mortality ranging from 15% (AKI only) to 80% (AKI in critically ill patients).[23] However, comparing patients with AKI to those without AKI does not distinguish between the increased risk for death caused by kidney disease per se and the increased risk associated with the underlying illness that was sufficiently severe to result in AKI. Therefore there is uncertainty about whether the association between AKI and mortality is truly independent. Nonetheless, the development of AKI signifies a poor prognosis in individual patients.

Small changes in serum creatinine of as little as 25% above baseline are a significant predictor of all-cause short-term mortality.[24] A

Risk of Acute Kidney Injury as a Function of Baseline Kidney Function (Albuminuria and eGFR) for People with and without Diabetes

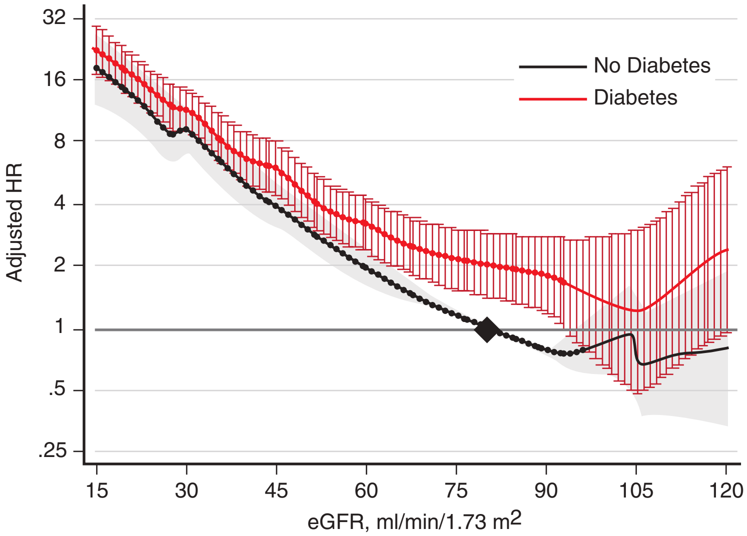

Fig. 69.2 Hazard ratio *(HR)* of acute kidney injury for people with and without diabetes according to baseline estimated glomerular filtration rate. *eGFR,* Estimated glomerular filtration rate.

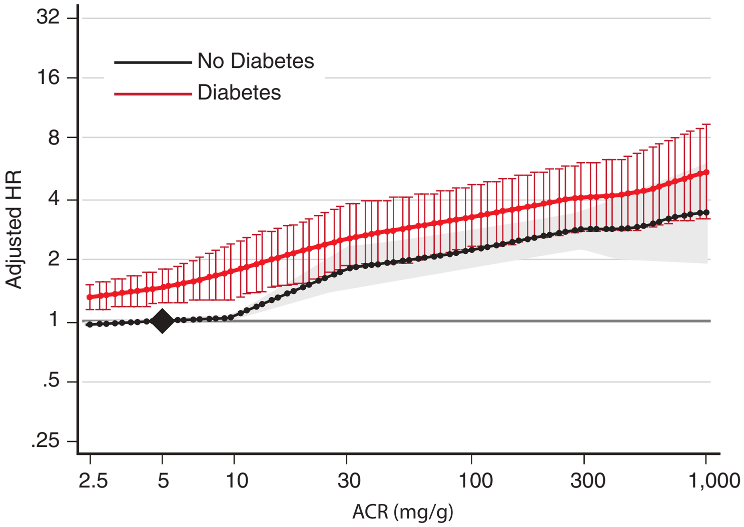

Fig. 69.3 Hazard ratio *(HR)* of acute kidney injury for people with and without diabetes according to the ratio of urine albumin to creatinine. *ACR,* Albumin:creatinine ratio.

meta-analysis of eight studies of hospitalized patients (most of whom were critically ill or had heart failure) confirmed a graded relationship between increasing severity of AKI and short-term mortality.[25] Most importantly, it confirmed that even mild forms of AKI are clinically relevant; an increase in serum creatinine of 0.3 mg/dl (26 μmol/l) was associated with a short-term relative risk for death of 2.3 (95% CI 1.8-3.0). After adjustment for comorbidities, the odds or hazards ratios for death associated with AKI ranged from 1.7 to 1.92. Similar findings were reported in several population-based studies of unselected hospitalized patients.[26]

The association between AKI and mortality is likely influenced by several factors, including the presence of underlying CKD, the duration and severity of AKI, and the degree of recovery of kidney function. A population-based study of hospitalized AKI patients in Canada found that the relation between AKI and in-hospital mortality was strongest in those with severe AKI and baseline eGFR greater than 60 ml/min/1.73 m^2 (adjusted hazard ratio [HR] 10.62, 95% CI 8.78-12.82).[26,27] The presence of CKD modifies this association; by comparison, in patients with a baseline eGFR less than 30 ml/min/1.73 m^2, the adjusted hazard ratio of in-hospital mortality was 4.71 (95% CI 3.61-6.15). An analysis of postoperative AKI comparing renal and survival outcomes in those with and without preexisting CKD (eGFR <45 ml/min/1.73 m^2) found a lower attributable mortality rate because of AKI (HR 1.26, 95% CI 1.09-1.78) when subjects with prior CKD but no AKI were used as the reference.[28]

Although the incidence of AKI continues to climb, there has been a corresponding improvement in survival. A recent analysis reported a 19% decrease in mortality between 2000 and 2009 in patients who required acute dialysis. Whether this represents a trend toward earlier use of dialysis (rather than a true improvement in survival) requires further investigation.

Chronic Kidney Disease

Until recently it was accepted that AKI survivors generally recovered renal function and remained independent from dialysis. This assumption was supported by the findings of small cohort studies of predominantly critically ill patients. One recent study described long-term outcomes of 226 critically ill patients with previously normal eGFR who required acute dialysis for AKI and reported that 86% of survivors had "normal" kidney function at 5 years.[29]

However, an increasing number of recent studies have linked AKI survivorship to the development of CKD or end-stage renal disease (ESRD). For example, in one study AKI (defined using ICD-9 codes) was associated with an eightfold increase in the risk for ESRD compared with subjects without AKI or CKD.[30] A second cohort study evaluated the risk for progressive CKD after AKI in subjects with baseline eGFR greater than 45 ml/min/1.73 m^2,[31] and found that survivors of dialysis-dependent AKI had a 28-fold increased risk for developing stage 4 CKD (eGFR <30 ml/min/1.73 m^2) or greater, compared with those without AKI.[31]

Since then, multiple studies have demonstrated an association between AKI and initiation or progression of CKD and/or ESRD in a variety of clinical settings, including cardiac surgery, cardiac catheterization and in unselected hospitalized patients. A meta-analysis of 13 cohort studies reported that the hazard ratios for CKD and ESRD were 8.8 (95% CI 3.1, 25.5) and 3.1 (95% CI 1.9, 5.0) compared with subjects without AKI. National renal registry data from the United States shows that approximately 2% to 3% of patients with AKI requiring dialysis will fail to recover kidney function and/or progress to ESRD within 1 year.[32] Recurrent episodes of AKI further increase the risk for progressive CKD; each additional AKI event after the first episode appears to double the risk for progression to stage 4 CKD.

It is possible that the apparent association between AKI and CKD is confounded by age, frailty, and unmeasured comorbidity. Also, it is sometimes difficult to distinguish AKI from progressive CKD, and there is the possibility that the observed associations are due to misclassification. However, AKI also has been linked to the development of CKD in children, in whom these potential confounders are less likely.[33] A prospective single-center study of 126 critically ill pediatric AKI survivors who fully recovered kidney function reported that 10% of patients developed CKD (albumin-to-creatinine ratio ≥30 mg/g or eGFR less than 60 ml/min/1.73 m^2) over 3 years of follow-up.[34] Importantly, 38% of the cohort had mildly decreased eGFR (60 to 90 ml/min/1.73 m^2), 3.2% had hypertension, and 8.7% had hyperfiltration—all risk factors for future CKD. Given that the median age of these patients at the time of the AKI episode was 0.5 years, these numbers likely underestimate the long-term risk for CKD for these children. Similar findings were reported in a meta-analysis of outcomes after pediatric hemolytic uremic syndrome.[35]

Cardiovascular Risk

Contrast-induced nephropathy after cardiac catheterization is known to be associated with excess risk for subsequent cardiovascular events; however, there are conflicting data about whether AKI is associated with an increased risk for cardiovascular events in patients without preexisting cardiovascular disease. Several large retrospective cohort studies of patients undergoing both vascular and nonvascular major surgery have recently confirmed an association between postoperative AKI and cardiovascular mortality.[36,37] Further, a recent systematic review analyzed data from 25 cohort studies of patients (n = 254,408) with and without AKI and reported that AKI is associated with an 86% increased risk for cardiovascular mortality, a 38% increased risk for major adverse cardiovascular events and a 40% increased risk for heart failure.[38] The pathophysiology of this association remains unclear.

In summary, the development of AKI during hospitalization identifies a cohort of patients at high risk for adverse outcomes. Recognition of AKI therefore presents an opportunity to mitigate future risk through appropriate monitoring and implementation of evidence-based care for CKD. However, U.S. data suggest that only 5% of AKI survivors saw a nephrologist after hospital discharge,[32] and AKI survivors with CKD and proteinuria often do not receive treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers after discharge from hospital.[39] This treatment gap is undoubtedly larger in patients with AKI from lower income countries.

Health Care Costs

A single-center study of AKI in hospitalized patients demonstrated a direct relationship between severity of AKI and associated hospital length of stay and hospital costs.[24] When defined as a 0.3 mg/dl (26 µmol/l) increase in serum creatinine, AKI was associated with an incremental hospitalization cost of $4886 USD; a doubling of serum creatinine was associated with an incremental cost of $9000. Studies of specific populations of hospitalized patients support these findings; a recent study of the cost of AKI after cardiac surgery suggests that the average difference in postoperative costs ranges between $9000 and $14,000 depending on AKI severity. Postoperative AKI in noncardiac surgery is associated with an $11,308 increase in the median cost compared with patients who do not experience postoperative AKI.[40] In multivariable analysis, AKI was the most costly postoperative complication for these patients and resulted in the largest proportion of resource use compared with all other complications. Another study of 5875 surgical patients found severe AKI requiring RRT to be the second most costly postoperative complication, with an estimated mean increase in hospital expenditures of $28,359 compared with an uncomplicated postoperative course, and resulted in almost twice the excess cost compared with cardiac arrest.[41] However, none of these studies accounted for the impact of CKD on AKI and attendant costs, which is likely to be significant.

ACUTE KIDNEY INJURY AS A PUBLIC HEALTH ISSUE

Conservative population-based estimates of AKI incidence in hospitalized adults are in the range of 3000 per 100,000 person-years[42]; the majority of these patients will survive to hospital discharge. The incidence of stage 4 CKD or greater in AKI survivors is approximately 120 per 100,000 person-years[43] and the number of adults developing new CKD after AKI may be as high as 100,000 per year in the United States alone. Extrapolated to a global scale, AKI is likely responsible for hundreds of thousands of new CKD cases each year. Given this tremendous burden of morbidity and mortality, strategies that mitigate the progression of CKD after AKI should be a public health priority.

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SELF-ASSESSMENT QUESTIONS

1. All of the following are risk factors for acute kidney disease (AKI) except:
   - **A.** Age
   - **B.** Chronic kidney disease
   - **C.** Congestive heart failure
   - **D.** Thyroid disorders
   - **E.** Diabetes
2. The incidence of AKI in hospitalized patients has:
   - **A.** Decreased by >10% annually over the last decade
   - **B.** Decreased by 1% over the last decade
   - **C.** Increased by >10% annually over the last decade
   - **D.** Increased by 1% annually over the last decade
   - **E.** Stayed the same
3. AKI is associated with:
   - **A.** Higher health care costs
   - **B.** Increased risk for CKD
   - **C.** Increased risk for chronic dialysis
   - **D.** All of the above
4. The incidence of stage 4 CKD (eGFR below 30 ml/min/1.73 m^2) or greater in AKI survivors is approximately:
   - **A.** 1200 per 100,000 person-years
   - **B.** 120 per 100,000 person-years
   - **C.** 12 per 100,000 person-years
   - **D.** 1.2 per 100,000 person-years

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Prevention and Nondialytic Management of Acute Kidney Injury

Josée Bouchard, Etienne Macedo, Ravindra L. Mehta

Acute kidney injury (AKI) often results from a combination of insults. The most commonly associated causes are failure of renal autoregulation, direct nephrotoxicity, ischemia/reperfusion, and inflammatory states. AKI severity predicts adverse outcomes, including requirement for renal replacement therapy (RRT), length of hospital stay, and mortality. Studies using the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease Improving Outcomes (KDIGO) classification systems (see Chapter 68) have shown that even small changes in creatinine levels are associated with short-term and long-term mortality.[1,2] Furthermore, the distant effects of AKI contribute to dysfunction of other organs, such as the heart, lungs, brain, and liver.[3] Consequently, primary prevention and early diagnosis of AKI are of primary importance. Once AKI has been detected, efforts to attenuate the effects of injury and treatment of its consequences are necessary.

RISK ASSESSMENT

Considering the conceptual model of AKI illustrated in Fig. 70.1, the first step in preventing AKI is an adequate risk assessment. The initial care of patients at risk should focus on identification and, if possible, reversal of the risk factors. Several factors are associated with AKI (Box 70.1 and Table 70.1). Risk scores are also available to help predict AKI, most often in specific conditions (see Table 70.1). However, in most clinical settings, there are scarce data to evaluate the prevalence and potential impact of modifiable risk factors on AKI development and progression. The most common risk factor is chronic kidney disease (CKD), and thus adequate determination of baseline kidney function is fundamental. Because 40% to 50% of patients do not have a baseline renal function available, and the first creatinine measured in the hospital may be affected by the disease process occurring before hospital admission, CKD status is sometimes difficult to determine. More sensitive and specific biomarkers of cellular damage may help enable early risk assessment. For a further discussion of risk factors and scoring systems, see Chapters 68 and 69.

PRIMARY PREVENTIVE MEASURES

Optimizing Volume and Hemodynamic Status

To prevent AKI, adequate renal perfusion is required. Prompt resuscitation of patients with hypoperfusion was shown to improve outcomes more than a decade ago.[4] Adequate perfusion is ensured by optimizing volume status and maintaining hemodynamic status and cardiac output. Common reasons for fluid administration and/or vasopressors to prevent AKI include hypovolemia, hypotension, and sepsis. However, assessment of volume status can be challenging, particularly in patients in the intensive care unit (ICU). In addition, studies in ICU patients or patients undergoing surgery have shown that only about half of hemodynamically unstable patients respond to fluid administration. There are no guidelines for optimizing hemodynamic and fluid status for renal function preservation. Too often, the effect of fluid expansion on hemodynamic status and renal function is retrospective and evaluated by trial and error. However, dynamic measures such as the passive leg raising maneuver and the fluid bolus test coupled with real-time stroke volume monitoring can determine fluid responsiveness accurately.[5,6] Unfortunately, these are rarely performed even in ICUs. On the ward, volume status assessment and response to fluid administration most often relies on blood pressure, heart rate, oxygen saturation, central venous pressure, and urine output. These parameters are known to be not specific or sensitive, thus better, simple tools are urgently needed to assess volume status and fluid responsiveness outside ICUs. In emergency settings, point of care ultrasound can be useful. For example, a collapsing inferior vena cava at the end of expiration is suggestive of hypovolemia.

Four phases of fluid therapy have recently been conceptualized, including rescue, optimization, stabilization, and deescalation.[7] *Rescue* implies the "administration of fluid for immediate management of life-threatening conditions associated with impaired tissue perfusion." *Optimization* refers to the "adjustment of fluid type, rate, and amount based upon context to achieve optimization of tissue perfusion." Fluid boluses are used during the rescue phase, whereas fluid challenges are administered during the optimization phase. Fluid bolus in an adult typically includes the infusion of 500 ml of isotonic fluids over 15 minutes or less without close monitoring. Fluid challenge involves the administration of 250 ml or 3 ml/kg of isotonic fluids over 5 to 10 minutes with stroke volume (SV) reassessment. Some studies have defined fluid responders as an increase of 10% to 15% of SV or cardiac output after fluid challenge. These two phases are essential in preventing AKI secondary to hypoperfusion. *Stabilization* aims for achieving a neutral or slightly negative fluid balance to favor organ support, and *deescalation* is defined by the "minimization of fluid administration; mobilization of extra fluid to optimize fluid balance." In the stabilization and deescalation phases, clinicians should target a neutral and then a negative fluid balance if fluid overload is present. To obtain a neutral or negative fluid balance, fluid administration should be minimized and oral or intravenous diuretics or even ultrafiltration may be required depending on the clinical scenario and underlying kidney and cardiac function. Adverse outcomes associated with fluid overload include cardiopulmonary complications, delayed wound healing and kidney function recovery, and increased mortality.[8,9] A retrospective study has shown that elevated central venous pressure within the first 24 hours

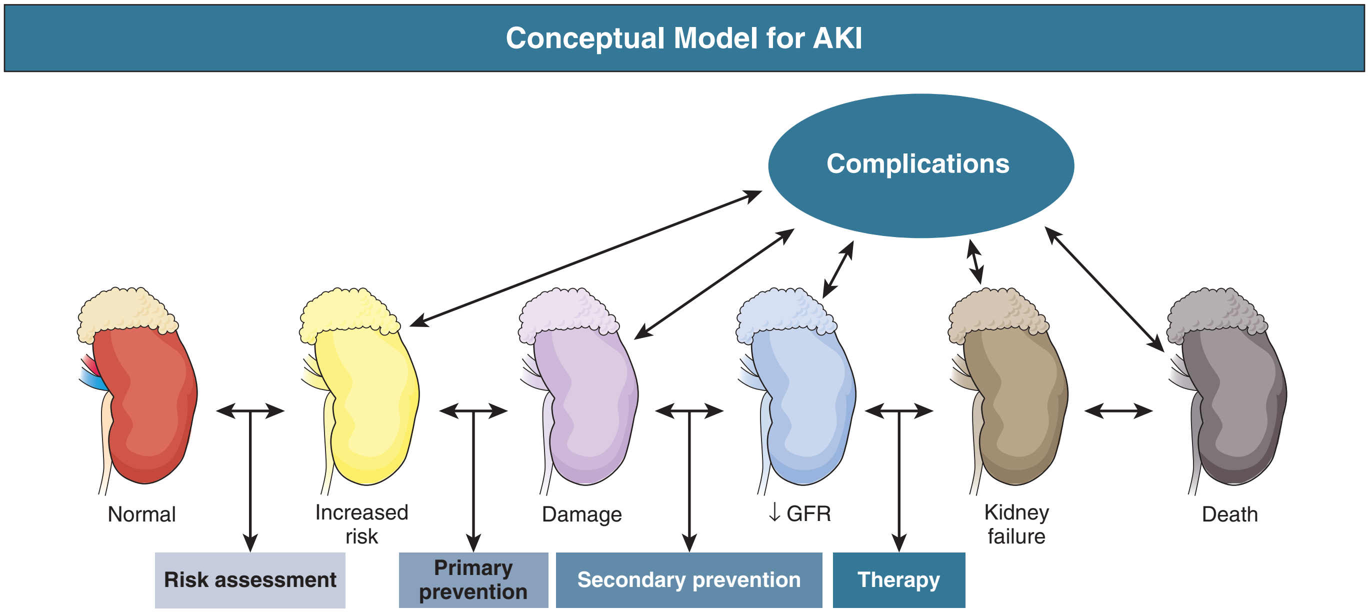

Fig. 70.1 Conceptual model for acute kidney injury (AKI). *GFR,* Glomerular filtration rate. (Modified from reference 48.)

BOX 70.1 Major Risk Factors for Acute Kidney Injury

Patient Factors

- Older age (>75 years)
- Diabetes
- Liver failure
- Chronic kidney disease
- Atherosclerosis
- Renal artery stenosis
- Hypertension
- Hypotension
- Hypercalcemia
- Hyperuricemia
- Sepsis
- Perioperative cardiac dysfunction
- Rhabdomyolysis
- Tumor lysis syndrome

Medications and Agents

- Nonsteroidal antiinflammatory drugs
- Cyclooxygenase-2 inhibitors
- Cyclosporine or tacrolimus
- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Iodinated radiocontrast agent
- Hydroxyethyl starch (HES)
- Aminoglycosides
- Amphotericin

Procedures

- Cardiopulmonary bypass procedures
- Surgery involving aortic clamp
- Increased intraabdominal pressure
- Large arterial catheter placement with risk for atheroembolization
- Liver transplantation
- Kidney transplantation

of ICU admission was associated with AKI, suggesting a role of venous congestion in the development of AKI.[10]

There is controversy about the optimal fluid to use for resuscitation. The recent KDIGO AKI guidelines suggest that isotonic crystalloids should be used instead of synthetic (hydroxyethyl starch [HES]) and nonsynthetic (albumin) colloids for intracellular volume expansion in patients at risk or presenting with AKI, in the absence of hemorrhagic shock.[11] Large studies have clearly demonstrated that HES solutions increase the risk for AKI. A randomized controlled trial (RCT) in 7000 ICU patients has shown that even solutions with lower molecular weight such as 6% HES 130/0.4 increased the need for RRT compared with 0.9% sodium chloride (normal saline).[12] Another large RCT including 804 patients with severe sepsis has shown that 6% HES 130/0.4 is detrimental to kidney function and also survival compared with Ringer acetate.[13] The mechanism of HES-induced AKI may be due to proximal renal epithelial cell uptake of HES causing an acquired lysosomal storage disease. Therefore HES should be avoided in patients at risk for and with AKI.

For albumin, the Saline Versus Albumin Fluid Evaluation (SAFE) trial of 6997 critically ill patients found that fluid resuscitation with saline or albumin resulted in similar relative risks for death.[14] In addition, no significant differences were found in new single-organ and multiple-organ failure or days on RRT. Two subgroup analyses from this study showed that use of albumin may be deleterious in patients with traumatic brain injury and potentially beneficial in sepsis. Therefore the use of albumin can be considered when substantial amounts of crystalloids (e.g., 2 liters) are required to maintain adequate mean arterial pressure (MAP), especially in septic patients. However, its effect must be balanced against its potential risks; that is, it is possibly deleterious in patients with trauma and has low potential for transmission of infectious diseases.

The type of crystalloids used may influence renal outcomes. A study comparing renal artery flow velocity and renal cortical tissue perfusion showed a significant reduction in renal artery flow and cortical tissue perfusion with saline but not with the use of chloride-restrictive fluids. Indeed, greater chloride delivery to the macula densa may activate tubuloglomerular feedback, triggering renal vasoconstriction and reduced glomerular filtration rate (GFR). A large retrospective study showed that chloride-restrictive fluids (lactated solution with balanced buffer–chloride concentration of 98 mmol/l or chloride-poor 20% albumin-chloride concentration of 19 mmol/l) compared with chloride-rich intravenous fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) were associated with a significant decrease in AKI and RRT requirement.[15] A meta-analysis confirmed that high-chloride fluids significantly increased the risk for AKI.[16] However, the recent SPLIT trial, a large RCT including 2278 patients, failed to show differences in renal outcomes with the use of the same buffered crystalloid than the aforementioned study compared with 0.9% saline.[17] In this study, AKI was defined as a rise in serum creatinine level of at least twofold. Critiques of this study included the low severity of disease at baseline

TABLE 70.1 Specific Risk Factors for the Development of Acute Kidney Injury in Common Clinical Situations

Postoperative (General)		
Miscellaneous	**Hemodynamic**	**Gastrointestinal and Endocrine**
Age	Congestive heart failure	Cirrhosis/biliary surgery
Proteinuria	Aortic cross-clamping	Obstructive jaundice
Hypertension	Cardiac instability	Diabetes mellitus
Massive blood transfusion	Major vascular surgery	Hyperglycemia
	Infection/sepsis	
	Multiorgan failure	
Cardiac Surgery		
Female gender	ACE inhibitor therapy	Emergency surgery
COPD	Heart failure	Valve surgery only
Proteinuria	LV ejection fraction <35%	Previous cardiac surgery
Preoperative S_{Cr} >2.1 mg/dl	Preoperative IABP	Other cardiac surgery
Anemia	Hyperglycemia	Combination of CABG + valve surgery
Insulin-requiring diabetes	Hyperuricemia	Blood transfusion
Critically Ill		
High A-a gradient*	Age	
Low serum albumin	S_{Cr} >1.3 mg/dl	
Proteinuria	Serum bilirubin >1.5 mg/dl	
Hyperglycemia	Elevated CVP >8 cm	
High intraabdominal pressure	Hemodynamic instability	
Active cancer	Sepsis	
Iodinated Contrast Administration		
Age >75 yr	Volume of contrast >100 ml	
Heart failure	Intraarterial injection	
Diabetes mellitus	Systolic BP <80 mm Hg for >1 hr and need for inotropic support or IABP 24 hr after procedure	
S_{Cr} >1.5 mg/dl or eGFR <60 ml/min/1.73 m^2	Use of IABP	
History of pulmonary edema		
Anemia/blood loss (Hct: <39% for men; <36% for women)		
Hyperuricemia		
Nephrotoxic Antibiotics		
Volume depletion	Amphotericin	
Older age	Aminoglycosides	
Chronic kidney disease		
Duration of therapy >7 days		
Volume depletion		
Divided dose regimens		
Liver disease		

(Modified from Lameire N, Van Biesen W, Vanholder R. Epidemiology, clinical evaluation, and prevention of acute renal failure. In: Feehally J, Floege J, Johnson RJ, eds. Comprehensive Clinical Nephrology. Philadelphia: Mosby-Elsevier; 2007:771–785.)

*A-a gradient, alveolar-arterial oxygen gradient calculated with the sea level standard formula (713 × FiO_2) – (PCO_2/0.8) – PaO_2, where FiO_2 is fractional inspired oxygen concentration, PaO_2 is arterial partial oxygen pressure, and PCO_2 is partial carbon dioxide pressure.

ACE, Angiotensin-converting enzyme; *CABG,* coronary arterial bypass graft; *COPD;* chronic obstructive pulmonary disease; *CVP,* central venous pressure; *Hct,* hematocrit; *IABP:* intraaortic balloon pump; *LV,* left ventricular; S_{Cr}, serum creatinine.

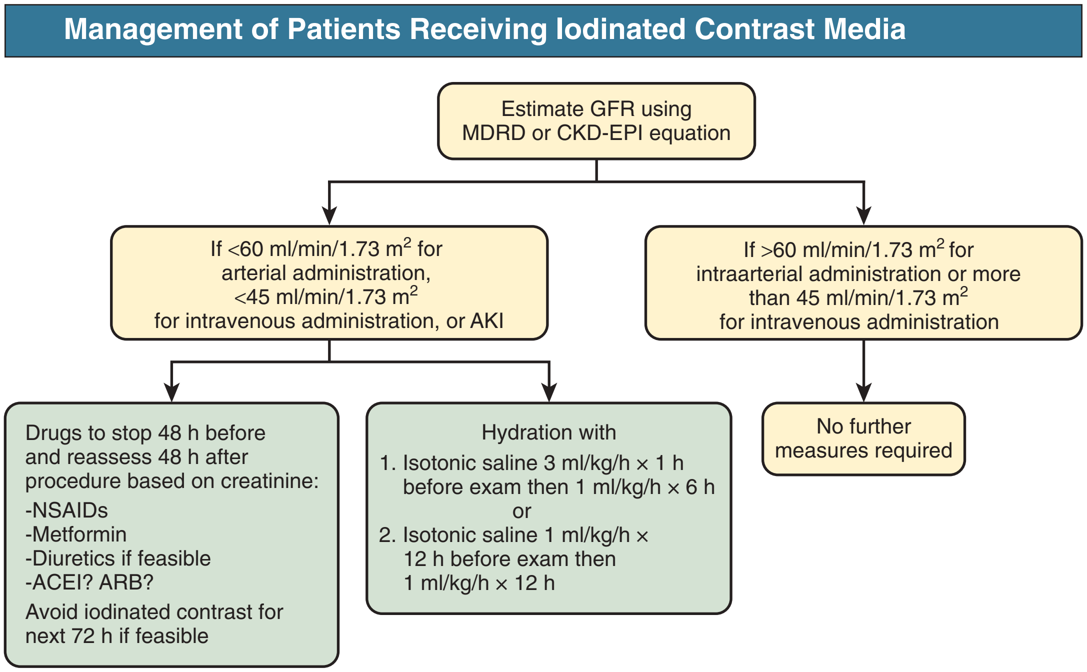
Management of Patients Receiving Iodinated Contrast Media
Estimate GFR using MDRD or CKD-EPI equation
If <60 ml/min/1.73 m^2 for arterial administration, <45 ml/min/1.73 m^2 for intravenous administration, or AKI
If >60 ml/min/1.73 m^2 for intraarterial administration or more than 45 ml/min/1.73 m^2 for intravenous administration
Drugs to stop 48 h before and reassess 48 h after procedure based on creatinine:
-NSAIDs
-Metformin
-Diuretics if feasible
-ACEI? ARB?
Avoid iodinated contrast for next 72 h if feasible
Hydration with
1. Isotonic saline 3 ml/kg/h × 1 h before exam then 1 ml/kg/h × 6 h
or
2. Isotonic saline 1 ml/kg/h × 12 h before exam then 1 ml/kg/h × 12 h
No further measures required

Fig. 70.2 Management of patients receiving iodinated contrast media. *ACEI,* Angiotensin-converting enzyme inhibitor; *AKI,* acute kidney injury; *ARB,* angiotensin receptor blocker; *CKD-EPI,* Chronic Kidney Disease Epidemiology Collaboration; *D5W,* 5% dextrose in water; *GFR,* glomerular filtration rate; *MDRD,* Modification of Diet in Renal Disease; *NSAIDs,* nonsteroidal antiinflammatory drugs.

and low volume of fluid administered (2.6 liters ± 2.1 to 3.0 liters in each group). In addition, the solution used contained acetate (which may cause myocardial toxicity) and gluconate (which may have other metabolic effects). In conclusion, the use of low-chloride solutions does not improve renal outcomes compared with normal saline in patients at low-moderate risk for AKI. Two large RCTs are ongoing to assess outcomes associated with different type of fluid solutions in high-risk populations. Currently, the choice of chloride-rich versus low-chloride solutions needs to be based on the patient's clinical condition, including electrolyte and acid-base balance, as well as availability and costs.

There is no consensus on how to use vasopressors to prevent AKI or avoid further deterioration of kidney function. According to international guidelines for sepsis management, after initial fluid resuscitation with 30 ml/kg of crystalloids and addition of albumin in patients requiring substantial amounts of crystalloids to maintain adequate MAP, vasopressors should be initiated targeting a MAP above 65 mm Hg.[18] In sepsis, norepinephrine is the first-choice vasopressor. With regard to the kidney, a recent RCT showed that vasopressin is equivalent or may be better than norepinephrine to improve kidney outcomes in patients with septic shock.[19] RRT was required in 25% of patients in the vasopressin group and in 35% of the norepinephrine group; however, rates of RRT were comparable among survivors from each group, and the overall mortality rate was also similar between groups.

Finally, inotropic agents such as dobutamine should be administered if myocardial dysfunction or ongoing signs of hypoperfusion are present. The optimal MAP values to prevent AKI need to be better delineated. One study has found that in hypertensive patients with septic shock, targeting MAP between 80 to 85 mm Hg instead of 65 to 70 mm Hg reduced the risk for AKI and RRT, whereas the risk for atrial fibrillation seemed to be heightened.[20] Therefore target MAP values may need to be individualized depending on age, hypertension status, and degree of peripheral artery and renovascular disease.

Prevention of Contrast-Induced Acute Kidney Injury

The concept of contrast-induced AKI (CI-AKI) has been recently questioned. However, physicians are less likely to prescribe contrast to patients with CKD and more likely to prescribe intravenous fluids if contrast is administered, which may affect results from observational studies.

The Prevention of CI-AKI Consensus Working Panel recommends that measures to reduce the AKI risk should be implemented in patients with a baseline estimated GFR (eGFR) below 60 ml/min/1.73 m^2. According to the KDIGO guidelines, this threshold could probably be lowered to 45 ml/min/1.73 m^2. For prevention of CI-AKI, patients at risk should receive intravenous hydration (Fig. 70.2). Hydration with isotonic saline is superior to half-isotonic (0.45%) saline.[21] An RCT compared isotonic saline with isotonic sodium bicarbonate (three 50-ml ampules of 1 mmol/ml sodium bicarbonate added to 850 ml of 5% dextrose) at 3 ml/kg/h for 1 hour before the procedure followed by 1 ml/kg/h for the 6 hours after the procedure. CI-AKI was significantly lower in the bicarbonate compared with the saline group (2% vs. 14%).[22] The superiority of bicarbonate was subsequently confirmed in some but not all RCTs. The rationale for isotonic bicarbonate was based on animal studies showing that bicarbonate is capable of scavenging reactive oxygen species, and the increased pH in the proximal tubule and the renal medulla associated with bicarbonate administration could reduce generation of superoxide. Most hydration studies with isotonic bicarbonate used shorter infusion protocols (7 hours) than those with isotonic saline (usually 12 to 24 hours), which is attractive for emergency procedures. However, there are risks for compounding errors with sodium bicarbonate that can lead to electrolyte disorders. The KDIGO AKI guidelines recommend either isotonic sodium chloride or sodium bicarbonate solutions in patients at risk for CI-AKI unless there are contraindications to volume expansion. However, the 2 × 2 factorial design (PRESERVE) trial aiming to compare the effectiveness of sodium bicarbonate with isotonic sodium chloride and oral *N*-acetylcysteine (NAC) with placebo in 8680 high-risk patients scheduled to undergo coronary or noncoronary angiography recently showed no difference in terms of AKI or mortality between the use of sodium bicarbonate and isotonic sodium chloride. The use of NAC is discussed later in this chapter.

Iodinated contrast can be categorized according to osmolality into high-osmolar contrast medium (approximately 2000 mOsm/kg), low-osmolar contrast medium (600 to 800 mOsm/kg), and iso-osmolar contrast medium (290 mOsm/kg). Clinical studies suggest that the risk for nephrotoxicity increases with increasing osmolarity but the higher cost of iso-osmolar agents prevents their universal use. The KDIGO AKI guidelines recommend either iso-osmolar or low-osmolar iodinated contrast for patients at risk for CI-AKI.

The volume of contrast administered is also an independent predictor of CI-AKI and should be reduced as much as possible. Based on the volume of contrast given (V; ml) and the creatinine clearance (CrCl; ml/min), a V/CrCl ratio above 3.7 independently predicts CI-AKI. Administration of iodinated contrast more than once over 48 to 72 hours should be avoided. The drugs used for CI-AKI prevention are included in the section on pharmacologic approaches.

Prevention of Drug-Induced and Nephrotoxin-Induced Acute Kidney Injury

Drug-induced nephrotoxicity often can be predicted because it is more common in certain patient populations and clinical situations. Prevention involves the knowledge of mechanisms of renal injury, patient-related risk factors, and drug-related risk factors. The most important patient-related factors are older age (60 years or older), CKD, diabetes, heart failure, volume depletion, and sepsis. Preventive measures include correctly estimating the GFR before initiation of therapy, adjusting the dosage, monitoring renal function and drug dosage during therapy, and the administration of intravenous saline before exposure if possible. Alternative non-nephrotoxic drugs should be used, and nephrotoxic drug combinations should be avoided whenever feasible.

Amphotericin

Amphotericin-associated nephrotoxicity can occur in as many as one third of treated patients, and the risk for AKI increases with higher cumulative doses. Lipid formulations cause less nephrotoxicity compared with the standard formulation, and therefore amphotericin deoxycholate is preferred over conventional amphotericin; however, it is significantly more expensive. Recently alternative antifungal agents such as itraconazole, voriconazole, and caspofungin have been more commonly used in patients at high risk for AKI and should be used rather than conventional amphotericin.

Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) cause vasodilation of the efferent glomerular arteriole, further reducing intraglomerular pressure already compromised by the blood pressure–lowering effect of these agents. After the initiation of an ACE inhibitor or ARB, if creatinine increases by more than 30%, bilateral renal artery stenosis, stenosis of the renal artery in a solitary kidney, diffuse intrarenal small-vessel disease, or generalized volume depletion should be suspected, and these drugs discontinued. It remains unclear whether withdrawing an ACE inhibitor or ARB before iodinated contrast administration is beneficial.

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided in CKD and intravascular volume depletion because they inhibit cyclooxygenase, which blocks prostaglandin-induced vasodilation of the afferent arteriole, potentially reducing GFR and renal blood flow. In critically ill patients, renal hypoperfusion caused by decreased effective circulating volume is relatively common and inhibition of prostaglandin-induced vasodilation may further compromise renal blood flow and exacerbate ischemic injury.

Aminoglycosides

AKI caused by aminoglycoside nephrotoxicity (AG-AKI) usually occurs 5 to 10 days after initiation of the treatment. AG-AKI is typically nonoliguric and associated with decreased urine concentrating ability and urinary magnesium wasting. A recent large population-based study in adults undergoing surgery receiving antibiotic prophylaxis found an association between one dose of gentamicin (4 mg/kg) and AKI that challenges the notion that AG-AKI only occurs after a few days of treatment.[23] Because of the toxicity of aminoglycosides, the KDIGO guidelines recommended against using them in patients with or at risk for AKI unless no other alternative is available. With multiple daily administration schedules, elevated aminoglycoside peak levels appear to correlate with nephrotoxicity. Because aminoglycoside uptake by proximal tubular cells is saturable, once-daily administration can decrease tubular cell toxicity. In the general population, extended intervals between doses maintains the target dose while decreasing the risk for nephrotoxicity compared with multiple daily doses; therefore, in patients with normal kidney function who are not at risk for AKI, aminoglycosides should be administered daily if possible.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is caused by uric acid and calcium-phosphate precipitation in the tubules. Identification of patients at high risk is fundamental to prevent AKI in this setting. The most common hematologic malignancies associated with TLS are aggressive lymphomas and acute lymphoblastic leukemia. The risk factors for TLS are related to patient (age, baseline renal function) and tumor characteristics (cell turnover rate, growth rate, extensive bone marrow involvement, tumor bulk, and chemosensitivity).[24] Baseline uric acid higher than 7.5 mg/dl, lactate dehydrogenase levels greater than 1500 U/l and white blood cells greater than 25×10^9/l are also risk factors. The diagnosis is based on two simultaneous laboratory abnormalities occurring within 3 days before or 7 days after chemotherapy: uric acid greater than 8 mg/dl, potassium greater than 6 mEq/l, phosphate above 4.5 mg/dl, calcium less than 7 mg/dl or any symptomatic hypocalcemia.

In patients at low risk for developing TLS, management includes hydration and close monitoring of volume status and renal function. The use of urine alkalinization to promote elimination of urate is not recommended because it can induce calcium phosphate deposition and therefore aggravate TLS. In patients at intermediate and high risk, aggressive hydration with isotonic saline 2 to 3 l/m^2 per day aiming for urine output between 80 to 100 ml/m^2/h should be initiated. In patients at intermediate risk with uric acid levels lower than 8 mg/dl, a xanthine oxidase inhibitor such as allopurinol also should be started 2 days before chemotherapy, whereas rasburicase should be used in patients with uric acid levels higher than 8 mg/dl. Rasburicase should not be used in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. For high-risk patients, a single dose of rasburicase (up to 0.2 mg/kg, although a lower dose is usually prescribed) is recommended, followed by close monitoring of uric acid levels. If uric acid normalizes, allopurinol treatment can be started. If urine output decreases despite adequate fluid administration, a loop diuretic should be added, and RRT will be required if oliguria persists.

Secondary prevention. After the renal insult has occurred, secondary preventive measures should be directed to avoid further injury, facilitate repair and recovery, and prevent complications. The timeliness of interventions is crucial to their effectiveness. Various approaches have been applied but are best appreciated in the context of specific clinical scenarios.

Traumatic and Nontraumatic Rhabdomyolysis

The main step in preventing AKI after traumatic rhabdomyolysis and crush syndrome is early and aggressive fluid therapy.[25] Intravenous isotonic saline should be initiated even before the crushed limb is relieved to prevent precipitation of the pigment in the tubular lumen. Fluid should be administered aiming to target urine output of 200 to 300 ml/h. Fluid composition is controversial because no direct comparative trials have been performed. Recommendations to use sodium bicarbonate intend to maintain alkaline urine and decrease precipitation of myoglobin and arteriolar vasoconstriction. However, sodium bicarbonate also can precipitate calcium phosphate deposition and worsen hypocalcemia and should be avoided in severe hypocalcemia or metabolic alkalosis. On the other hand, large volumes of normal saline can cause hyperchloremic metabolic acidosis. Some experts use both normal saline and sodium bicarbonate. For example, if urine pH is less than 6.5, each liter of normal saline can be alternated with 850 ml of 5% dextrose plus 150 mmol of sodium bicarbonate. Mannitol has been suggested to be beneficial because of its diuretic, antioxidant, and vasodilatory properties. Mannitol could prevent renal tubular cast deposition, expand extracellular volume, and reduce intracompartmental pressure, muscle edema, and pain. However, mannitol may exacerbate heart failure and nephrotoxicity, requires close monitoring, and is contraindicated in oliguria, hypervolemia, hypertension, and heart failure. Mannitol can be considered if urine flow is higher than 20 ml/h at a rate of 5 g/h added to each liter of infusate not to exceed 1 to 2 g/kg/day. Muscle damage induces stretch-activated ion channels, allowing for influx of calcium into cells after reperfusion. The resultant hypocalcemia is usually asymptomatic but can lead to cardiac dysrhythmias. Hence, care must be taken to avoid sodium bicarbonate–induced hypocalcemia, which can trigger tetany, seizures, and cardiotoxicity and worsen muscle damage. During AKI recovery, hypercalcemia is frequent, mainly in patients who received calcium infusion, as a result of the mobilization of previously precipitated calcium. Thus hypocalcemia should be treated only if symptomatic.

In treating patients with rhabdomyolysis, it is important to consider when to stop fluid resuscitation. A general recommendation is to stop when creatine kinase levels decrease to less than 5000 U/l and myoglobinuria disappears, as shown by a negative urine dipstick for blood. However, the risk for fluid accumulation and compartmental expansion always should be evaluated. Frequent assessment of serum creatinine, uric acid, and creatine kinase also help the clinician determine the appropriate volume expansion. RRT should be considered in resistant hyperkalemia or metabolic acidosis, rapidly rising serum potassium, oliguria, anuria, or volume overload.

Hyperglycemia

It remains uncertain whether strict control of blood glucose reduces AKI incidence and mortality. In a large RCT in ICU patients, intensive glucose control (glucose of 81 to 108 mg/dl [4.5 to 6.0 mmol/l]) increased the risk for death at 90 days compared with conventional glucose control (<180 mg/dl [<10 mmol/l]). Intensive glucose control also increased the risk for severe hypoglycemia. There was no change in the incidence of AKI or use of RRT. Other studies have not found an increase in mortality with intensive glucose control. In summary, intensive glucose control in ICU patients increased the incidence of severe hypoglycemia and either increased or had no effect on mortality compared with blood glucose ranges of 140 to 180 mg/dl (7.8 to 10 mmol/l) and 180 to 200 mg/dl (10 to 11 mmol/l). We recommend maintaining glucose concentration in the range of 110 to 149 mg/dl (6.1 to 8.3 mmol/l).

Remote Ischemic Preconditioning

Remote ischemic preconditioning (RIPC) is performed by applying inflation of a blood pressure cuff for four or five short cycles in the upper or lower limb. RIPC aims to create brief ischemia and reperfusion in the arm or leg to provide protection in distant organs, such as heart, kidney, lung, and brain. The underlying mechanisms include activation of humoral factors, including adenosine, bradykinin, cannabinoids, in addition to subcellular modulators, nuclear factor-B and nitric oxide (NO). Two recent large RCTs in cardiac surgery found that RIPC does not confer a benefit over sham conditioning (placebo).[26,27] In one RCT, the combined outcome of MACE (major adverse cardiovascular events: death from cardiovascular causes, nonfatal myocardial infarction, coronary revascularization, or stroke) 12 months after randomization was similar in RPIC compared with sham procedure. In the other, no difference was found in death, myocardial infarction, stroke, or AKI at hospital discharge. Currently, the use of RIPC for preventing cardiac surgery and contrast-induced AKI is controversial because its beneficial effects may be conditioned by the use of propofol as an anesthetic.

Pharmacologic Approaches

Because of the multiple different causes of AKI, various pathways have been targeted in studies to prevent or alter the course of AKI. These pathways include inhibition of inflammatory mediators, enhancement of renal perfusion by blocking vasoconstrictor mechanisms and intensifying vasodilator mechanisms, attenuation of leukocyte infiltration, inhibition of the coagulation cascade, and administration of growth factors to accelerate renal recovery. Most of these preventive strategies were successful in animal models but did not translate into beneficial effects in patients. Only a few have shown benefits (Table 70.2).

N-Acetylcysteine

N-Acetylcysteine (NAC) is a tripeptide analogous to glutathione and is able to cross cellular membranes. NAC may reduce vasoconstriction and oxygen free radical generation after the administration of contrast material. Because an increased production of free radicals by the kidneys is partly responsible for their cellular damage in postischemic and nephrotoxic AKI, several clinical studies have attempted to use NAC to prevent AKI, mainly in CI-AKI and during cardiac surgery.

In the initial study, NAC at a dose of 600 mg orally twice daily the day before and the day of the procedure prevented AKI after iodinated contrast administration. However, numerous subsequent studies have shown conflicting results. The recent PRESERVE trial has shown that the use of NAC does not provide any benefit to prevent CI-AKI. Therefore, we no longer recommend using NAC to prevent CI-AKI.

Loop Diuretics and Natriuretics

Diuretics are often used to manage fluid in patients who develop AKI. Although nonoliguric AKI has been associated with better outcomes than oliguric AKI, diuretics have been shown to be ineffective in the prevention of AKI or for improving outcomes once AKI occurs. In addition, diuretics should be avoided when AKI is attributed to prerenal causes. Meta-analyses have confirmed that the use of diuretics to prevent AKI did not reduce in-hospital mortality or need for RRT.[29] An RCT including 94 patients undergoing high-risk cardiac surgery showed that prophylactic nesiritide (β-type natriuretic peptide) did not reduce RRT requirement or lengths of stay, although AKI rates were lower with nesiritide.[30] In opposition, a Japanese RCT including 303 patients with CKD who underwent coronary artery bypass graft (CABG) surgery

TABLE 70.2 **Summary of Drugs Used in Prevention of Acute Kidney Injury**

Drug	Level of Evidence	Results	Comments
Dopamine	RCTs	No effect on kidney function	
Fenoldopam	Small RCTs One meta-analysis	No effect on kidney function Beneficial effect on kidney function	Further studies required
Norepineprine vs. vasopressin	RCT in septic shock	Tendency toward less renal replacement therapy with vasopressin	Further studies required
Loop diuretics	RCTs and meta-analysis	No effect on kidney function	
Nesiritide	RCTs in cardiac surgery	Decreased incidence of AKI Controversial effect on renal replacement therapy requirement	Further studies required
N-Acetylcysteine	RCTs and meta-analysis	No effect in CI-AKI	
Statins	Retrospective studies: Perioperative period RCTs in CI-AKI	Beneficial effect on kidney function Possible beneficial effect on kidney function	Further studies required Patients not receiving statins who need this drug for other indications may reasonably receive statins before their angiography
Insulin	Meta-analyses	Controversial effect	KDIGO recommends to target blood glucose 110-149 mg/dl (6.1-8.3 mmol/l)
Calcium channel blockers	RCT in peri-transplant period	No effect on kidney function	Further studies required
Levosimendan	Meta-analysis in cardiac surgery	Beneficial effect on kidney function and need for renal replacement therapy	Further studies required
Adenosine antagonists	RCTs	Controversial effect on kidney function	Further studies required
Erythropoietin	RCTs in cardiac surgery, critically ill and CI-AKI	No effect on kidney function	
Small interfering RNA targeting p53	Animal models and phase 1	Beneficial effect on kidney function	Phase 2 trial just finished in cardiac surgery
THR-184*	Phase 2 RCT	No effect on kidney function	
Multipotent stem cells	Animal models	Beneficial effect on kidney function	Human studies required
Mesenchymal stem cells	Phase I clinical trials	Decreased incidence of AKI	Further studies required

CI-AKI, Contrast-induced acute kidney injury; *KDIGO,* Kidney Disease: Improving Global Outcomes (KDIGO); *PO,* by mouth; *RCTs,* randomized controlled trials; *RNA,* ribonucleic acid; *, a bone morphogenetic protein-7 agonist.

showed that human atrial natriuretic peptide (hANP, carperitide) decreased postoperative serum creatinine and need for dialysis,[31] although other studies using the same medication have shown increased mortality in patients with acute heart failure. Further studies are required.

Vasoactive Agents

Renal-dose dopamine 0.5 to 3 mcg/kg/min given as a renal vasodilator increases urine output, but several studies have confirmed that this drug does not affect AKI outcome or mortality.[32] Dopexamine, a synthetic dopamine analogue, is a dopamine type-1 and less potent dopamine type-2 receptor agonist. Small studies performed in patients undergoing liver transplant surgery have not found a beneficial effect of dopexamine in preventing AKI.

An RCT in 409 patients with septic shock showed that norepinephrine is equivalent to vasopressin in terms of kidney failure–free days.[19]

Fenoldopam is a pure dopamine type-1 receptor agonist with hemodynamic renal effects similar to those of low-dose dopamine, without systemic α- or β-adrenergic stimulation. In a meta-analysis, fenoldopam was shown to reduce the risk for AKI in postoperative or critically ill patients (odds ratio 0.43).[33] Intrarenal administration of fenoldopam allows the use of a substantial dose of fenoldopam mesylate while avoiding systemic adverse effects, such as hypotension. In a registry of 268 patients treated with intrarenal fenoldopam infused for at least 1 hour, the incidence of CI-AKI was less than 1%, compared with 27% based on historic rates in that population. Data from experimental models suggest that fenoldopam may have additional antiinflammatory effects. Currently, we do not recommend use of fenoldopam to prevent AKI because no high-quality data support use of this agent.

Statins

Although the pathogenesis of CI-AKI is not completely known, multiple mechanisms may be involved. Statins induce downregulation of angiotensin receptors, decrease endothelin synthesis, decrease inflammation, improve endothelial function by inhibiting nuclear factor (NF)-κB, decrease expression of endothelial adhesion molecules, increase NO bioavailability, attenuate production of reactive oxygen species, and protect against complement-mediated injury. Those mechanisms may be involved in CI-AKI. A number of observational publications and some but not all RCTs support the potential for renal protection with statin administration. The statin most commonly studied in this setting was rosuvastatin, at doses varying between 10 and 40 mg/day for 1 to 7 days after the procedure. Therapy should continue in patients who are already receiving a statin, and those who need statins for another indication such as myocardial infarction may receive statins before their angiography. It is currently unclear whether statins should be specifically initiated to prevent CI-AKI.

Statins also may reduce the risk for AKI after elective surgery. In a large retrospective study of 213,347 patients who underwent surgery, 32% received a statin before surgery.[34] AKI occurred in 1.9% of these patients. After multivariable adjustment, statin use was associated with a decreased risk for AKI, need for RRT, and 30-day mortality. There was no difference between groups in dialysis requirement 90 to 120 days after surgery. Two other observational studies have found the same results. These findings need to be validated before clinical recommendations can be made regarding the use of statins to prevent perioperative AKI.

Calcium Channel Blockers

Calcium channel blockers (CCBs) have been shown to reverse the afferent arteriolar vasoconstriction induced by a variety of stimuli and also have an independent natriuretic effect. These drugs have been evaluated in the prevention of delayed graft function (DGF). A large multicenter RCT did not find any benefit on the incidence and severity of DGF. A systematic review did not find strong evidence for the routine use of CCBs to reduce the incidence of DGF after transplantation.

Adenosine Antagonists

Theophylline, a nonselective adenosine receptor antagonist, prevents adenosine-mediated vasoconstriction of the afferent arteriole. Adenosine is released in response to increased luminal chloride concentrations in the distal tubules as part of the tubuloglomerular feedback. Small studies have shown discordant results in the prevention of CI-AKI. A recent RCT adding theophylline to NAC showed reduced incidence of CI-AKI. A large meta-analysis found a significant reduction in CI-AKI with theophylline; however, beneficial effects were not observed in patients with baseline creatinine above 1.5 mg/dl (132 μmol/l).[35] There is insufficient evidence to recommend theophylline as a solo agent, and the KDIGO AKI guidelines do not suggest using theophylline to prevent CI-AKI.

Selective adenosine blocking agents, such as rolofylline, have been used in trials for prevention and treatment of cardiorenal syndrome. In a small double-blind RCT in decompensated heart failure with AKI, the coadministration of adenosine A_1 antagonist with furosemide increased diuresis and prevented further decrease in GFR.

Emerging Agents

Multipotent mesenchymal stem cells (MSCs) were shown to prevent ischemia/reperfusion–induced AKI in rats. A phase I clinical trial evaluated the feasibility and safety of suprarenal aorta infusion of allogeneic MSCs in patients undergoing on-pump cardiac surgery.[36] No adverse events were associated with the MSC infusion, and lengths of hospital stay and readmission rates were decreased by 40% compared with matched historical controls. Postoperative kidney function remained at baseline levels and no patients in the treatment group required hemodialysis (HD), whereas 20% of controls developed AKI. In addition, kidney function in the treatment group was stable for up to 16 months in patients with CKD, whereas matched controls showed progressive deterioration in kidney function.[36] The long-term safety of MSC is unknown.

In animal and preliminary human studies, therapeutic use of erythropoietin (EPO) seemed promising. EPO can prevent AKI and improve recovery through limitation of apoptosis, promotion of neovascularization, antiinflammatory action, and tissue regeneration. A clinical trial of preoperative EPO in patients who underwent elective CABG surgery showed a reduction in the incidence of AKI and improved postoperative renal function, but in another trial, different doses of recombinant EPO administered to patients after cardiac surgery did not result in a difference in urine NGAL between 48 hours and randomization compared with placebo, and the incidence of AKI was similar.[37] A recent meta-analysis demonstrated no benefit in administering EPO to reduce cardiac surgery-associated AKI.[38] In the ICU, a recent meta-analysis also failed to show renoprotective benefits of EPO.[39] Another RCT comparing the effect of EPO or placebo in preventing CI-AKI has not shown any benefit.[40]

A recent meta-analysis on the use of levosimendan, a calcium-sensitizing agent, has demonstrated reduced AKI after cardiac surgery, RRT requirement, and mortality.[41] Future studies are required to determine the dose effect of levosimendan, especially in patients with CKD.

In an animal model of AKI, animals treated with small interfering ribonucleic acid targeting p53 presented a significant decrease in creatinine levels 24 hours after ischemic injury, compared with those treated with a placebo. Because p53 has, among other activities, a tumor suppression function, one of the major drawbacks to the use of an inhibitor of p53 is its potential carcinogenic effect. A phase 2 trial has just been completed in patients undergoing cardiac surgery.

In a recent phase 2 RCT including 452 patients at risk for AKI undergoing cardiac surgery, THR-184, a peptide that activates the bone morphogenetic protein pathway, did not reduce AKI over the postoperative week (NCT01830920).

Summary

To prevent AKI, hypovolemia, hypotension, and sepsis should be quickly addressed. Isotonic fluids and vasopressors can be administered depending on the clinical scenario.

HES should definitively be avoided. Some experts also recommend avoiding a high volume of chloride-rich solutions in patients at high risk for AKI. Nephrotoxins should be avoided. For prevention of CI-AKI (see Fig. 70.2), patients with eGFR lower than 45 ml/min/1.73 m^2 receiving intraveinous contrast, or those with eGFR lower than 60 ml/min/1.73 m^2 receiving intraarterial contrast should receive intravenous hydration with isotonic saline. The benefit of statins and RIPC is controversial. To prevent TLS, patients at intermediate and high risk should receive aggressive hydration with isotonic saline. A xanthine oxidase inhibitor or rasburicase should be administered depending on the underlying risk. For rhabdomyolysis, normal saline is most often administered compared with sodium bicarbonate. Additional studies are required to assess whether fenoldopam, some vasopressors, nesiritide, levosimendan, and statins are beneficial to prevent AKI.

TREATMENT OF ACUTE KIDNEY INJURY

Once measures to prevent AKI have failed, a key question is whether AKI can be managed with nondialytic therapy alone or if RRT is necessary (see Chapter 71). Management of AKI in cardiac and liver failure is discussed in Chapters 72 and 73, respectively.

General Management

Appropriate management requires timely diagnosis of the clinical condition. Considerable effort and investment have been directed in the search for a more sensitive and specific biomarker to diagnose AKI. Initial management of AKI includes assessment of the cause and volume status. Adequate hemodynamic status should be maintained to ensure renal perfusion and avoid further kidney injury. In the injured kidney, autoregulation of blood flow, the mechanism responsible for maintaining a constant flow during fluctuations in BP, is lost. This loss increases the susceptibility to develop AKI after episodes of hypotension. Therefore fluid and vasoactive drug management is needed in both patients at risk for AKI and with AKI. In patients with AKI attributed to dehydration only, it is expected that the serum creatinine decreases after the administration of 1 to 3 liters of isotonic fluid over 24 to 48 hours, depending on the severity of the underlying condition. Of note, there is no standardized definition for AKI related to dehydration. As previously mentioned, the optimal MAP is unknown and probably needs to be individualized according to age, hypertension status, and degree of peripheral artery and renovascular disease. Any potentially nephrotoxic agents should be avoided, including intravascular iodinated contrast. Gadolinium-based contrast agents should be avoided because of the risk for development of nephrogenic systemic fibrosis. If gadolinium-based contrast agents need to be used in AKI, patients should be informed about the risk for nephrogenic systemic fibrosis, and macrocyclic chelate (i.e., gadobutrol, gadoteridol or gadoterate meglumine) should be preferred over linear chelates. The lowest dosage possible should be administered and repeated exposures avoided. Antimicrobial agents such as aminoglycosides, amphotericin, acyclovir, and pentamidine should be avoided whenever possible, or their dose adjusted to prevent further insult. Any medications associated with AKI also should be avoided if possible.

Fluid and Electrolyte Management

Whereas early and vigorous resuscitation with crystalloid solutions and aggressive infection control can reduce the incidence of AKI (see earlier discussion), the role of fluid resuscitation in established AKI not attributed to dehydration is less clear. Volume status is one of the most difficult parameters to assess, and fluid resuscitation should target a predefined preload, SV, or cardiac output rather than a set MAP. Nevertheless, many clinical studies have emphasized the limitations of static measures such as central venous pressure, right atrial pressure, and pulmonary artery occlusion pressure in predicting volume expansion efficacy. Other bedside indicators of preload, such as the right ventricular end-diastolic volume (evaluated by thermodilution) and the left ventricular end-diastolic area (measured by echocardiography), are ineffective in differentiating volume responder from nonresponder patients. As previously discussed, two techniques have an acceptable degree of clinical accuracy to determine fluid responsiveness: the passive leg raising maneuver and the fluid bolus test coupled with real-time SV monitoring. In ICU patients receiving mechanical ventilation, respiratory changes in left ventricular SV also can predict fluid responsiveness. In hypovolemic patients, positive-pressure ventilation may induce a fall in the venous return and consequently in cardiac output. Based on the positive relationship between ventricular end-diastolic volume and SV, the expected hemodynamic response to volume expansion is an increase in right ventricular end-diastolic volume, left ventricular end-diastolic volume, SV, and cardiac output.

Volume expansion in ICU patients can frequently result in a relative increase in body weight of 10% to 15% or more, sometimes doubling the total body water in a short time. As previously highlighted, studies have demonstrated an association between fluid accumulation and mortality in AKI. A prospective multicenter observational study found fluid overload at AKI diagnosis, defined as an increase in body weight relative to baseline of more than 10%, was independently associated with increased mortality.[9] The risk for death was proportional to the magnitude and duration of fluid accumulation. However, the effect of fluid overload on renal recovery was inconsistent. A second analysis from the Fluids and Catheters Treatment Trial (FACTT) in AKI patients confirmed that in early AKI, positive fluid balance is strongly associated with mortality. The study showed a protective effect of furosemide on mortality, which disappeared after adjustment for fluid balance. Other studies have shown a deleterious effect of fluid overload on kidney function. In summary, results from observational studies suggest that a conservative fluid approach may be beneficial in terms of mortality and kidney recovery in patients with severe AKI. Fluid resuscitation should be guided, and, after the initial resuscitation period, treatment focus should focus on preventing further fluid overload, monitoring signs of fluid overload, and early removal of excess volume. However, RCTs are required to confirm these findings before any formal recommendation can be made.

Drugs to Promote Recovery From Acute Kidney Injury

See Table 70.3 for a summary of drugs used in treatment of AKI.

Loop Diuretics

Although loop diuretics are often prescribed in established AKI, a meta-analysis confirmed that they are not associated with reduced mortality or improved kidney recovery.[42] Other meta-analyses have shown that loop diuretics do not affect mortality, need for dialysis, or the number of dialysis sessions. Diuretics are ototoxic, and thus concomitant prescription of aminoglycosides and diuretics should be avoided because of an increased risk for ototoxicity. We suggest using diuretics to manage fluid overload as needed but not to treat AKI.

Natriuretics

Atrial natriuretic peptide (ANP) has been studied as a treatment for AKI in four RCTs. ANP was initially shown to reduce need for dialysis but not mortality. In the largest study published, ANP improved dialysis-free survival in the subgroup of oliguric patients only. Unfortunately, a subsequent trial including 222 oliguric patients did not confirm that ANP reduces mortality or dialysis-free survival.[43] A smaller more recent study showed that ANP decreased the probability of dialysis and improved

TABLE 70.3 **Summary of Drugs Used in Treatment of Acute Kidney Injury**

Drug	Level of Evidence	Results	Comments
Dopamine	RCTs	No effect on mortality or kidney function	
Fenoldopam	Small RCTs One meta-analysis	No effect on mortality or kidney function Beneficial effect on mortality and need for dialysis	Further studies required
Norepinephrine	Prospective observational studies	Possible beneficial effect on kidney function	Further studies required
Loop diuretics	RCTs and meta-analyses	No effect on kidney function	Further studies required
Atrial natriuretic peptide	RCTs	Possible beneficial effect on survival and kidney function	Further studies required
B-type natriuretic peptide	RCT in acute heart failure	No effect on kidney function	
Multipotent stem	Animal models and human studies	Beneficial effect on kidney function in animal models but no effect in one human study	Further studies required; ongoing study in cisplatin-induced AKI
Erythropoietin	Animal models and human studies	Controversial effect on kidney function	Further studies required
Alkaline phosphatase	Small RCT	Beneficial effect on kidney function in sepsis	Further studies required; ongoing phase 2 trial

RCTs, Randomized controlled trials.

dialysis-free survival.[44] Therefore larger studies are required to confirm the benefits of ANP in AKI. Nesiritide, a β-type natriuretic peptide, has been studied to treat heart failure. Nesiritide induces vasodilation and an indirect increase in cardiac output but has no inotropic effects and neutral effect on heart rate. In addition, it inhibits adverse neurohormonal activation and can result in natriuresis and diuresis in some individuals. However, in a large RCT in patients with acute heart failure, this drug did not decrease mortality or rehospitalization rates and had a nonsignificant effect on dyspnea.[45] Nesiritide did not adversely affect renal function, but it increased hypotension. Nesiritide also has been assessed in high-risk cardiovascular surgery, in which it reduced AKI rates in the immediate postoperative period but did not improve long-term survival. The KDIGO guidelines do not support the use of ANP or nesiritide to treat AKI.

Vasoactive Agents

Dopamine use to treat AKI is not recommended (see earlier discussion). Vasopressors often have been considered detrimental for organ perfusion. In septic shock, a small prospective study showed that norepinephrine improved serum creatinine and creatinine clearance when MAP was raised above 70 mm Hg. However, in another small RCT, increasing MAP from 65 to 85 mm Hg with norepinephrine did not improve renal function. No studies have compared the effect of different target MAPs to treat AKI.

In a meta-analysis, fenoldopam decreased the need for dialysis (7% vs. 10%) and in-hospital mortality (15% vs. 19%) in postoperative or ICU patients.[33] Several limitations were present in this meta-analysis, such as absence of an independent measure of GFR and standardized criteria for initiation of dialysis, heterogeneity of populations, AKI definitions, dosage, and duration of treatments. In addition, fenoldopam has hypotensive properties and may be more dangerous in the real world outside of RCTs. No single prospective study has shown that fenoldopam can reduce the need for dialysis. These results need to be confirmed with an adequately powered trial, and we do not suggest using fenoldopam to treat AKI in concordance with the KDIGO guidelines.

Specific therapy for patients with the hepatorenal syndrome includes the use of terlipressin in combination with octreotide (see Chapter 73). In countries such as the United States, where terlipressin is not available, a combination of midodrine, octreotide, and albumin infusions is often used. Norepinephrine also has been used in these settings with good response equivalent to that of terlipressin.

Other Agents

Other agents have been studied for treatment of established AKI. One promising therapy is MSCs. MSCs are multipotent cells with antiinflammatory and immunomodulatory properties proven to be beneficial in animal models of myocardial ischemia, sepsis, and AKI. In animal models, infusion of MSCs improved recovery of renal function in cisplatin-induced ischemia/reperfusion injury and glycerol-induced AKI. A dose-escalating phase I clinical trial was conducted to test the safety and preliminary efficacy of MSCs in patients at high risk for AKI.[36] An experimental study using a model of progressive mesangioproliferative nephritis evaluated the long-term effects of intrarenal, syngeneic MSC transplantation. Although rats in the MSC-treated group had lower proteinuria and better kidney function on day 60, 20% of the glomeruli of MSC-treated rats contained single or clusters of large adipocytes with pronounced surrounding fibrosis. Therefore the MSC benefit of maintaining kidney function in the short term needs to be balanced with a possible long-term effect of partial mal-differentiation of intraglomerular MSC into adipocytes and subsequent glomerular sclerosis. There is an ongoing study on the use of MSC to improve AKI after cisplatin administration (clinical trials.gov CIS/MSC08).

EPO might be beneficial to treat AKI, as shown in animal models. However, a recent animal model showed that although EPO had protective effects on renal function in AKI, the supraphysiologic dose needed for renoprotection contributed to fibrogenesis and stimulated CKD in the long term. A small randomized trial in elective CABG showed a beneficial effect of EPO on recovery after AKI.[46] However, in a larger retrospective study, the use of EPO was not associated with renal recovery. There is insufficient evidence to promote the use of EPO as a treatment for AKI.

In severe sepsis and septic shock, a small study has shown that the infusion of alkaline phosphatase improves kidney function, possibly through reduced NO metabolite production and attenuated tubular enzymuria. There is an ongoing international phase 2 study assessing the effect of recombinant alkaline phosphatase on renal and nonrenal outcomes in septic patients with AKI.

Another potential agent is the endogenous antioxidative enzyme heme oxygenase-1 (HO-1), a stress-inducible enzyme. HO-1 has important antiapoptotic and antiinflammatory functions, and the induction of HO-1 has been shown to be protective in several forms of injury, including AKI.

Summary

Dehydration, hypotension, and infections should be rapidly treated. Any potentially nephrotoxic agents should be avoided, including intravascular iodinated contrast. Gadolinium-based contrast agents should also be avoided. Fluid overload should be minimized, and depending on the clinical condition corrected once the patient is stabilized. No agent has been clearly shown to facilitate renal recovery. Several studies are ongoing to test the efficacy of new drugs to treat AKI in specific conditions.

TREATMENT OF ACUTE KIDNEY INJURY COMPLICATIONS

Fluid Overload

When fluid overload occurs in AKI, all intakes should be minimized and medical treatment should be attempted before dialysis initiation. In patients with positive fluid balance with large fluid intakes and inadequate urine output and in those presenting with symptomatic volume overload, loop diuretic therapy can be initiated with measures to optimize systemic and renal perfusion. Intravenous bolus doses of diuretics may be necessary to optimize the response, especially in patients with heart failure and nephrotic syndrome. If there is a response to an intravenous bolus, continuous infusion can be tried because it is less ototoxic. Natriuretic peptides inhibit sodium reabsorption in the nephron, resulting in net sodium excretion. There is currently no evidence to support the use of natriuretic peptides as an adjunctive treatment in AKI.

Morphine and nitrates can be used to alleviate the respiratory symptoms of pulmonary edema in urgent situations. Morphine can be administered intravenously at an initial dose of 2 to 4 mg over a 3-minute period and repeated at 5- to 15-minute intervals as needed. Nitrates are also commonly used. Nitroglycerin reduces left ventricular filling pressure through venodilation; an initial dose of 5 mcg of intravenous nitroglycerin per minute can be used. When fluid overload cannot be rapidly treated with medical management, positive-pressure ventilation may be initiated with or without endotracheal intubation and dialysis, depending on the clinical situation (see Chapter 72).

Potassium Disorders

Hyperkalemia, covered in detail in Chapter 9, is a frequent complication of AKI that may affect cardiac conduction and lead to bradycardia or even asystole. If electrocardiographic changes are present, intravenous administration of calcium is urgently needed. Sources of potassium should be removed, including drugs with effect on potassium handling, such as β-adrenergic antagonists, potassium-sparing diuretics, ACE inhibitors, and ARBs.

The next step is to enhance the shift of potassium to the intracellular space by parenteral glucose and insulin infusions. Sodium bicarbonate also promotes shift of potassium and is most efficient when there is concomitant metabolic acidosis. It can be started if there is no concern regarding fluid overload. β-Adrenergic agonists given as aerosols are effective at very high doses but more likely to produce side effects and therefore are rarely prescribed to treat hyperkalemia.

Potassium excretion should be increased by the administration of saline, loop diuretics, and cation exchange resins such as sodium polystyrene sulfonate or calcium resins. The resins can be administered orally or rectally as a retention enema and are usually not effective after a single dose only. There is also a concern to promote intestinal necrosis when sodium polystyrene sulfonate is administered with sorbitol. Sodium polystyrene sulfonate should be avoided postoperatively until normal bowel function resumes and in patients with bowel obstruction or ileus. New agents, such as sodium zirconium cyclosilicate (ZS-9) and patiromer, have not yet been studied to treat acute hyperkalemia. If hyperkalemia is unresponsive to conservative measures, emergency HD is the treatment of choice. Continuous RRT (CRRT) can be used with higher volumes of replacement solution and/or dialysate and low or no potassium content if HD is unavailable. Because RRT initiation usually takes a few hours, medical management always should be used pending initiation of dialysis. Monitoring of potassium levels should continue after conservative or dialytic management to prevent and treat rebound hyperkalemia.

Sodium Disorders

Hyponatremia is more common in AKI associated with heart failure, liver failure, or diuretics. In these settings, water restriction to below the level of output is mandatory. Sodium restriction is usually necessary to treat fluid overload and edema. In patients with true volume depletion and prerenal AKI, isotonic saline needs to be administered to correct both disorders.

In patients with AKI and hypernatremia, treatment of the cause is necessary and water deficit should be estimated. Water should be administered orally or intravenously as dextrose in water to correct serum sodium concentration at a maximum rate of 8 to 10 mmol/l/day. Dialysis and CRRT may be required to optimally correct sodium disorders in AKI.

Calcium, Phosphorus, and Magnesium Disorders

Hyperphosphatemia and hypocalcemia are common in AKI. Hyperphosphatemia is usually caused by reduced excretion by the kidneys, and continuous release from rhabdomyolysis or TLS also can be contributive (see Chapters 10 and 66). As phosphorus levels increase, calcium levels decrease, resulting in hypocalcemia. Total calcium levels usually drop to 7 to 8 mg/dl (1.75 to 2.0 mmol/l). Other causes of hypocalcemia in AKI are skeletal resistance to parathyroid hormone (PTH) and low calcitriol production. Hypocalcemia is aggravated when bicarbonate is administered to correct acidosis. A high-calcium, high-phosphorus product could theoretically trigger tissue calcium deposition, which can cause cardiac arrhythmia. No RCT has evaluated the benefits of treating these disorders. However, because hyperphosphatemia caused by oral phosphorus-containing medications and TLS can cause AKI, severe hyperphosphatemia should be avoided to prevent further damage. Calcium-based phosphate binders and other phosphate binders can be used in this setting. If there is symptomatic hypocalcemia or hemodynamic instability, calcium gluconate infusion should be administered.

Hypercalcemia is rare in AKI and is usually seen in the recovery phase of rhabdomyolysis when calcium is released from calcium-containing complexes in muscle (see Chapters 10 and 66). In addition, when production of calcitriol is reestablished by the recovering kidney, an enhanced responsiveness to PTH can be seen. Hypercalcemia in this setting is rarely problematic and can be easily treated with medical management. Mild hypermagnesemia is frequent in AKI and usually does not have clinical consequences.

Acid-Base Disorders

In AKI, metabolic acidosis is the most common acid-base abnormality (see Chapter 12) because of reduced regeneration of bicarbonate and failure to excrete ammonium ions. Accumulation of phosphate and unexcreted unmeasured anions, such as sulfate, urate, hippurate, hydroxypropionate, furanpropionate, and oxalate, is contributory. Hypoalbuminemia can attenuate this acidification process, and it is exacerbated by lactic acidosis. Despite retention of unmeasured anions, the anion gap remains within normal in 50% of patients. Whereas metabolic acidosis is frequent, triple acid-base disturbances also can occur. The approach to acid-base disturbances in AKI needs to be adjusted according to the underlying causes.

There is controversy surrounding the optimal treatment of acute metabolic acidosis. When metabolic acidosis is simply a complication of AKI, sodium bicarbonate can be administered if the serum bicarbonate concentrations fall below 15 to 18 mmol/l. Volume overload can occur after the administration of bicarbonate. The administration of bicarbonate in shock with lactic acidosis is controversial, given the possibility of an increase in carbon dioxide generation, worsening of the intracellular acidosis, and volume overload. Rapid improvement in metabolic status may enhance hypocalcemia and lower cardiac output. Therefore in patients with lactic acidosis, most physicians restrict the administration of sodium bicarbonate to patients with severe metabolic acidosis (arterial pH <7.10 to 7.15) to maintain the pH above 7.15 to 7.20 until the primary process is reversed. Alternative forms of base treatment such as tris(hydroxymethyl)aminomethane (THAM) are not recommended in patients with AKI because THAM can cause hyperkalemia. Restriction of protein intake also has been suggested as a method of acidosis control because protein breakdown has been associated with worsening acidosis, as in CKD. However, protein restriction is not recommended in AKI.

Nutrition

Patients with AKI have an increased risk for protein-energy malnutrition because of poor nutrient intake and high catabolic rate. Nutritional assessment is difficult, especially in AKI patients with high metabolic demands. Subjective global assessment evaluates nutritional status, requires no additional laboratory testing, and is highly predictive of outcome.

Patients with AKI should receive a basic intake of 0.8 to 1.0 g of protein/kg/day if not catabolic and a total energy intake of 20 to 30 kcal/kg/day, as recommended in the KDIGO guidelines. In addition, in patients on RRT, 1.0 to 1.5 g of protein/kg/day should be administered up to 1.7 g/kg/day in CRRT and hypercatabolic patients. The enteral route should be favored if the gastrointestinal tract is functioning; parenteral nutrition should be prescribed only when the gastrointestinal tract cannot be used or when the enteral route is inadequate to reach nutrient intake goals.[47]

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SELF-ASSESSMENT QUESTIONS

1. In a general population of critically ill patients, administering starches has proven to be:
   A. Beneficial for kidney function (decrease in need for renal replacement therapy [RRT])
   B. Beneficial for hypotension
   C Detrimental for kidney function (increase in need for RRT)
   D. Detrimental for hypotension
2. Which of the following drugs should be stopped, if feasible, 48 hours before iodinated contrast administration in patients with chronic kidney disease and a glomerular filtration rate below 45 ml/min/1.73 m^2?
   A. Furosemide
   B. Metformin
   C. Nonsteroidal antiinflammatory drugs
   D. Thiazide diuretics
   E. All of the above
3. The measures to prevent AKI in patients with traumatic rhabdomyolysis include all of these statements, *except:*
   A. Urine output should be maintained around 300 ml/h until creatine kinase (CK) levels are lower than 1000 U/l.
   B. Urine output should be maintained around 300 ml/h until myoglobinuria disappears.
   C. Mannitol is beneficial because of diuretic, antioxidant, and vasodilatory properties.
   D. Mannitol can prevent renal tubular cast deposition, expand extracellular volume, and reduce intracompartmental pressure, muscle edema, and pain.
   E. Monitoring of ionized calcium is important to avoid $NaHCO_3$-induced hypocalcemia (as a result of metabolic alkalosis).
4. Regarding fluid administration for critically ill patients at risk for AKI, all of the following sentences are true *except:*
   A. Chloride-restrictive fluids (lactated solution, Plasma-Lyte 148, or chloride-poor 20% albumin) may be preferable to chloride-rich intravenous fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution), although further studies are needed.
   B. Volume expansion should be maintained after major vascular surgeries unless patients develop evidence of pulmonary congestion.
   C. Guidelines on sepsis management mention that septic patients should receive initial fluid resuscitation with crystalloids at a minimum of 30 ml/kg.
   D. Albumin should be considered in patients with sepsis who require substantial amounts of crystalloid to maintain adequate mean arterial pressure.
   E. Fluid expansion should be stopped when patients are no longer fluid responsive.

71

Dialytic Management of Acute Kidney Injury and Intensive Care Unit Nephrology

Mark R. Marshall, Luis A. Juncos

Intensive care unit (ICU) nephrology focuses on abnormalities of fluid, electrolyte, and pH homeostasis in ICU patients and the prevention and management of functional renal impairment relative to physiologic demand. This chapter describes best practices for acute renal replacement therapy (ARRT) and strategies for avoiding common treatment-related complications. The chapter uses appropriate clinical practice guidelines as starting points for discussion and summarizes their recommendations (Box 71.1).[1-11]

When the Acute Kidney Injury Network (AKIN) criteria are applied, approximately 40% of ICU patients develop acute kidney injury (AKI), an independent risk factor for death. The nondialytic therapy of AKI is discussed in Chapter 70. Approximately 10% of ICU patients require ARRT, and mortality in this population is improving over time despite greater illness severity.[12] Death attributable to AKI arises from nonresolving infection, hemorrhage, or nonresolving shock, despite optimal care. These conditions therefore may be considered an "acute uremic syndrome" that is a possible target for modulation with ARRT, analogous to the traditional uremic syndrome observed in end-stage renal disease (ESRD).

ORGANIZATIONAL ASPECTS OF ACUTE RENAL REPLACEMENT THERAPY PROGRAMS

ICUs can be described as open (patient care remains under the attending physician of record), closed (patient care is transferred to an intensivist), or comanaged (an open ICU in which patients receive mandatory consultation from an intensivist). Most ICUs in Australia are closed, whereas those in the United States and Europe vary. When AKI and ARRT are considered, advantages of intensivist-based management include immediate availability of service and decreased fragmentation of care. This model of care is supported by ecologic studies suggesting better outcomes in closed ICUs. Alternatively, advantages of nephrology-based management include greater understanding of the dialysis process and underlying AKI. This model of care is supported by studies suggesting better outcomes in ICU patients with AKI with earlier referral to nephrology. These studies have irreconcilable differences that make consistent interpretation difficult. Clinical governance over ARRT is likely to remain contentious, although the clinical expertise of staff will always be more important than their specialty. Specific training in ICU nephrology and exposure to ARRT is inadequate in many critical care and nephrology training schemes and should be included as a core component.

In many regions, ICU nurses deliver all modalities of ARRT; in others, support from nephrology staff is required. As the usability of continuous renal replacement therapy (CRRT) and intermittent hemodialysis (HD) machines improve, it is likely that ICU expertise will grow in all modalities, provided in-service education and support are adequate.

OVERVIEW OF ACUTE RENAL REPLACEMENT THERAPIES

The main modalities of ARRT are intermittent HD and its variants, CRRT, and peritoneal dialysis (PD). Intermittent HD and CRRT are most popular, although utilization varies regionally. Recently intermittent HD has undergone resurgence through lower efficiency variants that are applied for longer periods, with lower ultrafiltration rate (UFR) and slower solute clearance, resulting in improved hemodynamic stability and larger dialysis dose. These variants are most commonly referred to as *sustained low-efficiency dialysis* (SLED). Collectively, however, they are best referred to with the umbrella term *prolonged intermittent renal replacement therapy* (PIRRT), a term more aligned to nomenclature endorsed by the Acute Dialysis Quality Initiative (www.adqi.net) (Fig. 71.1). *Acute PD* is mostly used in resource- constrained settings and is not considered further in this chapter.

Therapeutic goals for ARRT are not well defined. The usual minimum recommendation is to correct acidosis or hyperkalemia, refractory hypervolemia, and uremic features such as pericarditis or coma. Serum electrolyte concentrations should be maintained in the normal range. Dialysis dose should meet targets, which are discussed later. The process of ARRT itself should not jeopardize the patient by exacerbating hemodynamic instability, increasing end-organ damage, or delaying renal recovery.

Determining goals with respect to a patient's extracellular volume status is not straightforward. Assessment itself is difficult; physical signs are generally not informative. Measures of cardiac filling (e.g., by central venous pressure, pulmonary capillary wedge pressure, left ventricular diastolic dimensions) may be inaccurate surrogates for intravascular volume status, especially for patients with sepsis. An alternative approach is to test the effect of therapeutic maneuvers such as fluid challenge on measures of cardiac filling, stroke volume, and blood pressure (BP). Even after fluid status has been assessed, determining the correct therapeutic goal is difficult. Ongoing severe fluid depletion is undesirable, but so is severe fluid overload, which is strongly associated with increased mortality and poorer renal recovery. Patients with extracellular fluid excess in the absence of intravascular hypervolemia will benefit from fluid removal if they develop abdominal compartment syndrome, poor wound healing, or especially impairment of lung compliance and oxygenation. Increasingly, fluid status is defined by fluid accumulation: (total input − total output in liters) expressed as a percentage of premorbid or pre-ICU weight. No clinical trials have evaluated the impact of different fluid accumulation thresholds, but strong observational evidence supports targeting less than 10% to 20% fluid accumulation and initiating or prescribing ARRT to keep fluid accumulation within this range.[13]

Variations of ARRT have been used to enhance removal of cytokines. Cytokines are medium and larger molecules that modulate the immune response. Their production becomes dysregulated during acute illness, and their clearance decreased during AKI, resulting in excessive levels that have cardiodepressant, vasodilatory, and immunosuppressive properties.[14] Consequently, there is interest in enhancing cytokine removal during acute illness or AKI, especially in high-cytokine states such as sepsis. Cytokines can be removed with high cut-off hemofilters (membranes with a molecular weight cut-off of 60 to 150 kDa), bioadsorption devices, coupled plasma filtration–adsorption, and high levels of convective clearance. However, some of these techniques will remove both proinflammatory and antiinflammatory cytokines, with an uncertain net effect on the overall inflammatory milieu. Others will remove beneficial circulating substances such as medications, including antibiotics. All of these techniques are experimental at present, supported by only observational studies and pilot clinical trials. Larger multicenter trials of high-volume hemofiltration and bioadsorption with polymyxin B have not shown clinical benefit, although more definitive studies are underway for polymyxin B and coupled plasma filtration–adsorption (ClinicalTrials.gov identifiers NCT01046669, NCT01639664). In general, progress in this area is hampered by a lack of biomarkers and/or clinical scores to trigger treatment decisions; it is not clear how to identify patients who might benefit from cytokine removal and when it should be applied.

BOX 71.1 Key Clinical Practice Guidelines

- Kidney Disease: Improving Global Outcomes (KDIGO): Clinical practice guideline for acute kidney injury (2012)[1]
- Kidney Disease Outcomes Quality Initiative (KDOQI) Vascular Access Work Group: Clinical practice guidelines for vascular access (2006)[2]
- Healthcare Infection Control Practices Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention (CDC): Guidelines for the prevention of intravascular catheter-related infections (2011)[3]
- National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England (2007)[5]
- Institute for Healthcare Improvement: *How-to Guide: Prevent Central Line–Associated Bloodstream* Infections (2012)[4]
- International Organization for Standardization documents ISO 11663 *(Quality of Dialysis Fluid for Haemodialysis and Related Therapies),* ISO 13958 *(Concentrates for Haemodialysis and Related Therapies),* ISO 13959 *(Water for Haemodialysis and Related Therapies),* and ISO 26722 *(Water Treatment Equipment for Haemodialysis Applications and Related Therapies)* (www.iso.org)
- Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th edition (2008)[6]
- European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. Section V: Chronic intermittent haemodialysis and prevention of clotting in the extracorporeal system (2002)[8]
- Locking solutions for haemodialysis catheters; heparin and citrate—a position paper by the American Society of Diagnostic and Interventional Nephrology (2008)[7]
- Clinical Practice Guidelines, 5th edition: UK Renal Association (2011)[9]
- Acute Kidney Injury: Prevention, detection and management: National Institute for Health and Care Excellence (2013)[10]
- Renal replacement therapy in adult and pediatric intensive care: Recommendations by an expert panel (2015)[11]

Timing of ARRT initiation is controversial, and specific thresholds for starting are unknown. Proponents of early initiation argue that it is in the patients' interest to prevent rather than treat the acute uremic syndrome and recommend initiation once kidney injury or failure is present. However, ARRT does have potential for harm, including catheter-related infection, intradialytic hypotension, and electrolyte disturbances. Recently completed clinical trials have had discordant results, with an overall treatment effect of 0.74 (0.43 to 1.27) directionally favoring earlier initiation.[15] All have been underpowered, and the two largest included a substantial proportion of patients who might not be considered for ARRT in usual clinical practice. Again, larger and more definitive studies are underway (ClinicalTrials.gov Identifiers: NCT0168259, NCT02568722).

Currently, a reasonable approach can be distilled from existing guidelines (Fig. 71.2)[1,10,11]; as long as the ARRT is not clinically inappropriate (e.g., the prognosis is not futile), ARRT should be initiated for life-threatening hyperkalemia or acidosis refractory to medical treatment, uremic features such as pericarditis or coma and refractory hypervolemia causing end-organ complications (e.g., pulmonary edema). ARRT should be initiated if the burden of fluid and solute derangements is increasing and anticipated to result in complications,

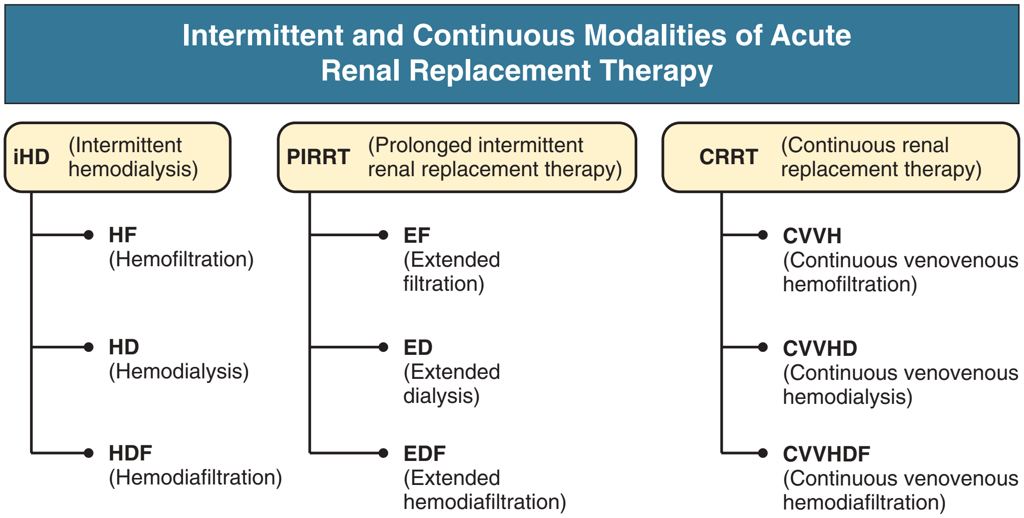
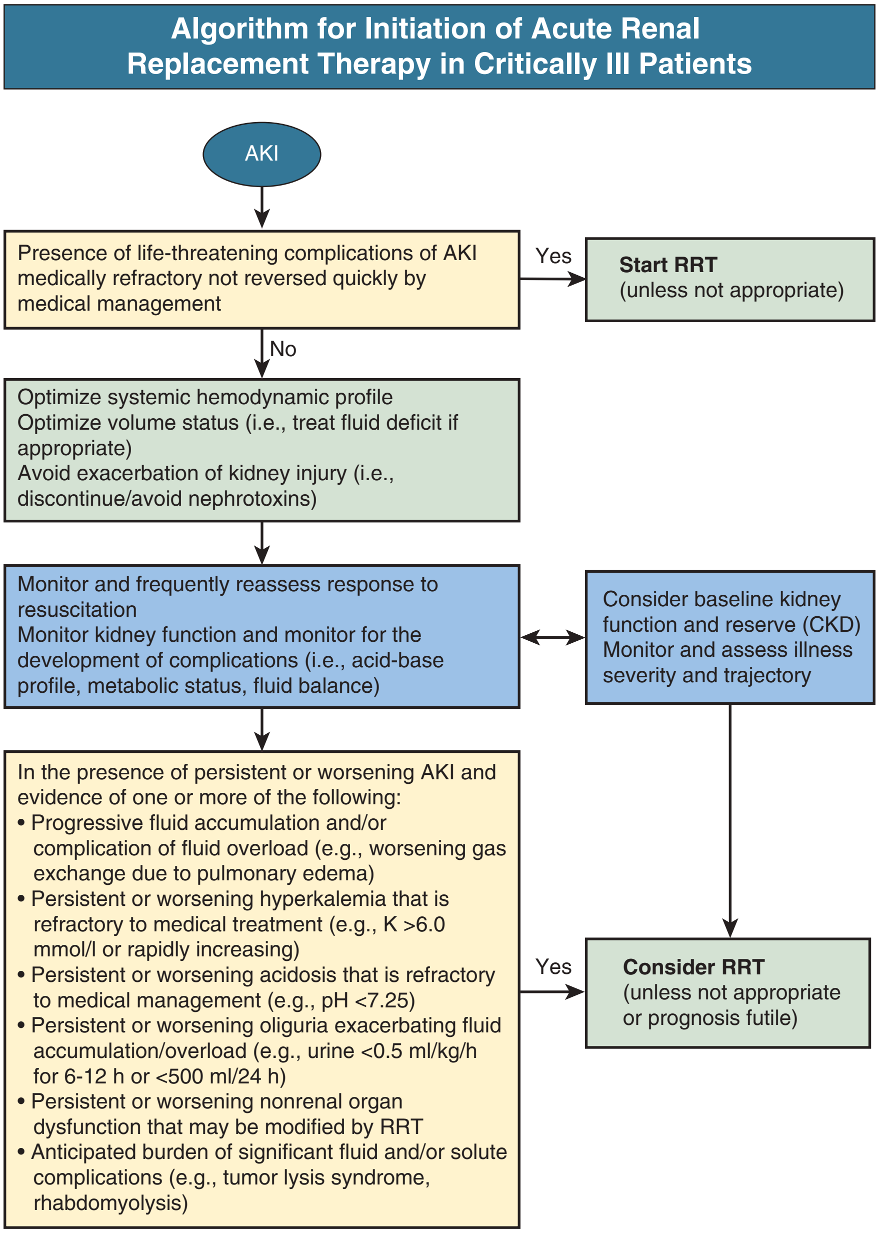

Intermittent and Continuous Modalities of Acute Renal Replacement Therapy
iHD (Intermittent hemodialysis)
HF (Hemofiltration)
HD (Hemodialysis)
HDF (Hemodiafiltration)
PIRRT (Prolonged intermittent renal replacement therapy)
EF (Extended filtration)
ED (Extended dialysis)
EDF (Extended hemodiafiltration)
CRRT (Continuous renal replacement therapy)
CVVH (Continuous venovenous hemofiltration)
CVVHD (Continuous venovenous hemodialysis)
CVVHDF (Continuous venovenous hemodiafiltration)

Fig. 71.1 Intermittent and continuous modalities of acute renal replacement therapy. (Modified from reference 22.)



Algorithm for Initiation of Acute Renal Replacement Therapy in Critically Ill Patients

Presence of life-threatening complications of AKI medically refractory not reversed quickly by medical management

Start RRT (unless not appropriate)

Optimize systemic hemodynamic profile
Optimize volume status (i.e., treat fluid deficit if appropriate)
Avoid exacerbation of kidney injury (i.e., discontinue/avoid nephrotoxins)

Monitor and frequently reassess response to resuscitation
Monitor kidney function and monitor for the development of complications (i.e., acid-base profile, metabolic status, fluid balance)

Consider baseline kidney function and reserve (CKD)
Monitor and assess illness severity and trajectory

In the presence of persistent or worsening AKI and evidence of one or more of the following:
- Progressive fluid accumulation and/or complication of fluid overload (e.g., worsening gas exchange due to pulmonary edema)
- Persistent or worsening hyperkalemia that is refractory to medical treatment (e.g., K >6.0 mmol/l or rapidly increasing)
- Persistent or worsening acidosis that is refractory to medical management (e.g., pH <7.25)
- Persistent or worsening oliguria exacerbating fluid accumulation/overload (e.g., urine <0.5 ml/kg/h for 6-12 h or <500 ml/24 h)
- Persistent or worsening nonrenal organ dysfunction that may be modified by RRT
- Anticipated burden of significant fluid and/or solute complications (e.g., tumor lysis syndrome, rhabdomyolysis)

Consider RRT (unless not appropriate or prognosis futile)

Fig. 71.2 Algorithm for initiation of acute renal replacement therapy in critically ill patients. *AKI,* Acute kidney injury; *CKD,* chronic kidney disease; *RRT,* renal replacement therapy. (Reproduced with permission from reference 15.)

rather than waiting for them. ARRT should probably be initiated earlier in patients who are less able to resolve fluid and solute derangements (e.g., advanced chronic kidney disease [CKD]), or to tolerate them (e.g., advanced chronic lung or heart disease).

INTERMITTENT ACUTE RENAL REPLACEMENT THERAPY

Techniques for Acute Intermittent Hemodialysis

Intermittent HD is categorized according to hemodialyzer membrane and mechanism of solute removal. High-flux membranes allow greater convective removal of middle and larger solutes, but limited clinical data do not show obvious advantages in the ICU setting. Biocompatibility is a membrane characteristic that includes a low capacity for activating complement and leukocytes. After complement activation, there is stasis of leukocytes in the lungs, renal parenchyma, and other organs and the release of products of leukocyte activation. Although studies have been inconsistent, the use of biocompatible membranes is recommended.

Hemodiafiltration (HDF) is usually performed in the ICU as a continuous modality. However, intermittent HDF also can be performed with use of sterile replacement fluid generated from ultrapure dialysate (“online”), which is infused directly into the extracorporeal blood circuit. Limited clinical data again do not show obvious advantages in an ICU setting.

Dialysate for intermittent ARRT can be delivered by either a batch or single-pass system. The latter uses concentrate and potable water that is purified by reverse osmosis in a central plant or portable unit. Most ICUs do not have a central plant, although this is increasingly common in units in which online HDF is performed. Water purity is important to avoid backfiltration of bacterial contaminants, specifically endotoxin, which could exacerbate cytokine-mediated injury. Reference standards for water purity in the ICU setting are the same as those for the ESRD setting (www.iso.org; see Box 71.1 and Chapter 93). Online replacement fluid for HDF is sterilized with ultrafilters in the dialysate pathway and does not differ from commercial batch preparations in terms of microbial counts, endotoxin concentration, and cytokine-inducing activity. Some suggest sterile dialysate for all acute intermittent HD; however, data are insufficient data to support a strong recommendation.

Strategies to Reduce Intradialytic Hemodynamic Instability During Intermittent Hemodialysis

Hypotension is detrimental for end-organ function and recovery. The consequences of specifically intradialytic hypotension are not well studied in the critically ill AKI population; for instance, it is unclear whether it leads to myocardial stunning and cardiovascular morbidity as it does in the ESRD setting. However, fresh ischemic lesions in kidney biopsy specimens can be found in AKI patients on intermittent HD for longer than 3 weeks, and residual renal function often decreases immediately after treatments, suggesting that intradialytic hemodynamic stability is desirable. Axiomatically, the most effective measure to minimize intradialytic hypotension is increasing the frequency and treatment time of intermittent HD, thereby minimizing ultrafiltration targets, but other measures should also be considered.

Bicarbonate-buffered dialysate should be used. It is associated with less hypotension than acetate dialysate, which has a peripheral vasodilating and myocardial depressant effect. Importantly, online bicarbonate-buffered dialysate still contains between 3 to 5 mmol/l of acetate, for chemical stability. Although this small amount of acetate may not compromise stable maintenance HD patients, a clinical trial has shown increased acetemia, hypotension, and arrhythmia in critically ill patients treated with conventional bicarbonate-buffered dialysate compared with acetate-free dialysate.[16] This may contribute to greater intradialytic hypotension during intermittent HD compared with CRRT.

Hemodynamic stability is facilitated by sodium profiling during intermittent ARRT. Rapid reduction in serum osmolality promotes water movement into cells, reducing effective circulating volume. The default dialysate [Na^+] for intermittent HD and PIRRT in critically ill patients is approximately 145 mmol/l and avoids such fluid shifts. Sodium profiling further ameliorates this process by inducing water flux into the vascular compartment. A clinical trial showed that intermittent HD with sodium profiling (starting 160 mmol/l, reducing 140 mmol/l) combined with ultrafiltration profiling (50% of ultrafiltration volume removed in first third of treatment) improved hemodynamic stability.[17] Similar data exist for PIRRT. Profiling should not be used in patients with dysnatremias, in whom serum [Na^+] should be corrected slowly to minimize the risk for neurologic complications.

Online blood temperature and blood volume monitoring involves biofeedback systems that automatically adjust treatment operating parameters. Blood volume monitoring adjusts UFR and dialysate [Na^+] in response to a fall in circulating blood volume, and blood temperature monitoring maintains blood temperature at a target value by controlling thermal transfer to and from dialysate to avoid vasodilation and decreased vascular resistance. Although helpful in the ESRD setting, neither technique prevents intradialytic hypotension in the ICU setting.[18,19] The likely reasons pertain to different causes and compensatory mechanisms for hypotension in the two settings.

High-dialysate calcium (1.75 mmol/l) has been used to improve hemodynamic stability during intermittent HD in ESRD patients with cardiomyopathy. This technique is limited by the development of hypercalcemia and has not been studied in the ICU setting.

A number of studies have suggested less intradialytic hypotension during intermittent HDF than HD in the ESRD setting.[20] It is unlikely that is also the case in critically ill AKI patients, although definitive studies are yet to be conducted.

Extensive cumulative clinical experience shows that lower efficiency modalities of ARRT provide better hemodynamic stability because of slower fluid and solute removal. Meta-analyses show better preservation of BP and lower vasopressor requirements in those treated with CRRT rather than intermittent HD.[1,21] Some studies have shown comparable hemodynamic stability between CRRT and lower efficiency prescriptions of PIRRT,[22-24] and they are the first choice for hemodynamically unstable patients.[1]

Prolonged Intermittent Renal Replacement Therapy

PIRRT uses standard intermittent HD equipment, but with lower solute clearances and UFR maintained for prolonged periods.[25] One issue that hampers consistent interpretation of the PIRRT literature is the lack of treatment standardization and wide range of operating parameters. Treatment duration can vary from 6 to 18 hours and dialysate flow rate *(Qd)* from 100 to 300 ml/min. In either case, urea clearances are lower and higher than in intermittent HD and CRRT, respectively. This allows for the convenience of scheduled downtime, without compromising dialysis dose. With longer treatments, phosphate replacement is usually required at 0.1 to 0.2 mmol/kg and dietary protein should be supplemented by at least 0.2 g of protein/kg/day. A prescription algorithm is shown in Fig. 71.3.

Prescribed correctly, PIRRT provides a high dose of dialysis with minimal urea disequilibrium, excellent control of electrolytes, and good tolerance to ultrafiltration. PIRRT is usually delivered as a diffusive therapy, although there is increasing experience with combined diffusive and convective clearance.

Dosage of Intermittent Acute Renal Replacement Therapy

The relationship between small-solute clearance and outcomes of critically ill AKI patients is now established. A key study showed that delivered single-pool *Kt/V (spKt/V)* below 1.0 per intermittent HD treatment was associated with decreased survival in patients with intermediate illness severity, although the study did not relate outcomes to frequency of treatments.[26] Definitive clinical trials have shown a "ceiling effect" to small-solute clearance, above which survival becomes dose-independent,

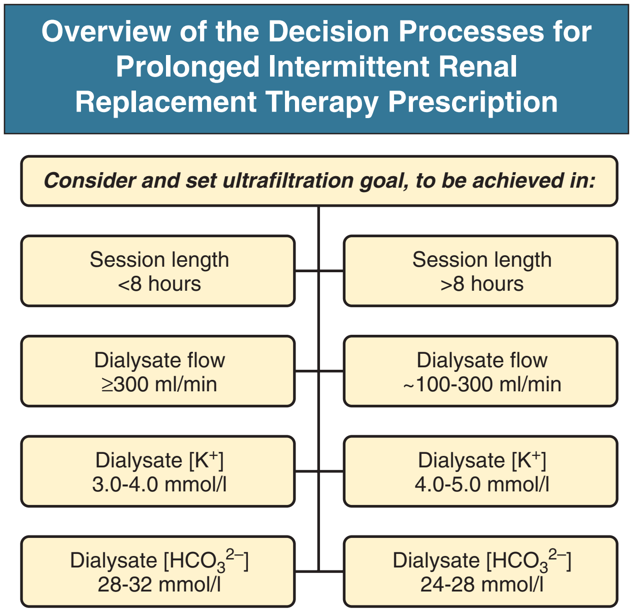

Overview of the Decision Processes for Prolonged Intermittent Renal Replacement Therapy Prescription
Consider and set ultrafiltration goal, to be achieved in:
Session length <8 hours
Session length >8 hours
Dialysate flow ≥300 ml/min
Dialysate flow ~100-300 ml/min
Dialysate [K^+] 3.0-4.0 mmol/l
Dialysate [K^+] 4.0-5.0 mmol/l
Dialysate [HCO_3^{2-}] 28-32 mmol/l
Dialysate [HCO_3^{2-}] 24-28 mmol/l

Fig. 71.3 Overview of the decision processes for prolonged intermittent renal replacement therapy prescription.

with no benefit with intermittent ARRT that delivers small-solute clearance greater than a *spKt/V* of 1.2 to 1.4 per treatment thrice weekly.[27,28]

The minimum recommended intermittent HD and PIRRT dose in ICU patients with AKI is delivered *spKt/V* of at least 1.3 per treatment at least thrice weekly.[1] Underdelivery of acute intermittent HD is common, and routine measurement of dose should be undertaken to guide appropriate adjustment of operating parameters as summarized in Box 71.2. If this dosage target cannot be achieved, treatment frequency should be increased. The required number of treatments per week can be established from the nomogram in Fig. 71.4, which expresses combinations of HD dose and frequency as a continuous small-solute clearance (corrected equivalent renal urea clearance [EKRc]). The target EKRc is a value of 13 ml/min or higher.[29,30] This framework can be used to interpret the Hannover Dialysis Outcome Study of PIRRT; patients treated with daily PIRRT to keep plasma urea at 11.3 ± 4 mmol/l (EKRc of 20 ml/min, assuming urea generation of 20 mg/min) had outcomes indistinguishable from those of patients treated to keep plasma urea at 19 ± 6 mmol/l (EKRc of 13 ml/min, equal to a *spKt/V* of 1.2-1.4 per treatment thrice weekly).[28]

BOX 71.2 Measures to Increase Intermittent Hemodialysis Dose

Maximize hemodialyzer surface area (up to 2-2.2 m^2)
Maximize hemodialyzer porosity (high flux)
Maximize blood flow rate by:
  Maximizing internal lumen diameter of catheter (up to 2.0-2.2 mm)
  Titrating blood flow to maximum arterial and venous pressure (up to – and + 300-350 mm Hg, respectively)
  Correcting position of catheter tip in SVC and IVC as appropriate
  Use right-sided IJ and SC in preference to left-sided IJ and SC
Minimize access recirculation by correcting position of catheter tip in superior or inferior vena cava as appropriate using internal jugular and subclavian, rather than femoral, catheters
Maximize dialysate flow (up to 800-1000 ml/min)
Add postdilution HDF
Optimize anticoagulation to reduce hemodialyzer fiber bundle clotting
Optimize circulation to reduce compartmental urea sequestration
Increased treatment frequency (up to daily)
Increased treatment duration (up to 6-8 hours, then consider PIRRT [SLED] or CRRT)

(Modified from reference 61).
CRRT, Continuous renal replacement therapy; *HDF,* hemodiafiltration; *IJ,* internal jugular; *IVC,* inferior vena cava; *PIRRT,* prolonged intermittent renal replacement therapy; *SC,* subclavian; *SLED,* sustained low-efficiency dialysis; *SVC,* superior vena cava.

CONTINUOUS RENAL REPLACEMENT THERAPY

CRRT involves the application of lower UFR and solute clearances for substantial periods every day. The lower UFR provides the best hemodynamic stability of any ARRT modality, and the longer treatment duration results in better and more consistent control of uremic solutes, especially for severely catabolic patients.

Interruptions to CRRT because of circuit clotting leads to a reduction in dose from downtime, as well as expense related to blood circuitry changes. Mean operating time for CRRT is reported to be between 17 and 22 h/day,[31] although a given session can be extended as long as 72 hours with rigorous application of protocols related to anticoagulation and catheter placement and positioning.

Techniques for Continuous Renal Replacement Therapy

The Acute Dialysis Quality Initiative (www.adqi.net) classification of CRRT is the standard and uses nomenclature based on the type of vascular access and the method of solute removal.

Venovenous (VV) denotes CRRT using a central venous catheter and mechanical blood pump. This provides reliable and rapid blood flow rate *(Qb)* of approximately 250 ml/min, but is more complex and costly and has the disadvantage of potential inadvertent disconnection of lines, resulting in hemorrhage or air embolism with continued pump operation; this risk is minimized by monitors and alarms.

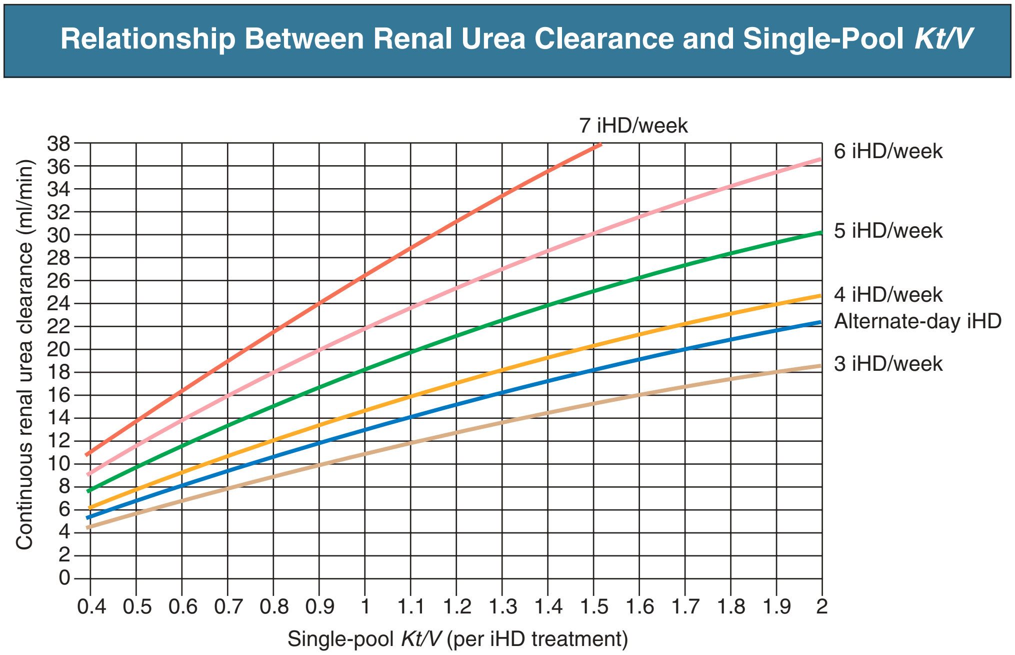


Fig. 71.4 Relationship between corrected continuous renal urea clearance and single-pool Kt/V (weekly urea clearance/volume of distribution of urea) per treatment for a frequency of three to seven treatments per week. *iHD,* Intermittent hemodialysis. (From reference 62.)

Arteriovenous (AV) denotes CRRT in which an arterial catheter allows blood to circulate by systemic BP. A venous catheter is placed for return. AV circuits are simple but involve arterial puncture, which can lead to distal embolization, hemorrhage, and vessel damage. A *Qb* of 90 to 150 ml/min is typical with mean arterial pressure above 80 mm Hg, although even then flow can be erratic, predisposing to clotting. This is largely an obsolete practice because of these issues.

Mechanisms of Solute Removal

Hemodialysis

Continuous HD provides diffusive small-solute transport. *Qb* and *Qd* during CRRT are usually comparatively low (~150 ml/min and ~2 l/h, respectively). Under these conditions, the ratio of dialysate urea nitrogen to blood urea nitrogen (DUN/BUN) is 1.0, indicating complete saturation. Urea clearance therefore equals *Qd* and is unaffected by *Qb* until *Qb* decreases to less than 50 ml/min.

With increasing *Qd*, there are decreasing gains in small-solute clearance as the DUN/BUN progressively decreases. Fig. 71.5 illustrates this principle.[32] The flattening of the curves indicates conditions in which increasing *Qb* does not enhance clearance. For instance, at a *Qb* of 200 ml/min, urea clearance will correspond to *Qd* at a rate of 2 l/h (or less) and will not increase with increased *Qb*.

Hemofiltration

Continuous hemofiltration (HF) provides convective small- and medium-solute transport. An important determinant of clearance is the site of fluid replacement, which can be infused either prefilter into the arterial blood-line (predilution) or postfilter into the venous blood-line (postdilution). The standard method is postdilution. However, higher UFR can lead to hemoconcentration in the hemofilter, increased resistance in the blood flow pathway, reductions in *Qb*, and ultimately clotting of the hemofilter. In practice, UFR should not exceed 30% of the plasma water flow rate (i.e., filtration fraction should be below 0.30). The problem can be ameliorated by increasing *Qb* to at least 200 to 250 ml/min or diluting the blood and clotting factors with replacement fluid before it reaches the hemofilter (predilution).

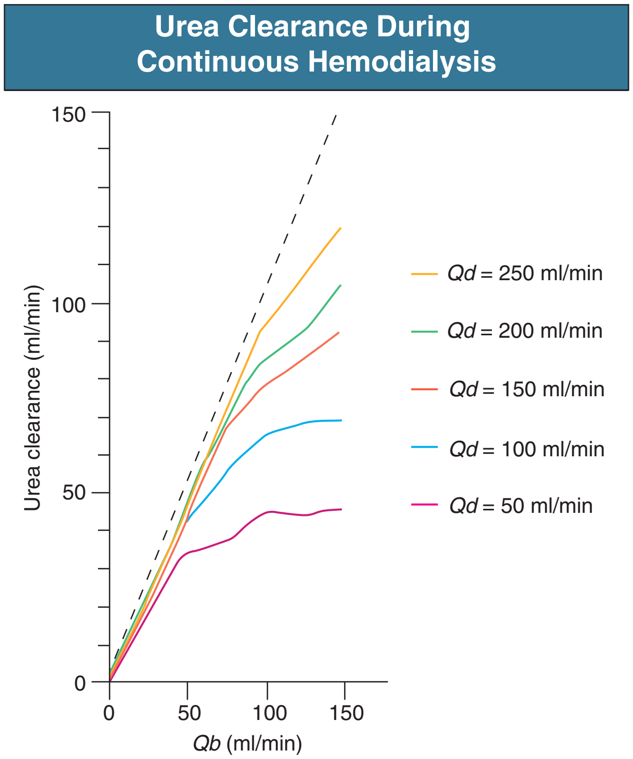


Fig. 71.5 Determinants of urea clearance during continuous hemodialysis. Relationship among urea clearance, *Qb* (blood flow), and *Qd* (dialysate flow) during continuous hemodialysis. The flattening of the urea clearance curves describes the conditions in which increases in *Qb* do not enhance clearance. (From reference 32.)

The disadvantage of predilution is that filtrate is generated from blood is diluted with replacement fluid, containing a lower concentration of uremic solutes. Small-solute clearance is reduced by approximately 15% at low UFR, although this increases to about 40% with a higher UFR.[33,34] Clearance of any given solute during continuous HF is calculated as follows:

$$\text{K (postdilution)} = \text{UFR} \times \text{S} \times 60 \,/\, \text{body weight}$$

$$\text{K (predilution)} = \text{UFR} \times \text{S} \times [\text{Qbw(Qbw} + \text{Qr)}] \times 60 \,/\, \text{body weight}$$

where K is clearance (mL/kg/hr), S is the sieving coefficient of the solute, *Qbw* is blood water flow rate (mL/min) equal to the product of *Qb* and (1 − hematocrit), and *Qr* is the replacement fluid rate (ml/min).

Hemodiafiltration

Continuous HDF refers to a combination of the preceding techniques. With large enough membranes, the small-solute clearances approach the sum of the individual techniques.[33]

Specific Techniques

CRRT techniques are shown in Fig. 71.6. The choice of technique depends on equipment availability, clinician expertise, prospects for vascular access, and whether the primary need is for fluid and/or solute removal. For isolated fluid removal, slow continuous ultrafiltration (SCUF) can be used. Given its minimal solute clearance (equal to the UFR at generally 4-5 ml/min), SCUF is primarily used for treatment of cardiorenal syndrome. Between HD and HF, the benefit of larger solute clearance is uncertain in this population, whereas those of small-solute clearance are more evident (see later). A meta-analysis comparing HD to HF showed no differences in patient survival or kidney recovery.[35]

Of note, the practice of treating lactic acidosis with CRRT should be discarded. The only effective treatment is addressing the cause of lactate formation (improving tissue oxygenation, removing dead gut, etc.); extracorporeal lactate clearance is 10-fold to 100-fold lower than plasma clearance through hepatic metabolism.

Dosage of Continuous Renal Replacement Therapy

CRRT dose is expressed as effluent volume flow rate per unit of premorbid or pre-ICU weight (ml/kg/h). The relationship between CRRT dose and mortality has now been established in several definitive clinical trials, the most important of which are the Acute Renal Failure Trial Network Study and the Randomised Evaluation of Normal versus Augmented Level of replacement therapy (RENAL) trial. As with intermittent HD, there appears to be a dose of CRRT (20 to 25 ml/kg/h) above which survival becomes dose-independent. In clinical practice, interruptions to CRRT will compromise prescribed dose, and to achieve delivered goals it is generally necessary to prescribe 25 to 30 ml/kg/h while minimizing downtime. Optimal CRRT dose appears to be related more to small-solute than larger solute clearance, and there are no specific guidelines for monitoring of larger solute clearance.

Technical Aspects of Continuous Renal Replacement Therapy

Equipment

Dedicated CRRT machines are commercially available that integrate blood pump, arterial and venous pressure monitors, an air detection

Continuous Renal Replacement Therapies

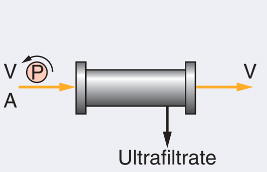
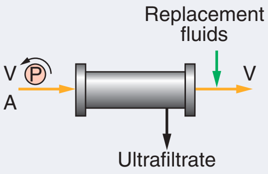
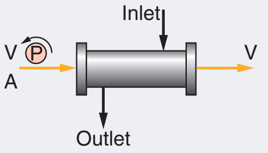
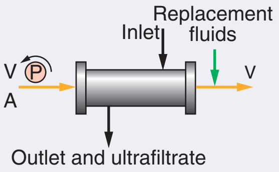
	Slow continuous ultrafiltration	Continuous hemofiltration	Continuous hemodialysis	Continuous hemodiafiltration
				 V P A Inlet Replacement fluids V Outlet and ultrafiltrate
Arteriovenous (AV) or venovenous (VV)	AV or VV	AV or VV	AV or VV	AV or VV
Blood flow (ml/min)	50-100	50-200	50-200	50-200
Dialysate flow (ml/min)	–	–	10-20	10-20
Clearance (l/24 h)	–	12-36	14-36	20-40
Ultrafiltration rate (ml/min)	2-5	8-25	2-4	8-12
Blood filter	Highly permeable filter	Highly permeable filter	Low-permeability dialyzer with countercurrent flow through the dialyzer compartment	High-permeability dialyzer with countercurrent flow through the dialyzer compartment
Ultrafiltrate	Corresponds exactly to the patient's weight loss	Replaced in part or completely to achieve purification and volume control	Corresponds to patient's weight loss; solute clearance by diffusion	In excess of patient's weight loss; solute clearance by both diffusion and convection
Replacement fluid	None	Yes	None	Yes, to achieve fluid balance
Efficiency	Used only for fluid control in overhydrated states	Clearance for all solutes equals ultrafiltration	Limited to small molecules	Extends from small to large molecules

Fig. 71.6 **Continuous renal replacement therapy modalities.** The pump *(P)* is used only in venovenous modes. (Modified from reference 63.)

system, a method for removing air bubbles, and computerized volumetric or gravimetric systems to balance dialysate inflow/replacement fluid with dialysate outflow/filtrate.

Hemofilters

Specific devices for CRRT are usually referred to as hemofilters. However, conventional hemodialyzers can serve as hemofilters. For adequate UFR to be achieved, the surface area must be large (>1.5 m^2) for low-flux hemodialyzers, although it can be smaller for high-flux ones. Some CRRT machines use a specific hemofilter because of a dedicated cartridge system. Sieving coefficients of small solutes are maintained throughout the life of hemofilters only in the absence of fiber bundle clotting and membrane repolarization, and a progressive decrease in dialysate or ratio of filtrate urea nitrogen to BUN will be noted with prolonged treatments. Monitoring of this parameter is recommended by some to avoid the advent of total extracorporeal circuit clotting and wastage of blood, as well as compromise of CRRT dose from declining saturation of effluent; proponents recommend prophylactic change of hemofilter if this ratio falls to 0.6 or less.

There is keen interest in high cut-off hemofilters, as discussed previously, although albumin losses may prevent their prolonged use. There is also interest in hemofilters with adsorptive membranes, such as those based on polymethyl methacrylate and polyethyleneimine grafted polyacrylonitrile. These provide adequate small-solute clearance and cytokine adsorption. In both cases, studies are under way to determine safety and efficacy.

Replacement Fluids and Dialysate

CRRT requires sterile replacement fluid or dialysate for blood purification, with composition that is determined by the clinical requirements for acid-base control and electrolyte management. Fluids are available commercially, but can be prepared aseptically in hospital pharmacies, albeit at greater cost and potential for human error during compounding.

Buffer choice is between bicarbonate and lactate, the latter being metabolized in the liver to bicarbonate in a 1 : 1 ratio. Although many patients tolerate lactate solutions, bicarbonate solutions are superior in terms of acid-base control, hemodynamic stability, urea generation, cerebral dysfunction, and also possibly survival in patients with a history of cardiac failure. Overall, bicarbonate has become the buffer of choice and is preferred in patients with lactic acidosis and/or liver failure. If lactate-buffered fluids are used, the development of lactate intolerance (>5 mmol/l increase in serum lactate during CRRT) should trigger a switch to bicarbonate-based fluid. Bicarbonate concentrations in fluid are typically 25 to 35 mmol/l; concentrations in the lower part of this range are indicated during high-dose or prolonged CRRT and during regional citrate anticoagulation therapy to prevent metabolic alkalosis.

Glucose concentrations in fluids range from 0.1% in commercially prepared fluids to 1.5% to 4.25% in PD fluids adapted for use with CRRT. To avoid hyperglycemia, glucose intake should be less than 5 g/kg/day, with a glucose concentration in fluid of 100 to 180 mg/dl (5.5 to 10 mmol/l) to maintain zero glucose balance.

Intravenous phosphate supplementation is often required during CRRT and is usually administered separately because of the potential for precipitation with calcium and magnesium in dialysate or replacement fluid. This concern may be unjustified, and phosphate has been safely supplemented by injecting phosphate into these solutions. Importantly, phosphate oversupplementation carries a risk for nephropathy caused by calcium phosphate crystal formation. There are no evidence-based guidelines for phosphate supplementation in critically ill patients with AKI, and phosphate kinetics are notoriously complex and multicompartmental to model. In general, an approach involving careful monitoring is warranted, with redosing or adjustment according to response to therapy; 1 or 2 doses of 20 mmol infused over several hours each will safely correct hypophosphatemia in moderate hypophosphatemia (<0.65 mmol/l), even if there are ongoing losses (e.g., from CRRT). Axiomatically, the most logical approach is prevention. One practice is to use continuous infusions starting when phosphate levels are dropping and in the lower range of normal. In this approach, a starting dose of 30 mmol over 24 hours is adjusted to keep the levels between 0.8 to 1.1 mmol/l. There is increasing experience with commercial replacement solutions containing up to 1.2 mmol/l of phosphate. They are generally safe and effective, but should be avoided in those with severe metabolic acidosis in whom narrowing of strong ion differences has potential to worsen acidemia.

VASCULAR ACCESS

A prerequisite for all ARRT modalities is reliable vascular access characterized by low resistance to flow and minimal access recirculation. If the patient has an AV fistula or graft, this should be used for intermittent HD. Otherwise, access is usually via uncuffed untunneled (temporary) double-lumen polyurethane or silicone catheters in the internal jugular or femoral veins. The subclavian veins are used less frequently because of a higher incidence of procedural complications, venous stenosis, and thrombosis.

For CRRT and PIRRT, *Qb* less than 250 ml/min is usually sufficient. For acute intermittent HD, higher *Qb* is usually required to allow sufficient solute clearance within a clinically or logistically appropriate dialysis schedule. Flows can be safely increased until venous and arterial pressures are plus and minus 350 mm Hg, respectively, after which hemolysis can occur. Left-sided internal jugular and subclavian catheters provide flows that are more erratic and up to 100 ml/min lower than elsewhere. Femoral and right-sided internal jugular or subclavian catheters provide the best *Qb*.[36]

Overall access recirculation is approximately10% at *Qb* 250 to 350 ml/min and may increase to as much as 35% at higher *Qb*. Recirculation is least in internal jugular catheters and highest in femoral catheters less than 20 cm in length. For that reason, catheters in the femoral position should be at least 24 cm long. Up to half of acute intermittent HD treatments will require catheters to be used in reversed configuration, such that the original venous line is used for blood inflow (relative to dialyzer) and the original arterial line for outflow. In this configuration, access recirculation doubles to approximately 20% at 250 to 350 ml/min, resulting in a reduction in dialysis dose.[36] Recent advances in catheter design include the use of symmetric (nonstepped) bias-cut spiraled ports on their tips. Unlike catheters with stepped tips, this design results in minimal or acceptable access recirculation in both normal and reversed configuration. Overall, data support a recommendation for right-sided internal jugular catheters with bias-cut spiraled ports as the first choice for intermittent HD and PIRRT, with femoral and left-sided internal jugular catheters as the second and third choices, respectively.[1]

In the ICU setting, catheter-associated bloodstream infection is common and is associated with a mortality risk estimated at 10% to 50%. There is ongoing controversy around the risk for infection with different insertion sites, but on balance the internal jugular site is preferred, especially in those with a larger body mass index. However, it is likely that the way the catheter is handled is more important at preventing infection than the site in which it is inserted.

BOX 71.3 Best Practices to Minimize Catheter-Associated Bloodstream Infection

Insertion

- Hand hygiene and aseptic technique (including early replacement of catheters inserted in uncontrolled settings if adherence to these measures cannot be ensured)
- Maximum barrier precautions (hat, mask, sterile gloves, sterile gown, and full patient drape)
- Appropriate skin preparation (2% chlorhexidine in 70% alcohol)
- Avoidance of the femoral site for catheter placement, especially in obese patients
- Avoidance of catheter placement near open wounds

Maintenance

- Daily review of the need for the line, with prompt removal of unnecessary lines
- Appropriate dressing with sterile gauze or a sterile, transparent, semipermeable dressing
- Appropriate schedule for dressing changes according to condition and type of dressing
- Daily review of the catheter exit site by inspection or palpation with minimal disturbance to the dressing unless clinically indicated
- Appropriate skin preparation before ports are accessed
- Daily cleansing of patients with a 2% chlorhexidine wash
- Use of a sutureless securing device for catheter stabilization

Low rates of infection require both adherence to specific clinical guidelines and grounding of activities within a formal quality improvement framework.[37] There is strong evidence that standardizing catheter insertion techniques to best practice results in a close to zero catheter-related infection rate.[38] The relevant interventional bundles are contained in position statements of the Institute for Healthcare Improvement (IHI) and the Centers for Disease Control and Prevention (CDC) Healthcare Infection Control Practices Advisory Committee (HICPAC).[3,4] The core elements appropriate for dialysis catheters are listed in Box 71.3.

Antibiotic- or antiseptic-impregnated lines are recommended by the CDC for patients whose catheters are expected to remain in place for longer than 5 days and those at high risk for infection (e.g., extensive burn injury, neutropenia, etc.). A potential downside of these impregnated lines is anaphylaxis. Topical antibiotic ointments are not recommended because of their potential to promote fungal infections and antimicrobial resistance. Catheter-restricted locking solutions are effective at reducing catheter-associated infections in chronic intermittent HD.[3,5] However, their safety and efficacy in the ICU setting is unresolved and warrants further study.

ANTICOAGULATION IN ACUTE RENAL REPLACEMENT THERAPY

Most ICU patients can avoid any anticoagulation during intermittent HD because of short treatment duration. Only a minority can do so during PIRRT or CRRT. Most commonly, unfractionated heparin is used, keeping the activated partial thromboplastin time (APTT) in the venous blood-line 1.5 to 2 times the control value and the systemic APTT below 50 seconds. This typically requires an initial bolus dose of approximately 2000 U and a maintenance infusion of approximately 500 U/h. Advantages of unfractionated heparin include low cost, relative safety, and ease of monitoring. Risks include bleeding, hyperkalemia, elevated hepatic transaminases, and heparin-induced thrombocytopenia (HIT) in 3% to 5% of patients.

Low-molecular-weight heparin (LMWH) is theoretically advantageous because of increased antithrombotic activity and decreased hemorrhagic risk. However, disadvantages include a prolonged half-life (approximately doubled in AKIN stage 3, with no significant clearance during ARRT), incomplete reversal with protamine, and limited availability of appropriate monitoring by serial anti–factor Xa determinations (recommended level 0.25 to 0.35 U/ml). Meta-analyses and the American College of Chest Physicians (ACCP) guidelines conclude that the use of LMWH is associated with major bleeding in patients with a creatinine clearance below 30 ml/min, and recommend either unfractionated heparin or a reduction in LMWH dose by 50% for such patients.[6,39] LMWH dosage is not interchangeable between different drugs. Most experience is with dalteparin administered as a single bolus of approximately 20 to 30 U/kg for intermittent HD, followed by an infusion of approximately 10 U/kg/h for PIRRT or CRRT. Overall, evidence does not support a recommendation of LMWH over unfractionated heparin in the critically ill AKI setting.

Other approaches to anticoagulation include direct thrombin inhibitors (e.g., argatroban), antithrombin-dependent factor Xa inhibitors (e.g., fondaparinux), and serine protease inhibitors (nafamostat mesilate). Argatroban does not cross-react with heparin antibodies and is the preferred approach for HIT because of its hepatic clearance (half-life ~35 minutes, no significant clearance during intermittent HD or PIRRT[40]) and ease of monitoring with APTT. It is administered as a 0.1 to 0.25 mg/kg bolus before intermittent HD or an infusion of 0.1 to 0.2 mg/kg/h during PIRRT, titrated according to APPT. Further management of HIT is provided in guidelines from the ACCP and the European Best Practice Guidelines.[6,8]

For those receiving systemic anticoagulation with heparin, the incidence of significant bleeding complications is up to 25% to 30%. A regional strategy mitigates this risk, and the preferred technique is regional citrate anticoagulation, which provides the lowest rates of hemorrhage and greatest prolongation of filter life. Regional citrate anticoagulation involves calcium chelation in the extracorporeal blood circuit with calcium reversal.

For intermittent HD and PIRRT, this involves an infusion of 4% trisodium citrate into the arterial blood-line, with zero- or low-calcium dialysate and an infusion of calcium chloride into the venous blood-line. A simpler approach has been described in which the citrate infusion is combined with normal calcium dialysate and no calcium infusion. The positive calcium flux through the hemodialyzer maintains calcium balance, and provides partial chelation of the undialyzed citrate.

For CRRT, regional citrate anticoagulation is performed with either 4% trisodium citrate or anticoagulant citrate dextrose A. For continuous HD, a prefilter infusion of between 3% to 7% of *Qb* is used, with a postfilter infusion of calcium chloride. This requires dialysate that is hyponatremic and devoid of alkali because citrate metabolizes to bicarbonate in the liver in a 1 : 3 ratio (Table 71.1). Frequent monitoring and titration of citrate dose have usually been advocated to keep the ionized calcium within a therapeutic range. Many centers now use a simplified fixed-dose anticoagulant citrate dextrose, a protocol that minimizes the need to measure postfilter calcium or adjust the citrate infusions. Major complications of regional citrate anticoagulation include systemic hypocalcemia and metabolic alkalosis from citrate toxicity.

There is increasing experience with commercial replacement solutions containing citrate as buffer; this chelates calcium in the blood without the need for a separate citrate infusion. This also allows for direct coupling of citrate and calcium infusions by CRRT machinery, such that a change in *Qb* leads to an automatic change in citrate delivery into the extracorporeal blood circuit and calcium infusion into the venous line (relative to dialyzer) or catheter. This does not obviate monitoring for systemic hypocalcemia and metabolic alkalosis, but is expected to be safer and will likely become the standard approach in the future.

TABLE 71.1 **Comparison of Regional Citrate Anticoagulation Protocols**

	Modality	Blood Flow (ml/min)	Replacement Fluid Composition (mmol/l)	Dialysis Fluid Composition (mmol/l)	Citrate Source
Mehta et al[53] (1990)	CAV-HD	52-125	Normal saline	Na 117, Cl 122.5, Mg 0.75, K 4, dextrose 2.5%	4% Trisodium citrate
Hoffmann et al[55] (1995)	CVV-HD	125	*Prefilter:* Normal saline + KCl 4, alternate with 0.45% saline + KCl 4 *Postfilter:* 0.45% saline + $MgSO_4$ + $CaCl_2$	—	4% Trisodium citrate
Palsson and Niles[54] (1999)	CVV-HD	180	Citrate 13.3, Na 140, Cl 101.5, Mg 0.75, dextrose 0.2%	—	Customized citrate solution
Tolwani et al.[56] (2001)	CVV-HD	125-150	—	Normal saline + $MgSO_4$ 1.0, KCl 3	4% Trisodium citrate
Tobe et al.[57] (2003)	CVV-HDF	100	Normal saline	Normocarb	ACD-A
Mitchell et al.[58] (2003)	CVV-HD	75	—	Variable Ca 1.75-1.78	ACD-A
Swartz et al.[59] (2004)	CVV-HD	200	—	Na 135, HCO_3 28, Cl 105, $MgSO_4$ 1.3, glucose 1 g/l	ACD-A
Gupta et al.[60] (2004)	CVV-HDF	150	Normal saline ± $MgSO_4$ and KCl	PD fluid: Na 132, Ca 1.25, Cl 95, Mg 0.5, lactate 360 mg/dl, 1.5% dextrose	ACD-A

ACD-A, Anticoagulant citrate dextrose form A; *CAV-HD,* continuous arteriovenous hemodialysis; *CVV-HD,* continuous venovenous hemodialysis; *CVV-HDF,* continuous venovenous hemodiafiltration; *PD,* peritoneal dialysis. Number behind electrolytes are concentrations in mmol/l.

Regional heparin anticoagulation involves neutralization of heparin by infusion of protamine into the venous blood-line. It may be complicated by rebound bleeding, occurring when neutralization with protamine wears off faster than the anticoagulation from heparin. Furthermore, protamine may cause sudden hypotension, bradycardia, or anaphylactoid reactions.

Prostacyclin is an effective alternative anticoagulant. However, it is a vasodilator, causing a variable but occasionally marked decrease in BP. Moreover, there is a risk for worsening ventilation-perfusion mismatch and lactic acidosis in patients with multiorgan dysfunction and a risk for increasing intracranial pressure in patients with combined liver and kidney failure.

MODALITY CHOICE AND OUTCOMES IN ACUTE RENAL REPLACEMENT THERAPY

On the basis of current evidence, the use of one modality of ARRT over another is unlikely to translate to overall clinical benefit, if applied as an initial modality to all patients.[1,21] This does not mean the modalities are clinically equivalent. In comparative trials, 5% to 15% of patients treated initially with HD require a change to CRRT because of progressive hemodynamic instability or poor metabolic control.[41,42] The evidence can be summarized thus: the use of intermittent HD as initial modality results in the same outcomes as the use of CRRT as initial modality, as long as a switch is made in a timely manner as best practice and clinical indications dictate.

The relationship between modality choice and mortality is modified by clinical context. In those at risk for dialysis disequilibrium syndrome (e.g., those with raised intracranial pressure or abdominal compartment syndrome), solute disequilibrium should be minimized to avoid water influx into tissues; lower efficiency PIRRT and CRRT are more desirable for such patients.[20] For most, modality choice still depends mostly on the most clinically appropriate rate of solute and fluid removal.[1] Patients who are hemodynamically unstable, including those with cardiogenic shock, appear to have better organ recovery if they are treated with PIRRT and CRRT.[43] Other studies are examining modality selection and outcomes in acute lung injury, sepsis, and acute cardiac decompensation, although there are no definitive data as of yet.

The role of is PIRRT is difficult to determine, partly because of the lack of standardization with respect to prescription. In the older descriptions of PIRRT, the duration (12 to 18 hours) and other operating characteristics ($Qd \leq 100$ ml/min, $Qb \leq 200$ ml/min) were closer to those of CRRT, and treatment tolerance was excellent. Currently, the typical duration is 6 to 8 hours and Qd is usually 300 ml/min, and outcomes may not be as good as those with CRRT, especially in high-risk populations such as those with septic shock.[44] It is clear that PIRRT is not a homogenous modality. Practically, lower efficiency prescriptions (i.e., with lower UFR and slower solute removal) should be used for hemodynamically unstable patients and perhaps those with sepsis, as well as when it is imperative to avoid fresh ischemic injury, such as those with cardiovascular disease and CKD (see Fig. 71.3).

Outcomes other than survival are important for patients who survive critical illness and AKI. The risk for ESRD is increased several-fold after critical illness with AKI requiring ARRT, and this drives longer term risk for death that results in up to a third of 90-day survivors dying at 44 months. Therefore it is a high priority to optimize renal recovery, and observational studies suggest that this can be achieved by the more rigorous application of lower efficiency modalities to hemodynamically unstable patients and those with a low renal reserve, such as those with CKD. For quality of life and other patient-centered outcomes, it does not appear that the intensity or modality of ARRT is the main determinant, although more studies are needed.

CRRT is generally more expensive than intermittent HD or PIRRT. However, economic evaluations of ARRT are all limited by wide variation in ICU cost and reimbursement structures, and many do not consider longer term outcomes such as the development of ESRD. At present, economic evaluations comparing modalities needs to be conducted locally, with careful consideration of underlying assumptions about costs and outcomes.

ACUTE RENAL REPLACEMENT THERAPY DURING MECHANICAL CIRCULATORY SUPPORT

The two forms of mechanical circulatory support (MCS; Box 71.4)[45-47] that are most commonly encountered by ARRT providers are extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs). ECMO can be venovenous or venoarterial; deoxygenated blood is taken from a central vein and pumped through an oxygenator back into either a central vein or the arterial system, thereby providing respiratory or cardiorespiratory support, respectively.[48] VADs are devised to assist the left and/or right ventricles (LVAD and RVAD, respectively) in patients with refractory heart failure or cardiogenic shock. They are used as a bridge to recovery or transplantation or as destination therapy for patients ineligible for transplant. Early versions had pulsatile flow, but newer versions have continuous flow, an improved safety profile, and they now comprise 90% of implanted VADs in the United States. Another modality of respiratory support increasingly used is extracorporeal carbon dioxide removal ($ECCO_2R$). It removes carbon dioxide via a minimally invasive approach that requires lower blood flow and smaller cannulas than ECMO. Of particular interest for ARRT providers is respiratory dialysis, a form of $ECCO_2R$ that decarboxylates blood using a hemofiltration system linked to a gas exchange membrane.[49]

AKI is common in patients with circulatory and/or respiratory failure. If hypoperfusion is causing AKI, initiating MCS may improve renal function.[50] However, the incidence of intrinsic AKI (and the need for ARRT) is high because patients requiring MCS are sicker and MCS can

BOX 71.4 Select Types of Mechanical Circulatory Support Devices

- Intraaortic Balloon Pump

Neurohormonal Adaptation Devices

- Vagal Nerve Stimulation: *CardioFIT*

Continuous Aortic Flow Devices

- Continuous aortic flow augmentation: *Cancion CRS*
- Implantable augmented aortic flow pump: *Exeleras*
- Reitan catheter pump

Ventricular Assist Devices (VAD)*

- Left ventricular assist device (LVAD)
- Right ventricular assist device (RVAD)
- Biventricular assist device (BiVAD) or total artificial heart

Extracorporeal Membrane Oxygenation (ECMO)

- Venovenous ECMO: Provides respiratory support
- Venoarterial ECMO: Provides full cardiorespiratory support
- Extracorporeal carbon-dioxide removal ($ECCO_2R$)[†]
- Respiratory dialysis

*For a classification of VADs based on generation or type, see references 45 and 46.

[†] For list of available devices, see reference 49.

be complicated by periprocedural hypotension, inflammation, thromboembolism, and hemolysis. Although scant data are available regarding the use of ARRT during MCS, the general principles are similar to those for other ICU patients. However, prolonged or continuous ARRT modalities may be especially advantageous during MCS because they allow for more effective management of patients receiving large fluid volumes. Maintaining adequate volume balance facilitates weaning of MCS, whereas volume overload is associated with worse outcomes.[51]

Technical Aspects of Acute Renal Replacement Therapy During Mechanical Circulatory Support

Access Options and Techniques

Patients on MCS present several access options.[52] The first is through standard HD catheters (see Chapter 93), which have the advantage of maintaining the two circuits independent of each other. This is the preferred access for ARRT in patients with VADs. The risks are similar to those in other patients, but infections are an important cause of mortality.

The second option, which can be used in ECMO or RVADs, but not LVADs (thromboembolism risk), is to directly link the ARRT device to the MCS circuit. This is achieved by creating a shunt along the MCS circuit using two three-way taps, the placement of which depend on the type of ARRT. During inline RRT, the shunt is created between an arterial port (placed after the pump, where the pressure is positive) and a venous port (placed before the pump, where the pressure is negative). This pressure gradient drives blood flow through a hemofilter placed directly in line (Fig. 71.7A). The ultrafiltrate, dialysate, and/or replacement fluid rates are regulated by infusion pumps. This method is simple

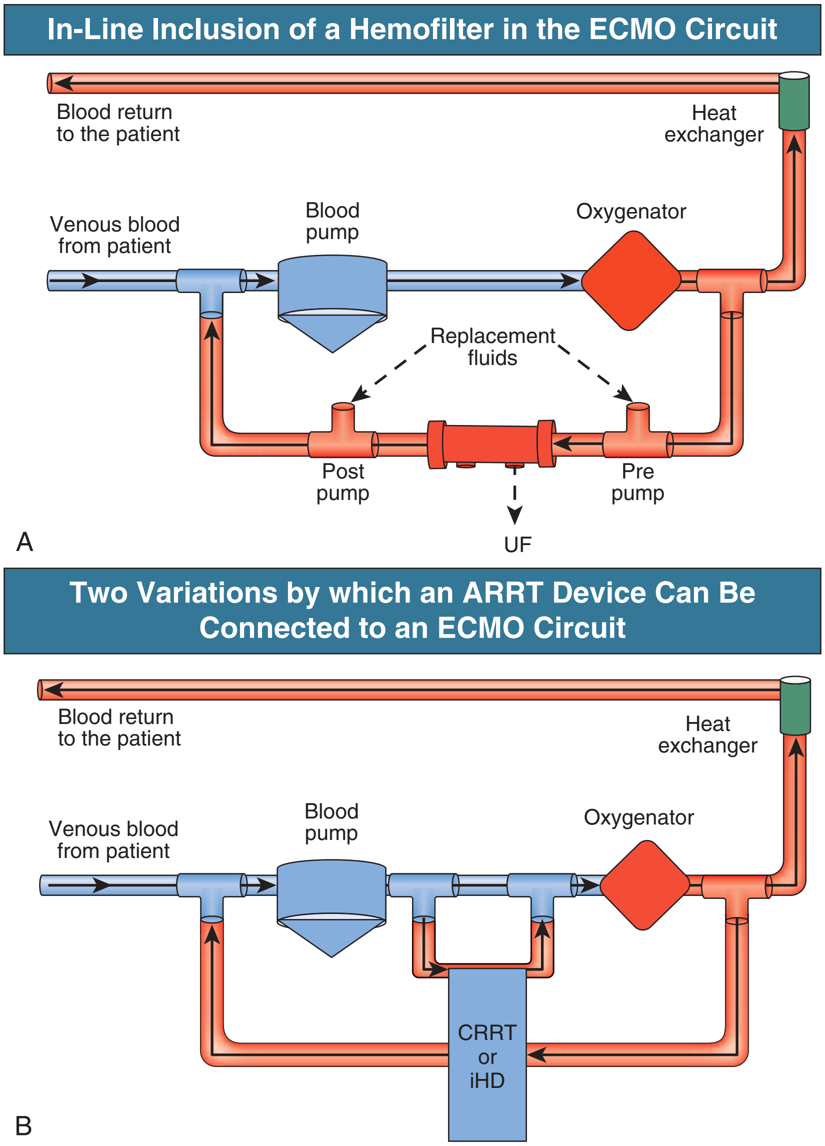

In-Line Inclusion of a Hemofilter in the ECMO Circuit
Blood return to the patient
Heat exchanger
Venous blood from patient
Blood pump
Oxygenator
Replacement fluids
Post pump
Pre pump
UF
A
Two Variations by which an ARRT Device Can Be Connected to an ECMO Circuit
Blood return to the patient
Heat exchanger
Venous blood from patient
Blood pump
Oxygenator
CRRT or iHD
B

Fig. 71.7 Techniques used to incorporate acute renal replacement therapy *(AART)* into extracorporeal membrane oxygenation *(ECMO)* and ventricular assist device (VAD) circuits. (A) Inline inclusion of a hemofilter in the ECMO circuit. Note that inclusion into a right VAD (RVAD) circuit would be similar except simplified in that blood comes from the body to the pump and then goes back to the body without passing through an oxygenator. (B) Two variations by which an ARRT device can be connected to an ECMO circuit. Note that flow in the mechanical circulatory support circuit is high enough that recirculation is not a concern even when the arterial access port is distal to the venous return port. *CRRT,* Continuous renal replacement therapy; *iHD,* intermittent hemodialysis; *UF,* ultrafiltration.

TABLE 71.2 Special Considerations in Patients on Mechanical Circulatory Support Requiring Acute Renal Replacement Therapy

Monitoring Blood Pressure, Volume Status, and Mechanical Circulatory Support Function

Parameters Monitored During ARRT	Method/Affected Parameter	Target
Blood pressure	Terumo slow-deflating cuffs Doppler audible ultrasound Arterial line in critically ill patients	MAP 70-80 mm Hg Not to exceed 90 mm Hg
Volume status/preload	Central venous pressure Filling volumes (echocardiography) Pulsatility index Pump flow	Parameters vary with each device Contact the VAD coordinator for targets

Considerations and Complications of MCS/ARRT

Volume Shifts/Hypovolemia/UF	*Hematologic Issues*	*Other*
Errors	Bleeding	Stroke
Hypotension	Thrombosis	Infection
Reduced pump filling (low-flow events)	Hemolysis	
Suckdown events		
Chattering		

Advanced Cardiac Life Support

NO chest compressions (could dislodge the cannulae)
Standard ACLS protocols are used
VAD ejection is asynchronous with the underlying cardiac rhythm
VAD patients tolerate arrhythmias and remain asymptomatic

ACLS, Advanced Cardiac Life Support; *MAP,* Mean arterial pressure; *UF,* ultrafiltration; *VAD,* ventricular assist device.

and inexpensive, but the infusion pumps are relatively inaccurate and can thus be a source of error. Connecting an ARRT machine to the MCS circuit is achieved in a similar manner. However, because blood flow through the filter is achieved via the CRRT pump (rather than pressure gradients), a variety of access sites along the MCS can be used (see Fig. 71.7B). This setup uses commercially available ARRT machines that control the renal replacement therapy procedure and hence depends on the availability of appropriate equipment and properly trained staff.

Monitoring and Management of Key Acute Renal Replacement Therapy–Related Issues

The concurrent usage of continuous-flow MCS and ARRT creates challenges that are distinct from those in other critically ill patients (Table 71.2). Monitoring BP, volume status, and MCS function is particularly challenging and of fundamental importance.[52] BP needs to be adequately assessed and treated because continuous-flow MCS is vulnerable to changes in afterload; increases can reduce pump output. However, because these patients have minimal pulses, standard methods for measuring BP are unreliable. Thus specialized BP cuffs with low pulsatility modes or determining mean arterial pressure with Doppler ultrasonography are used (see Table 71.2).

The changes in intravascular volume during ARRT pose a particular risk for these patients because their MCS is dependent on preload. Volume status is best assessed by central venous pressure, echocardiogram, or the pulsatility index (a dimensionless value calculated in the Heartmate II from the magnitude of flow pulses averaged over 15-second intervals). Hypovolemia leads to left ventricular collapse with subsequent fall in MCS flow, pump overdrive, hypotension, and ventricular arrhythmias. This is corrected by gentle volume administration, as other causes of preload reduction (e.g., bleeding, sepsis) are considered. Decreasing the pump speed and treating arrhythmias usually should be performed only after consultation with appropriate MCS personnel.

DRUG DOSAGE IN ACUTE RENAL REPLACEMENT THERAPY

For patients undergoing CRRT, 20 liters of daily filtrate corresponds to a glomerular filtration rate of approximately 14 ml/min and the dose of drugs should be calculated accordingly. Any drug with a low therapeutic index that can be readily measured should be measured frequently early in the course of ARRT, until a stable pattern appears. One day of CRRT is in general comparable to one intermittent HD treatment with regard to drug removal.

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SELF-ASSESSMENT QUESTIONS

1. Survival of critically ill patients who require acute renal replacement therapy (RRT) is improved through the routine application of which *one* of the following interventions?
   - **A.** The routine use of continuous rather than intermittent modalities
   - **B.** Pulsed high-volume continuous venovenous hemofiltration (CVVH) (effluent rate of 60-100 ml/kg/h) for those with sepsis
   - **C.** The routine use of daily rather than thrice-weekly treatment schedules for those receiving intermittent RRT modalities
   - **D.** Ensuring single-pool *Kt/V* of 1.3 or more for those receiving intermittent RRT modalities delivered on a thrice-weekly schedule
2. Which *one* of the following statements is true regarding central venous catheters for acute RRT in critically ill patients?
   - **A.** Catheter brand and design choice can and should be standardized between continuous and intermittent RRT modalities.
   - **B.** Catheters should be placed and used for intermittent hemodialysis (HD), rather than use of arteriovenous fistulas or prosthetic bridge grafts in patients who have them.
   - **C.** Access recirculation is reduced by characteristics of catheter design and site of placement.
   - **D.** Left-sided internal jugular catheters are routinely preferred to femoral ones.
3. Which of the following interventions is *not* recommended to reduce central venous catheter–associated bloodstream infection during RRT for critically ill patients?
   - **A.** A formal quality improvement framework and program for catheter insertion and maintenance
   - **B.** The routine use of topical antibiotic ointments at the exit site
   - **C.** Antibiotic- or antiseptic-impregnated catheters for patients at high risk for catheter-associated bloodstream infection
   - **D.** Routine placement of catheters in the internal jugular site
4. Which *one* of the following statements is true regarding anticoagulation for acute RRT in critically ill patients?
   - **A.** For those receiving systemic anticoagulation with heparin, the incidence of significant bleeding complications is 10%.
   - **B.** Argatroban is the preferred approach in those with heparin-induced thrombocytopenia.
   - **C.** Certain low-molecular-weight heparins are cleared significantly by acute RTT and therefore are preferable.
   - **D.** Complications from regional citrate anticoagulation are greater than those from systemic unfractionated heparin.
5. Which of the following interventions is useful to prevent intradialytic hypotension for critically ill patients receiving intermittent RRT modalities?
   - **A.** Combined sodium and ultrafiltration profiling
   - **B.** Blood temperature monitoring and biofeedback control
   - **C.** Circulating blood volume monitoring and biofeedback control
   - **D.** The use of hemodiafiltration rather than hemodialysis

72

Dialytic Management of Refractory Heart Failure

Edward A. Ross, Kevin Damman, Amir Kazory

Nephrologists are increasingly consulted regarding fluid management in patients with refractory heart failure (HF). Renal expertise extends beyond diuretics and electrolyte homeostasis and now includes recent advances in drug therapies, acute and chronic fluid removal by extracorporeal dialysis machines or isolated ultrafiltration (UF) devices, and peritoneal modalities.

DEFINITION AND SCOPE OF THE PROBLEM

HF and renal dysfunction may coexist, but each disease also can cause or exacerbate the other. Poor cardiac output results in reduced renal perfusion and potentially kidney ischemia and progressive chronic kidney disease (CKD).[1] Conversely, CKD may result in salt and water retention with subsequent venous congestion, hypertension, activation of the renin-angiotensin-aldosterone system (RAAS), and vascular calcification that cause cardiac dysfunction, accelerated atherosclerosis, and left ventricular hypertrophy and remodeling. These conditions may exacerbate HF, creating a vicious cycle of reduced cardiac output and kidney dysfunction.

Of the 100,000 patients in the Acute Decompensated Heart Failure National Registry (ADHERE), 57% had CKD stages 3 or 4, 7% were at stage 5, and only 9% had normal kidney function. In patients with HF who presented with CKD at the time of admission, there was greater use of diuretics and inotropes, less angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) administration, and a 5% higher in-hospital mortality rate.[2]

PATHOGENESIS

Fig. 72.1 illustrates the pathogenesis of refractory HF. The pathophysiology and treatment strategies for combined heart and kidney failure (cardiorenal syndrome)[3] highly depend on whether the HF occurs with reduced (HFrEF) versus HF with preserved ejection fraction (HFpEF). In the former, low cardiac output HF plays a key role resulting in worsening renal perfusion and function, activating the RAAS and sympathetic nervous system (SNS), leading to salt and water retention with a paradoxical further worsening of cardiac function. Central to this vicious cycle is tubuloglomerular feedback (TGF; Chapter 2), which is maladaptive in HF, especially when certain drugs (e.g., diuretics) alter tubular sodium delivery. Secondary (hyper)aldosteronism (resulting in increased sodium retention), increased systemic vascular resistance (putting more strain on the heart), and higher cardiac filling pressures may reduce cardiac output, as further increases in preload lead to lower stroke volume. This further activates the SNS, which worsens vasoconstriction, cardiac function, and renal perfusion. Excessive activation of both the RAAS and SNS has long been considered the hallmark of worsened HF. Other pathophysiologic mechanisms are discussed in the following paragraphs.

Venous Congestion

Right-sided congestion and renal venous hypertension also contribute to kidney dysfunction.[4] In this regard, HF is analogous to abdominal compartment syndrome, portal hypertension, or renal venous thrombosis; however, some of these conditions differ in whether there is extravascular versus intravascular hydrostatic pressure transmitted to the kidneys. Venous hypertension is thought to trigger neuromyogenic changes that decrease renal perfusion, raise kidney interstitial pressure, narrow the arterial-to-venous pressure gradient, lower renal blood flow and glomerular filtration rate (GFR), trigger maladaptive autoregulatory responses, and exacerbate neurohumoral pathways already problematic in HF. Furthermore, there is also a direct effect of higher renal venous pressure that transmits to the renal parenchyma. This higher pressure directly opposes glomerular filtration, causes collapsing of tubules, and may be the first trigger for tubulointerstitial fibrosis.[5] These mechanisms are consistent with a critical role of the adrenergic system in modulating venous tone and thus capacity. In that veins contain nearly 70% of the circulatory volume, changes to venous capacitance (and pressure) can decompensate or ameliorate HF, without changes to total body salt, fluid, or weight.[6] This variation in the venous reservoir volume reconciles how approximately a third of outpatients have HF decompensation with minimal change in weight and why approximately 15% of HF inpatients can symptomatically improve despite no weight loss. Changes in reservoir capacity also confound interpretation of simultaneous changes in volume by extracorporeal UF. Besides these hemodynamic effects, volume overload from either cardiac or renal dysfunction causes circumferential stretch of endothelial cells of the venous system, which can trigger the release of tumor necrosis factor and interleukin-6 (IL-6), potentially impairing myocardial contractility and renal function.[7,8]

Some studies report that kidney function in decompensated HF correlates better with right-sided pressures than the ejection fraction or cardiac index. In addition, elevated central venous pressures correlated with mortality and inversely with kidney function.[9,10]

Adenosine

Adenosine receptors maintain intrarenal vascular tone via multiple pathways, including A_1 receptors (which cause afferent arteriolar vasoconstriction) and A_2 receptors (which induce efferent vessel dilation). Actions of adenosine at the macula densa and mesangium depend on angiotensin, renin, nitric oxide, and prostaglandin levels. The great appeal of A1 receptor antagonists is that they also have beneficial direct vascular effects: vasodilating cortical arterioles, and thereby blocking

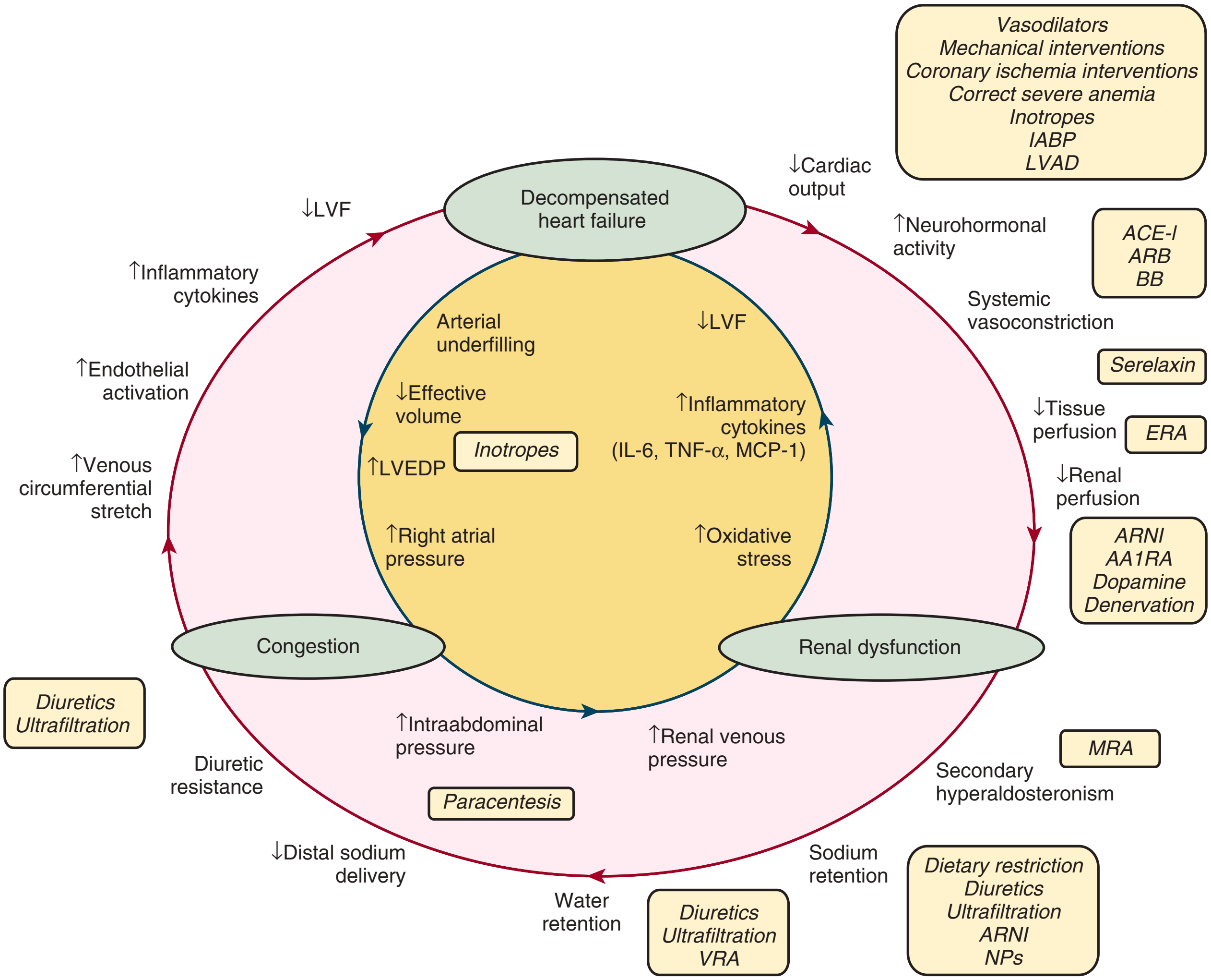
Vasodilators
Mechanical interventions
Coronary ischemia interventions
Correct severe anemia
Inotropes
IABP
LVAD
↓Cardiac output
Decompensated heart failure
↓LVF
↑Inflammatory cytokines
↑Endothelial activation
↑Venous circumferential stretch
↑Neurohormonal activity
ACE-I
ARB
BB
Systemic vasoconstriction
Serelaxin
↓Tissue perfusion
ERA
↓Renal perfusion
ARNI
AA1RA
Dopamine
Denervation
Arterial underfilling
↓LVF
↓Effective volume
Inotropes
↑LVEDP
↑Inflammatory cytokines (IL-6, TNF-α, MCP-1)
↑Right atrial pressure
↑Oxidative stress
Congestion
Renal dysfunction
Diuretics
Ultrafiltration
Diuretic resistance
↑Intraabdominal pressure
↑Renal venous pressure
Paracentesis
MRA
Secondary hyperaldosteronism
↓Distal sodium delivery
Sodium retention
Water retention
Diuretics
Ultrafiltration
VRA
Dietary restriction
Diuretics
Ultrafiltration
ARNI
NPs

Fig. 72.1 Reciprocal pathophysiologic pathways linking heart failure, renal dysfunction, and congestion in cardiorenal syndrome. Decompensation of heart failure can lead to deterioration in renal function via exacerbated neurohormonal activity (i.e., low forward flow) or through fluid overload and renal venous congestion (i.e., high backward pressure). The impact of various pharmacologic and nonpharmacologic therapeutic options on the underlying pathophysiologic mechanisms is illustrated. *AA1RA,* Adenosine A_1 receptor antagonist; *ACE,* angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *ARNI,* angiotensin receptor neprilysin inhibitor; *BB,* β-blocker; *ERA,* endothelin receptor antagonist; *IABP,* intraaortic balloon pump; *IL-6,* interleukin-6; *LVAD,* left ventricular assist device; *LVEDP,* left ventricular end-diastolic pressure, *LVF,* left ventricular function; *MCP-1,* monocyte chemoattractant protein-1; *MRA,* mineralocorticoid receptor antagonist; *NPs,* natriuretic peptides; *TNF-α,* tumor necrosis factor-α; *VRA,* vasopressin receptor antagonist.

TGF so as to permit a continued diuresis in HF. In addition, there is a growing literature on the effects of adenosine on the myocardial fibrosis in animal ischemia-reperfusion models. Over-expression of the A1 receptor induces dilated cardiomyopathy and fibrosis.

Anemia

Anemia may be caused by chronic disease or coexistent CKD, or it may be the consequence of hemodilution by venous congestion. Relative EPO deficiency and resistance to EPO are among the pathologic phenomena that link the anemia of CKD with that of HF. The term *cardiorenal anemia syndrome* emphasizes this pharmacologically remediable aspect of HF.

Diuretic Resistance and Adverse Effects

Many patients with HF develop diuretic resistance, failing to have appropriate natriuresis despite escalating doses, with worsening neurohumoral mediator levels.[11] Indeed, morbidity and mortality in advanced HF increased up to fourfold with higher doses of diuretics,[12] and higher doses have been associated with worse GFR (despite equivalent fluid losses),[14] although differences in baseline characteristics likely contributed to these outcomes.[13] In the Diuretic Optimization Strategies Evaluation (DOSE) trial (see later), there was no difference in outcome in high- versus low-dose diuretic therapy, despite a higher incidence of (transient) worsening GFR in the high-dose diuretic group.[15]

TREATMENT

General Approach and Limitations

A pragmatic approach is to first address potentially treatable causes of HF such as valvular disease, conduction disorders and arrhythmias, pericardial effusion, or coronary ischemia (Box 72.1). The clinician approximates the volume of excess fluid and crafts a daily therapeutic

BOX 72.1 Treatment Modalities for Refractory Heart Failure

Traditional Treatment
- Diuretics: Loop diuretics, long-acting thiazides
- Digoxin
- ACE inhibitors and ARBs
- Mineralocorticoid receptor antagonists
- β-Blockers
- Vasodilators
- Blood transfusions

Pharmaceuticals
- Neprilysin inhibitor/ARB combination for HFrEF
- Inotropes: For example, milrinone, dobutamine*
- Synthetic natriuretic peptides*
- Aquaretics: Vasopressin antagonists*
- Erythropoiesis-stimulating agents*
- Adenosine receptor blockade*

Mechanical Treatment
- Biventricular pacing
- Ventricular assist devices

Ultrafiltration
- Peritoneal dialysis
- Manual (CAPD) and automated using a cycler (APD)
- Extracorporeal therapies
- Intermittent short-duration ultrafiltration
- Slow continuous ultrafiltration (SCUF)

*No clinical benefit established.

ACE, Angiotensin-converting enzyme; *APD,* automated peritoneal dialysis; *ARB,* angiotensin receptor blocker; *CAPD,* continuous ambulatory peritoneal dialysis; *HFrEF,* heart failure with reduced ejection fraction.

goal concurrent with reducing excess salt intake.[16] Medication-naïve patients then can be cautiously treated as described later, with serial monitoring because hypotension or renal dysfunction commonly limit the use of pharmaceuticals. Determining to what degree a particular patient may be able to tolerate drug-induced lower levels of blood pressure (e.g., from afterload-reducing agents) is clinically challenging. If there is marked sensitivity of the blood pressure or GFR to low doses of RAAS blockade, bilateral renal artery stenosis should be considered (see Chapter 41).

Pharmacologic Therapeutic Strategies

The pharmacologic management of HF is summarized in Box 72.1 and includes traditional approaches for arrhythmias (e.g., for atrial fibrillation) and afterload reduction, SNS, and RAAS blockade. Although diuretics remain the mainstay of treatment of congestion in HF, salt and water excretion in acute HF is often inadequate; registry data indicated that of patients admitted with acute HF, approximately 16% were discharged at a higher body weight.[17]

Diuretics

Despite the concerns described, most patients initially respond to intensified diuretic regimens, which may require increasing the dose or frequency of loop diuretics, coadministering a long-acting thiazide diuretic, or continuously infusing loop diuretic. In the DOSE study,[15] high versus low doses and continuous versus bolus infusion of loop diuretics were tested in acute HF, and no clinically relevant differences were no found in the regimens. For patients with up to 80 mg of oral furosemide equivalent dose as outpatient, an intravenous bolus of 40 mg furosemide followed by infusion of 5 mg/hour can be considered. For those with higher doses as outpatient, a bolus of 80 mg followed by 10 mg/hour infusion would be a reasonable start point. The dose would then need to be tailored according to the clinical and laboratory parameters such as serum creatinine, blood pressure, and urine output.

Loop diuretic efficiency, defined as urine output per diuretic dose, has been identified as an important prognostic indicator in decompensated HF, independent of the underlying kidney function. The most obvious explanation for this finding is that characteristics of more advanced cardiac and renal disease are contributing to decreased diuretic efficiency. However, one might speculate that the loop diuretic efficiency can be modulated by therapeutic interventions (e.g. addition of thiazide diuretics) and wonder if such strategies would improve outcomes. While there have been successful attempts for rapid and reliable prediction of poor natriuretic response in patients treated for acute decompensated HF, future large scale trials are needed to confirm the results of these preliminary studies.

Although higher dose regimens increased the risk for transient decreases in GFR, they did not affect long-term outcomes. Based on the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, in which there was worsened renal function in decompensated HF, efficacious and safe algorithms can be crafted for stepped pharmacologic care in which inotropes, nesiritide, or nitroglycerin are added to diuretics sequentially.[18]

Renin-Angiotensin-Aldosterone System Antagonists

Although decreases in GFR after RAAS blockade do not necessarily portend worse outcomes,[19] if GFR falls substantially, ACE inhibitors and ARBs may need to be temporarily decreased or withdrawn in patients undergoing diuresis or in those with advanced CKD. Alternatively, it may be necessary to reduce diuretic dosage before the ACE inhibitor dose is adjusted. Hyperkalemia also may limit the use of RAAS blockers or could be an indication for concurrent use of medications that enhance gastrointestinal potassium excretion.

Neprilysin Inhibitors

Neprilysin is a neutral endopeptidase that degrades several vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling. The Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial evaluated the effects of sacubitril/valsartan versus enalapril in 8442 patients with HFrEF. Sacubitril/valsartan was superior to enalapril in reducing mortality, the risk for hospitalization for HF, and the symptoms and physical limitations of HF.[20] Importantly, the rates of renal dysfunction were less with sacubitril/valsartan versus enalapril. Thus sacubitril/valsartan could replace ACE inhibitors or angiotensin receptor antagonists as the cornerstone of therapy for HFrEF.[16] Studies on the use of neprilysin inhibitors for patients with HFpEF are under way.

Miscellaneous Therapies

A number of pharmacologic agents (e.g., nesiritide, endothelin receptor antagonists, adenosine-A1 receptor antagonists, and selective or nonselective vasopressin receptor antagonists) have been investigated, but so far large-scale trials have unfortunately proven them to be suboptimal, ineffective, or unsafe. Severe anemia should be treated based on concurrent conditions and their severity, using iron repletion,[16] transfusions (e.g., for acute hemorrhage), and erythropoiesis stimulating agents as per CKD guidelines (see Chapter 82).

Medications Under Development

Serelaxin, a recombinant form of human relaxin-2, has shown promise in management of patients with concomitant heart and renal failure. Relaxin is a peptide hormone secreted during pregnancy and is associated with increase in cardiac output and decrease in systemic vascular resistance. The RELAXin in Acute Heart Failure (RELAX-AHF) compared the effects of serelaxin versus placebo in 1161 patients admitted for acute HF.[21] Serelaxin use was associated with significantly lower serum creatinine and plasma cystatin C levels in the first 5 days after enrollment. All-cause and cardiovascular mortality were also lower at 180 days in the serelaxin arm. However, it had no effect on readmission to hospital.

Catheter-based renal denervation is a promising therapy designed to reduce renal sympathetic activity and systemic sympathetic activation, which contribute to cardiorenal syndrome. Although animal studies showed positive results in the setting of HF, the effect of renal denervation in humans is still unclear. The Renal Artery Denervation in Chronic Heart Failure (REACH-Pilot) study on seven patients reported symptomatic improvement and significant increase in the 6-minute walk distance at 6 months.[22] Larger studies are now under way to assess the safety and efficacy of renal denervation in HF.

Nonrenal Salt and Water Removal

Nonrenal methods for salt and water removal have been proposed because they avoid TGF-mediated neurohumoral pathway activation and are effective in patients whose condition is refractory to pharmaceutical treatment. However, establishing their benefits and determining their optimal use (Box 72.2) have been controversial.

Paracentesis

In a subset of patients, intraabdominal hypertension may cause renal venous hypertension and kidney congestion. In five patients, removal of approximately 3 liters of ascites decreased intraabdominal pressure and improved GFR.[23] However, repeated paracentesis causes significant protein losses, often the need for albumin repletion, and the possibility of subsequent fluid leakage and/or infection. Nevertheless, this approach warrants further investigation, especially in low-resource settings.

Peritoneal Dialysis

Compared with more complex peritoneal dialysis (PD) exchange prescriptions for end-stage renal disease, simplified regimens can be used for fluid removal in HF (one to three exchanges per day or thrice-weekly intermittent 12-hour treatments).[24] Use of PD has restored diuretic responsiveness, reduced body weight, resulted in better echocardiographic or other objective cardiac hemodynamic parameters, improved HF biomarkers (e.g., brain natriuretic peptide and aldosterone), improved New York Heart Association (NYHA) class, increased 6-minute walk capacity, provided a bridge to cardiac transplantation, decreased hospitalization days, and improved quality of life.[25]

In a systematic review that included 21 studies and 673 patients with refractory congestive HF, after initiation of PD therapy, hospitalization days declined (6.30 vs. 1.22 days/year) and cardiac function improved significantly (both left ventricular ejection fraction and NYHA classification).[26] PD was also associated with a marked reduction in body weight (73.4 vs. 69.7 kg). The mean peritonitis rate was 14.5% per year, and the mean mortality rate was 20.3% per year. PD also might help control HF-induced ascites (thereby lowering the risk for spontaneous bacterial peritonitis and intraabdominal hypertension). However, most reports on use of peritoneal dialysis (PD)-based UF to treat HF are from small series,[27] and outcomes are confounded by baseline severity of kidney dysfunction and use of hemofiltration.

BOX 72.2 Stepwise Treatment Approach for Symptomatic Heart Failure and Cardiorenal Syndrome

Step 1

1. Compliance: Optimize adherence to medication regimen and salt restriction.
2. Electromechanical: Evaluate and treat arrhythmias and dyssynchrony
3. Anatomic, with imaging (cardiac catheterization, echocardiogram) as appropriate for:
   a. Ischemic: Angioplasty, stents, or surgery when appropriate for coronary artery stenoses
   b. Other remediable disorders, such as valvular heart disease, pericardial effusions, and constrictive pericarditis
4. Anemia control, after CKD guidelines (see Chapter 83)
5. Pharmacologic, with dose reductions for hypotension:
   a. ACE inhibitors, ARBs, or neprilysin inhibitor/ARB combination
   b. β-Blocker therapy
   c. Mineralocorticoid receptor antagonists
   d. Diuretics if volume overloaded, congestion, symptoms are present
   e. Other agents: Afterload-reducing medications (e.g., hydralazine) and digoxin

Step 2: For Worsened Renal Function, Ineffective Diuresis, Persistent Heart Failure

1. Begin stepped approach to escalate pharmacologic treatment, preferably algorithm-based. Focus on dose adjustments to avoid hypotension and further renal impairment.
2. Reevaluate for concurrent renal disease (i.e., renocardiac syndrome).
   a. Consider primary nephrologic disorders (e.g., parenchymal, obstruction)
   b. Consider evaluation for unilateral or bilateral renal artery stenosis
   c. If necessary, paracentesis or other specific therapies to reduce intraabdominal hypertension, relieve renal venous hypertension and renal congestion

Step 3: For Persistent Hypotension, Renal Dysfunction, and Acute Decompensated Heart Failure

1. Reassess to further optimize pharmacologic care with diuretics and inotropes.
2. Consider ultrafiltration but acknowledge risks for renal deterioration and catheter-related and/or anticoagulation-related complications.
3. Begin cautious extracorporeal ultrafiltration, especially if patient's condition is refractory to pressors:
   a. Intermittent slow ultrafiltration, when hypotension does not preclude adequate fluid removal over typically 4- to 6-hour sessions
   b. Continuous ultrafiltration, when equipment is available and patient becomes hypotensive or has worsening renal function with intermittent treatment sessions

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CKD,* chronic kidney disease.

As with any rapid use of newly placed PD catheters, patients with acute HF have increased risk for early fluid leaks and peritoneal infection. In addition, PD-induced electrolyte disturbances (e.g., hypokalemia or hypomagnesemia) may worsen rhythm control if not monitored and addressed appropriately. Because approximately half of PD ultrafiltration occurs through aquaporins, PD removes less sodium for a given ultrafiltration volume than hemofiltration. Large peritoneal fluid volumes also can potentially compromise respiration, which can be avoided by more frequent lower volume exchanges via automated cyclers.

Overall the studies suggest that chronic PD in HF has an acceptably low rate of complications and is well tolerated (i.e., the morbidity of HF has not been substituted with morbidity from PD), but no beneficial effect on mortality has been shown.[24] In practice, PD for HF is most commonly advocated as a chronic treatment, with pharmaceutical and extracorporeal methods used as initial strategies for acute decompensation.

Conventional Hemodialysis or Hemofiltration

There is extensive experience with intermittent hemodialysis techniques for fluid removal in HF, using temporary or tunneled dual-lumen catheters (see Chapter 91). Arteriovenous fistulas or grafts are often precluded because their high flow rates may further compromise cardiac function. Technical approaches include isolated UF (see Chapter 93) or traditional dialysis techniques when electrolyte disorders are already present. Many patients with unstable HF will not tolerate removal of 2 or more liters during typical 2- to 4-hour treatment times. Dialysis-related hypotension will prevent further fluid removal and can induce acute kidney injury (AKI), potentially making the patient dialysis-dependent. The key to hemodynamic stability may be to dramatically slow the UF rate (see later) using longer or continuous treatment modalities (e.g., slow extended-duration isolated UF, continuous venovenous hemofiltration). However, the literature lacks reports on larger groups of patients treated with such techniques, homogenous patient populations, appropriate control groups, well-defined outcome measures, and strict treatment protocols.

Setting the Rate of Fluid Removal

The key concept is to avoid intravascular fluid depletion by ensuring the UF rate does not exceed the rate at which the vascular plasma compartment is being refilled from interstitial spaces. The plasma refill rate can vary over the course of fluid removal because it is dependent on Starling forces (generated by the plasma oncotic pressure and the gradient between interstitial and vascular hydrostatic pressures) and the permeability of vascular basement membranes. If the UF rate exceeds the plasma refill rate, hemoconcentration, hypovolemia, hypotension, and decreased renal perfusion and function develop. Equipment that optically monitors hemoconcentration or bioimpedance vector analysis can be used to guide UF in patients with refractory HF, although the optimal way to use these technologies has yet to be elucidated.

Effect of Extracorporeal Ultrafiltration on the Pathophysiology of Heart Failure

In a report of 24 patients with refractory HF, removal of up to 4 liters of fluid in a few hours[28] did not affect plasma volume—that is, UF matched the plasma refill rate. Even at 24 hours after the procedure the patients had reduced right atrial, pulmonary artery, and wedge pressures; increased stroke volume; stable heart rates and systemic vascular resistance; and improved responsiveness to diuretics. Despite intravascular volume contraction, UF could decrease levels of norepinephrine, aldosterone, and renin in HF patients.[29] In contrast to diuretics alone, UF reduced systemic levels of inflammatory cytokines and perhaps improved exercise capacity and pulmonary function. Finally, the isotonic fluid removal with UF would be expected to remove more sodium than the hypotonic losses associated with diuretics.

Effect of Extracorporeal Ultrafiltration on Renal Function

It has been proposed that the benefits of UF for renal function occur predominantly in patients with low urine output (<1 l/day), in whom UF reverses the RAAS and SNS activation, thereby improving renal perfusion and GFR and restoring sensitivity to diuretics.[30] In contrast, in HF patients with a mean baseline GFR of 48 ml/min and preserved diuretic sensitivity, there were no significant differences in the kidney parameters before or after 2 days of either UF or intravenous diuretic therapy.[31] Although there are encouraging (but not unanimous) reports of renal function improving after UF, clinicians should target fluid removal rates that avoid a significant fall in GFR or worsen renal hemodynamics.[32,33]

Recent Advances in Extracorporeal Techniques

The barriers of extended treatment times and the need for one-to-one supervision by nurses have been overcome with commercially available modern devices dedicated to isolated UF. These devices have small extracorporeal blood volumes (<100 ml), allow blood flow rates low enough (<50 ml/min) to permit use of temporary peripheral or central venous catheters, and have preassembled tubing for one-step loading, computerized simple user interfaces with embedded help screens, remote monitoring capabilities, and miniaturization for portability. Treatment times range from 6 h/day to continuous treatment over multiple days. A feasibility study[34] demonstrated that 16- to 18-gauge catheters could deliver blood at up to 40 ml/min, resulting in up to 3.7 liters of UF over approximately 7 hours. In another study[35] of 20 patients with decompensated HF and serum creatinine levels of at least 1.5 mg/dl (132 μmol/l) and/or diuretic resistance, more than 8 liters of fluid was removed. Patients were discharged earlier without changes in GFR and had improved HF scores; some had resolution of hyponatremia and fewer readmissions. In the Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial on 40 patients, UF did not significantly affect weight loss but did improve fluid removal and symptoms compared with usual care.[36] However, two subsequent large prospective studies did not demonstrate these benefits.

In the UNLOAD trial (Ultrafiltration Versus Intravenous Loop Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure), 200 HF patients were randomized to early UF or intravenous diuretics and followed for 90 days.[32] The UF achieved by the study was 241 ml/h for 12.3 ± 12 hours, which led to a weight reduction of 5.0 ± 3.1 kg over the 2 days, approximately 2 kg more than those in the diuretic group. Although dyspnea was improved in those undergoing UF at 8 hours, there was no difference in dyspnea or renal outcomes at 48 hours. At 90 days the UF group had fewer total rehospitalizations, rehospitalization days, and unscheduled office and emergency department visits, but the study was not powered to allow conclusions on these clinical end-points. Potential weaknesses of the study design included sponsorship by the manufacturer, submaximal medical therapy in the diuretic group, and uncertainties regarding posthospitalization care and readmission. In the CARRESS-HF[37] (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial, 188 patients with cardiorenal syndrome were compared at 96 hours after randomization to a protocol of stepped drug therapy (sequential use of diuretics, intravenous inotropes, nesiritide, and nitroglycerin) or extracorporeal UF at a fixed rate of 200 ml/h. UF did not improve weight loss, dyspnea, well-being scale scores, or diuretic dose, and the UF group (but not the pharmacologic group) experienced a decline in GFR. At 60 days there were no differences in mortality, emergency visits, or rehospitalizations between groups. It remains unclear whether these disappointing findings for UF can be extrapolated to all such patients and methodologies; CARRESS-HF enrolled only patients with HF-related AKI, and most UF was accomplished early in the protocol, with a mean duration of only 40 hours compared with the pharmacologic care over 96 hours. Thus it remains possible that alternative protocols with slower or more prolonged UF might have demonstrated more benefit. Furthermore, a large proportion of patients in the UF group (10%) did not receive the randomized treatment for various reasons, and 30% in this group also received intravenous diuretics after UF had ceased.

The AVOID-HF[38] (Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure) trial was initially designed to include 810 hospitalized patients with acute HF but, because of slow recruitment, was terminated after just 224 patients had been enrolled. Similar to UNLOAD, the AVOID-HF trial compared early flexible UF therapy to a pharmacologic treatment that was similar to the algorithm used in CARRESS-HF. The net fluid loss was again found to be greater in the UF group than the diuretics (12.9 vs. 8.9 liters) without any adverse impact on renal function. The patients in the UF arm showed a nonsignificant trend toward better outcomes such as higher estimated number of days to first HF event.

A meta-analysis[39] that pooled results from seven randomized controlled trials (771 patients) concluded that UF therapy is associated with more efficient fluid removal and more pronounced reduction in patient weight compared with medical therapy and might also have a salutary effect on reducing the rate of rehospitalization for HF. This efficacious decongestion does not seem to be at the cost of increasing the incidence of renal dysfunction or mortality. However, given the limitations of prior trials, important questions remain about the potential benefits of UF in acute HF and further studies are needed. Based on the currently available data, use of ultrafiltration can be recommended in patients with severe fluid overload and suboptimal response to medical therapy, especially if they have a history of frequent hospital admissions for heart failure.

Safety and Risks of Extracorporeal Therapies

In CARRESS-HF,[37] UF-related complications included catheter exit-site hemorrhage and systemic infection. Similarly, a higher number of patients in the UF arm of AVOID-HF experienced "serious adverse events deemed to be related to the study therapy" (e.g., gastrointestinal bleeding and hematuria) compared with the diuretic arm. More patients in that group also experienced an "adverse event of special interest" such as symptomatic hypotension necessitating intervention, central line–associated bloodstream infection, and bleeding requiring transfusion. However, in the UNLOAD trial,[32] UF therapy proved very safe. The machines dedicated to isolated UF have an added margin of safety conferred by low rates of filtration and blood flow, as well as more robust automated monitoring software. Nevertheless, all complications that can occur in hemodialysis therapies are of course also relevant for HF patients receiving isolated UF (see Chapter 96).

SUMMARY

Despite long-standing evidence concerning the pathophysiology of fluid overload in HF and adverse neurohumoral effects from diuretics, it has been difficult to reach a consensus on the benefits or techniques of UF or diuretic therapy. PD appears to have a role in chronic HF care, especially for individuals whose management is complicated by CKD. For acutely decompensated HF, recent evidence suggests that protocolized stepped pharmacologic care can be efficacious and safer than rapid UF; however, it remains to be determined whether there can be benefits from alternative extracorporeal protocols.

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SELF-ASSESSMENT QUESTIONS

1. What is the main contributing mechanism for the development of renal failure in acute heart failure (HF)?
   A. Decreased renal blood flow
   B. Increased central and renal venous pressure
   C. A and B
   D. Increased renin-angiotensin-aldosterone system (RAAS) activation
2. The established therapy in patients with acute decompensated HF and renal dysfunction is:
   A. Ultrafiltration
   B. High-dose intravenous and continuous diuretic therapy
   C. Low-dose intravenous bolus therapy
   D. No established therapy for these patients has been shown to improve outcome.
3. In the management of HF:
   A. Ultrafiltration by peritoneal dialysis is most efficacious when used for acute HF.
   B. Compared with pharmacologic care in acute HF, extracorporeal ultrafiltration has reduced mortality.
   C. Vasopressin antagonists reduce HF mortality and morbidity.
   D. Hemoconcentration is an indicator of plasma refill during ultrafiltration.
4. What is the next step in pharmacologic therapy for a 65-year-old man who has a history of HF with reduced ejection fraction who is already receiving an angiotensin-converting enzyme (ACE) inhibitor, β-blocker, and mineralocorticoid receptor antagonist, is in sinus rhythm, and has an estimated glomerular filtration rate greater than 30 ml/min/1.73 m^2?
   A. Add digoxin
   B. Add angiotensin II receptor blocker therapy
   C. Replace ACE-inhibitor with sacubitril/valsartan
   D. Replace β-blocker with ivabradine

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Hepatorenal Syndrome

Javier Fernández, Vicente Arroyo

DEFINITION

Hepatorenal syndrome (HRS) is a potentially reversible functional renal failure that occurs in patients with acute or chronic liver disease, advanced hepatic failure, and portal hypertension. Although it may occur in patients with subacute liver failure or severe acute alcoholic hepatitis, it is mainly observed in patients with advanced cirrhosis. HRS is characterized by impaired renal function and marked abnormalities in the arterial circulation and endogenous vasoactive systems. In the kidney, there is pronounced vasoconstriction resulting in low glomerular filtration rate (GFR). In the splanchnic circulation, there is marked arteriolar vasodilation resulting in reduction of systemic vascular resistance and arterial hypotension.[1-3] Along with cardiocirculatory dysfunction secondary to portal hypertension, systemic inflammation also seems to play a major role in the pathogenesis of HRS.[4] Two forms of HRS can be identified on the basis of the progression of the disease (Box 73.1). The acute form (type 1 HRS) is characterized by an acute and rapid deterioration in renal function that occurs in the setting of multiorgan failure (acute-on-chronic liver failure [ACLF]), whereas the chronic form (type 2) has an insidious onset and is characterized by moderate renal failure that follows a steady or slowly progressive course.[1-3]

PSEUDOHEPATORENAL SYNDROME

Pseudohepatorenal syndrome describes concurrent hepatic and renal dysfunction secondary to a wide variety of infectious, systemic, circulatory, genetic, and other diseases and after exposure to a variety of drugs and toxins (Table 73.1).[5] These entities must be excluded before the diagnosis of HRS can be established. In these conditions, the liver does not play a causative role in the pathogenesis of renal failure. Pseudohepatorenal syndrome is usually easy to exclude because the causative agent is frequently known and both renal and liver functional abnormalities are often found at first clinical presentation, when there is no evidence of advanced liver failure and portal hypertension. In contrast, HRS invariably occurs after liver failure and portal hypertension are fully established and frequently develops when the patient is undergoing treatment for these conditions or their complications.

PATHOPHYSIOLOGY AND PATHOGENESIS

Circulatory Dysfunction: Renal and Systemic Hemodynamic Changes

In HRS, reduction in GFR occurs mainly because of renal cortical hypoperfusion after intense cortical renal vasoconstriction, which can be demonstrated angiographically as marked beading and tortuosity of the interlobular and proximal arcuate arteries and the absence of a distinct cortical nephrogram and vascular filling of the cortical vessels (Fig. 73.1). Intense renal vasoconstriction is the final consequence of marked systemic circulatory dysfunction, characterized by progressive splanchnic arterial vasodilation, reduction of the effective arterial blood volume, hypotension, and homeostatic activation of the vasoconstrictor systems.[3] This further compromises renal perfusion because intense renal vasoconstriction results in blunting of the autoregulation of renal blood flow, so that renal perfusion becomes more pressure dependent. In HRS, filtration fraction is also reduced, reflecting a dominant increase in afferent arteriolar tone and a decrease in the ultrafiltration coefficient. Serial systemic hemodynamic studies showed that HRS occurs in the setting of reduced mean arterial pressure (MAP), cardiac output, and wedge pulmonary pressure without change in systemic vascular resistance. These findings suggest that an inability to increase cardiac output to compensate for a decrease in preload (secondary to the accentuation of splanchnic arterial vasodilation) also contributes to the pathogenesis of HRS.[6] Vasoconstriction is not confined to the renal vascular bed. In HRS it is also observed in other extrasplanchnic territories, including the liver, brain, muscle, and skin.[2,3]

Neurohumoral Abnormalities

The renal and systemic hemodynamic changes that characterize HRS are a direct consequence of neurohumoral disturbances.[2,3] Activation of the vasoconstrictor systems (the renin-angiotensin-aldosterone system [RAAS], the sympathetic nervous system [SNS], and vasopressin) is the cause of renal vasoconstriction; meanwhile, activation of the vasodilator systems occurs mainly in the splanchnic circulation and leads to splanchnic vasodilation. Increases in the serum and urinary levels of vasoconstrictors and in the plasma level of vasodilators are observed in patients with HRS. The vasoconstrictors include renin, norepinephrine, neuropeptide Y, arginine vasopressin, endothelin and F_2 isoprostanes, and urinary cysteinyl leukotrienes; the vasodilators include plasma endotoxin, nitrite and nitrate (end-product of nitric oxide [NO] metabolism), and glucagon. The sympathetic discharges through the renal nerves are also markedly increased.

In contrast to increased plasma and urinary levels of vasoconstrictors and plasma level of vasodilators, decreased urinary levels of vasodilators have been observed in HRS. These include prostaglandin E_2, 6-keto-prostaglandin F_1 (a stable metabolite of renal prostacyclin), and kallikrein. Because the urinary level of these vasodilators is normal in compensated cirrhosis and higher than normal in decompensated cirrhosis with ascites and normal renal function, it is postulated that a reduction in the renal synthesis of renal vasodilators is the final event that leads to the development of HRS.[3]

BOX 73.1 Main Clinical Characteristics of Type 1 and Type 2 Hepatorenal Syndrome

Type 1 HRS

- Acute and rapid deterioration in renal function (serum creatinine rise ≥ 2.5 mg/dl or 220 μmol/l in <2 weeks)
- Occurs in parallel with the failure of other organs or systems (e.g., coagulopathy, hepatic encephalopathy)
- In cirrhosis, is a form of acute-on-chronic liver failure
- Frequently follows a precipitating event, mainly bacterial infection
- Rapidly fatal without treatment: Mean survival 2 to 3 weeks

Type 2 HRS

- Moderate stable renal impairment (average serum creatinine 2 mg/dl [176 μmol/l])
- Mainly causes refractory ascites
- Mean survival without treatment: 6 months

HRS, hepatorenal syndrome.

TABLE 73.1 Causes of Pseudohepatorenal Syndrome

Potential Causes	Predominantly Tubulointerstitial Involvement	Predominantly Glomerular Involvement
Infections	Sepsis, leptospirosis, brucellosis, tuberculosis, Epstein-Barr virus, hepatitis A virus	Hepatitis B and C viruses, HIV infection, *Schistosoma mansoni*, liver abscess
Drugs	Tetracycline, rifampin, sulfonamide, phenytoin, allopurinol, fluroxene, methotrexate (high dose), acetaminophen overdose	
Toxins	Carbon tetrachloride, trichloroethylene, chloroform, elemental phosphorus, arsenic, copper, chromium, barium, amatoxins,* raw carp bile toxins†	
Systemic diseases	Sarcoidosis, Sjögren syndrome	Systemic lupus erythematosus, vasculitis, cryoglobulinemia, amyloidosis
Circulatory failure	Hypovolemic or cardiogenic shock	
Malignancy	Lymphoma, leukemia	
Congenital and genetic disorders	Polycystic liver and kidney disease, nephronophthisis, congenital hepatic fibrosis	
Miscellaneous	Fatty liver of pregnancy, Reye syndrome	Eclampsia, HELLP syndrome,‡ cirrhotic glomerulopathy

Data from reference 12.

*Accidental poisoning after ingestion of mushrooms of the *Amanita* genus.

†Accidental poisoning after ingestion of the raw gallbladder or bile of the grass carp (a common practice in rural East Asia).

‡Hemolysis, elevated liver enzymes, low platelet count.

Most of these neurohumoral abnormalities found in HRS are also detected, albeit to a lesser extent, in decompensated cirrhosis (with ascites) with normal renal function and in compensated cirrhosis (without ascites). These findings support the hypothesis that HRS most likely represents one end of the spectrum of homeostatic abnormalities that occur in liver failure and portal hypertension.

Systemic Inflammation

HRS is often precipitated by bacterial infections, particularly when they trigger a severe inflammatory response.[3] This feature suggests that inflammation may represent an important pathogenic factor for HRS. There is now evidence that type 1 HRS is part of a complex syndrome (ACLF) characterized by multiorgan and/or system failure (kidneys, liver, brain, heart, peripheral circulation, gut, lungs, adrenal glands, defensive mechanisms against infections).[4,7] The mechanism of ACLF has been related to a systemic inflammatory response syndrome, activation of cytokines, NO, and other mediators, acute deterioration of systemic circulation, and organ failure. Systemic inflammation in cirrhosis mainly derives from the translocation of viable bacteria and/or pathogen-associated molecular patterns from the intestinal lumen into the intestinal mucosa and the systemic circulation with or without overt bacterial infection. The subsequent sustained activation of innate host immunity leads to the release of proinflammatory cytokines and oxidative stress that impair cardiovascular function and could also damage the kidney and other organs, impairing their function.[4]

Summary of Pathogenetic Events

Fig. 73.2 shows the pathogenesis of HRS. Liver failure and portal hypertension through pathologic bacterial translocation and endotoxemia increase systemic inflammation and vascular production of vasodilators, including NO, carbon monoxide, and glucagon in the splanchnic circulation, leading to the initiating event of splanchnic arteriolar vasodilation (the peripheral arterial vasodilation hypothesis). Splanchnic vasodilation leads to a decrease in systemic vascular resistance, but MAP is initially maintained by an increase in cardiac output, resulting in a hyperdynamic circulation. Splanchnic vasodilation also decreases arterial filling and reduces the effective arterial blood volume. The subsequent stimulation of the central volume baroreceptors leads to compensatory activation of the vasoconstrictor systems, in particular the arginine vasopressin system, RAAS, and SNS (including its hormones norepinephrine and neuropeptide Y), which help restore effective arterial blood volume. This restoration is achieved in patients with compensated cirrhosis but not in patients with decompensated cirrhosis, in whom progressive splanchnic arteriolar vasodilation leads to increased splanchnic capillary pressure, resulting in an increase in lymph formation that exceeds reabsorption capacity. In parallel, further contraction of the effective arterial blood volume leads to reduction of systemic MAP and further stimulation of the vasoconstrictor systems, resulting in sodium and water retention. The net result of these combined effects is continuous ascites formation (the forward theory of ascites formation).[2,3]

The splanchnic circulation is resistant to the effects of vasoconstrictors because of local release of vasodilators; progressive splanchnic vasodilation continues to occur as liver failure and portal hypertension progress. This leads to continued contraction of effective arterial blood volume, which, together with the progressive inability of the cirrhotic heart to respond to reduced preload, results in further reduction of MAP and more intense stimulation of the vasoconstrictor systems. Normally, the effect of vasoconstrictors on the renal circulation is counterbalanced by the reactive production of intrarenal vasodilators. It is

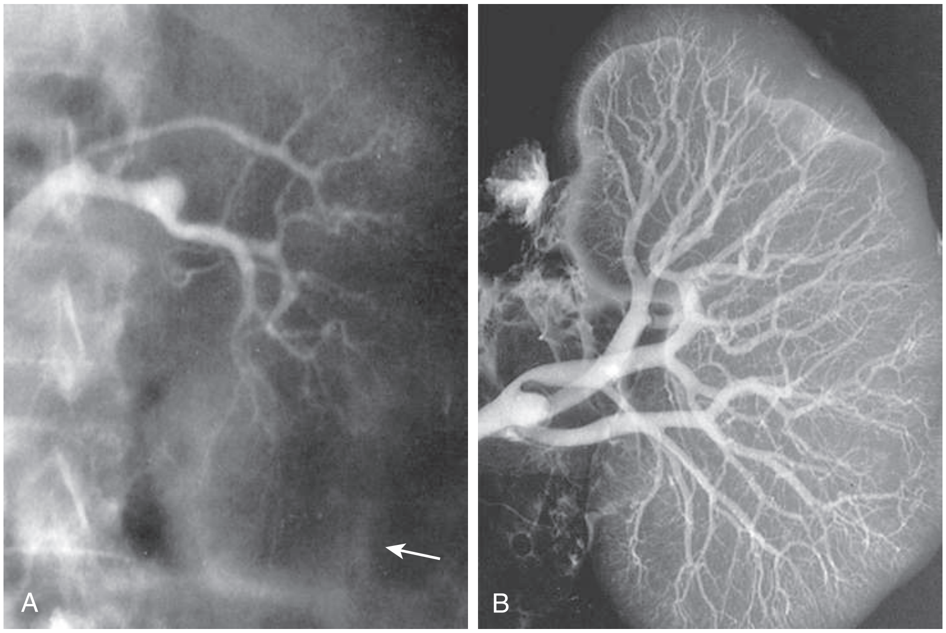

Fig. 73.1 **Renal arteriography of a patient with hepatorenal syndrome (HRS).** (A) Renal angiogram (the *arrow* marks the edge of the kidney). (B) The angiogram carried out in the same kidney at autopsy. Note complete filling of the renal arterial system throughout the vascular bed to the periphery of the cortex. The vascular attenuation and tortuosity seen previously (A) are no longer present. The vessels are also histologically normal. This indicates the functional nature of the vascular abnormality in HRS.[5]

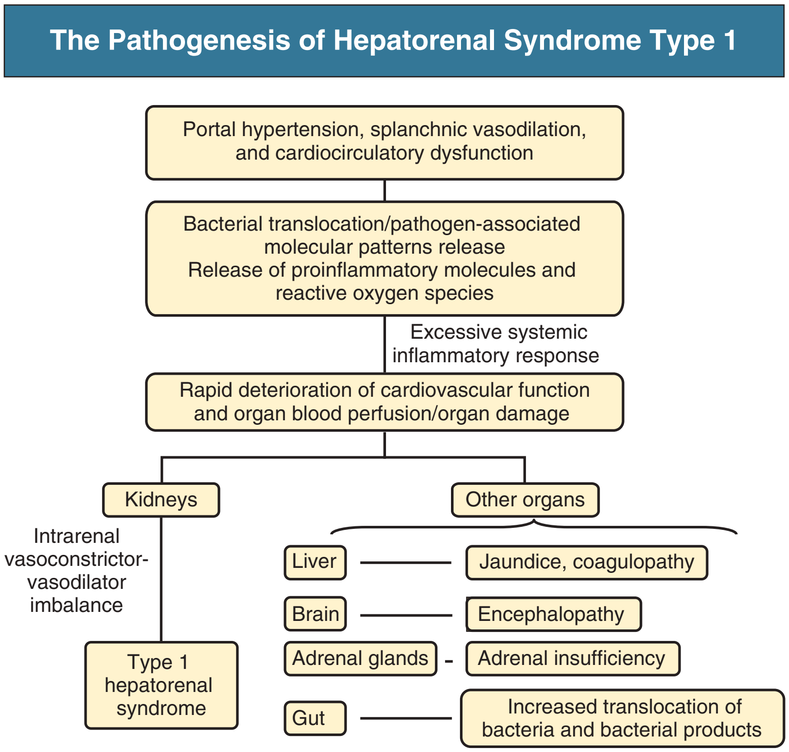
The Pathogenesis of Hepatorenal Syndrome Type 1
Portal hypertension, splanchnic vasodilation, and cardiocirculatory dysfunction
Bacterial translocation/pathogen-associated molecular patterns release
Release of proinflammatory molecules and reactive oxygen species
Excessive systemic inflammatory response
Rapid deterioration of cardiovascular function and organ blood perfusion/organ damage
Kidneys
Other organs
Intrarenal vasoconstrictor-vasodilator imbalance
Type 1 hepatorenal syndrome
Liver
Jaundice, coagulopathy
Brain
Encephalopathy
Adrenal glands
Adrenal insufficiency
Gut
Increased translocation of bacteria and bacterial products

Fig. 73.2 **The pathogenesis of hepatorenal syndrome *(HRS).*** Mechanisms leading to type 1 HRS and multiorgan failure. Patients with cirrhosis and ascites present a severe cardiocirculatory dysfunction that may be further aggravated by infection. Although circulatory dysfunction predominantly affects the kidneys and leads to the development of type 1 HRS, it also decreases the perfusion of other organs and systems such as the liver, with marked impairment in hepatic function and aggravation of portal hypertension; the brain, with the development of hepatic encephalopathy; the adrenal glands, with the development of relative adrenal dysfunction; and the gut, decreasing intestinal motility and promoting intestinal bacterial overgrowth and bacterial translocation.[2,3]

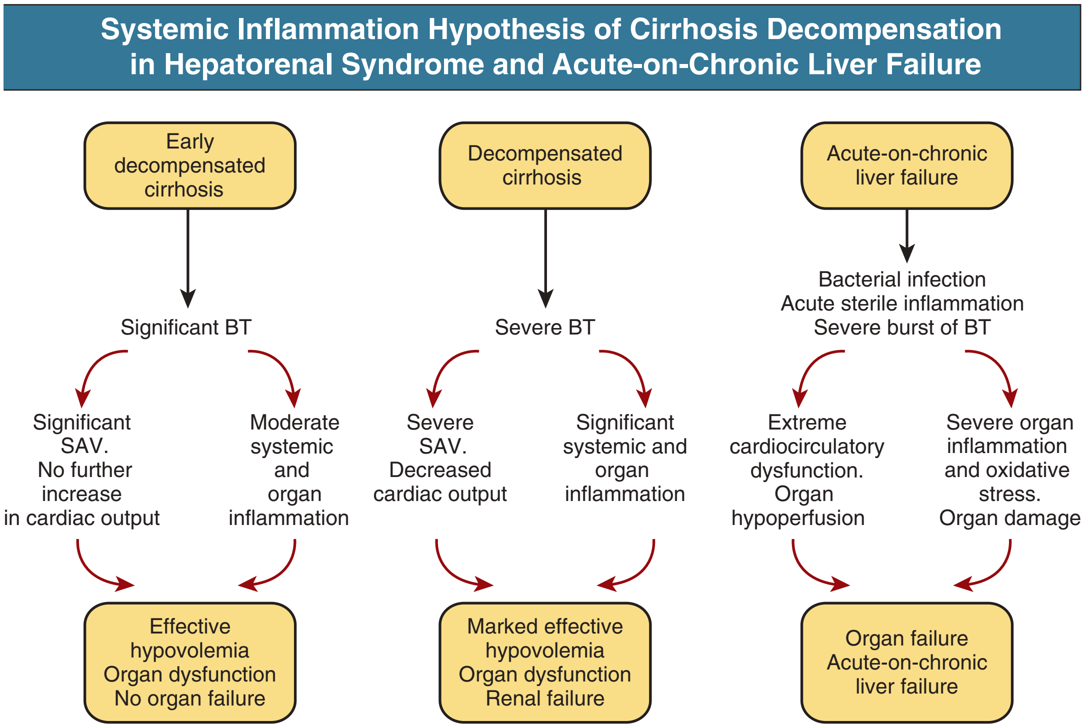
Systemic Inflammation Hypothesis of Cirrhosis Decompensation in Hepatorenal Syndrome and Acute-on-Chronic Liver Failure
Early decompensated cirrhosis
Decompensated cirrhosis
Acute-on-chronic liver failure
Significant BT
Severe BT
Bacterial infection
Acute sterile inflammation
Severe burst of BT
Significant SAV. No further increase in cardiac output
Moderate systemic and organ inflammation
Severe SAV. Decreased cardiac output
Significant systemic and organ inflammation
Extreme cardiocirculatory dysfunction. Organ hypoperfusion
Severe organ inflammation and oxidative stress. Organ damage
Effective hypovolemia
Organ dysfunction
No organ failure
Marked effective hypovolemia
Organ dysfunction
Renal failure
Organ failure
Acute-on-chronic liver failure

Fig. 73.3 Systemic inflammation hypothesis of cirrhosis decompensation in hepatorenal syndrome and acute-on-chronic liver failure *(ACLF)*. According to the systemic inflammation hypothesis, bacterial translocation *(BT)* progressively affects the natural course of cirrhosis, from the compensated stage to hepatorenal syndrome and ACLF. An abrupt increase in systemic inflammation represents the pathophysiologic background for ACLF.[4] *SAV*, splanchnic arterial vasodilation.

postulated that HRS develops when the balance of activities between the renal vasoconstrictors and intrarenal vasodilators finally breaks down. The likelihood that this will occur increases with progressive or acute deterioration in liver function or increasing severity of portal hypertension (e.g., after acute alcoholic hepatitis) and is precipitated by events that lead to further volume contraction and reduction of the effective arterial blood volume (e.g., spontaneous bacterial peritonitis [SBP]; see later discussion).

Recently the peripheral arterial vasodilation hypothesis has been revisited. This hypothesis does not consider that patients with advanced cirrhosis frequently develop multiorgan failure (ACLF), a syndrome characterized by systemic inflammation and high short-term mortality.[4,7] The sustained activation of the innate immune system caused by an abnormal translocation of bacteria and bacterial products from the intestinal lumen (pathogen-associated molecular patterns) would lead to the persistent activation of the innate pattern recognition receptors and subsequent chronic inflammation. This inflammatory process would have two major consequences: first, splanchnic arterial vasodilation secondary to local release of endogenous vasodilators, a feature impairing systemic hemodynamics and organ perfusion, and second, the extension of splanchnic inflammation to the peripheral blood and organs, a feature that could damage these organs, contributing to multiple organ failure (Fig. 73.3).[4]

EPIDEMIOLOGY

The incidence of HRS in the cirrhotic patient is estimated to be 18% at 1 year and 39% at 5 years.[8] Neither the cause nor the Child-Pugh score or the model for end-stage liver disease (MELD) score (www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality/) predicts the incidence of HRS. Rather, independent predictors of HRS include dilutional hyponatremia, impairment in systemic hemodynamics (high plasma renin activity, noradrenaline concentration, and low cardiac output),[6,8] and abnormal renal duplex Doppler ultrasound study findings (resistive index >0.7),[9] and low GFR.[3]

CLINICAL MANIFESTATIONS

Type 1 and type 2 HRS are considered to be different syndromes rather than different expressions of a common underlying disorder.[2,3] Type 1 HRS is characterized by a rapid decline in renal function (see Box 73.1) and is observed in patients with acute decompensation of advanced cirrhosis, severe acute alcoholic hepatitis, or subacute liver failure. In addition to developing rapidly progressive acute kidney injury (AKI), patients also develop multiorgan dysfunction, including severe hepatic failure (jaundice, coagulopathy), brain failure (hepatic encephalopathy), and frequently relative adrenal insufficiency. Hyponatremia is almost always present, and arterial blood pressure is usually low. Type 1 HRS may be precipitated by bacterial infections (especially spontaneous bacterial peritonitis), severe gastrointestinal bleeding, or total paracentesis without albumin administration. Left untreated, type 1 HRS tends to run a rapid and progressive downhill course, resulting in death of the patient within 2 to 3 weeks.[8]

Type 2 HRS is characterized by insidious onset and slowly progressive deterioration of renal function. This is most often observed in patients with cirrhosis and portal hypertension. These patients tend to be less severely jaundiced and mainly present with refractory ascites caused by poor response to diuretics. Low-normal arterial blood pressure, modest prolongation of prothrombin time, and moderate or marked hypoalbuminemia and hyponatremia are usually present. Type 2 HRS tends to run a slowly progressive downhill course over months, which most likely reflects the natural course of the disease because additional precipitating factors are not usually identified.[2,3,8] Mean survival time after onset of type 2 HRS is 6 months.

PATHOLOGY

HRS is a functional renal disorder, and the presence of significant glomerular and/or tubular disease excludes the diagnosis. However, glomerular abnormalities, including mesangial expansion, capillary wall thickening, mesangial and capillary wall electron-dense deposits, and immune deposits of C3 and immunoglobulin A (IgA), IgM, and IgG, are frequently found in cirrhotic patients with normal renal function and minimal urinary abnormalities. The presence of such glomerular abnormalities in a cirrhotic patient, therefore, does not exclude the diagnosis of HRS. Protrusion of the proximal tubular epithelium into the Bowman space (glomerulotubular reflux) is not specific for HRS and is found in other conditions associated with profound renal ischemia and terminal hypotension. Although early autopsy studies demonstrated normal tubular morphology in patients who had died of HRS, detailed light and electron microscopic studies have documented proximal tubular lesions consistent with ischemic injury. However, these lesions do not explain the low GFR in HRS patients.[3]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of HRS is mainly one of exclusion and should be suspected in any patient with subacute or chronic liver disease with advanced liver failure and portal hypertension who develops progressive renal impairment. In patients with preexisting liver failure, portal hypertension, and renal failure, the use of nephrotoxic agents (e.g., nonsteroidal antiinflammatory drugs [NSAIDs] and aminoglycosides) must be stopped, and other conditions leading to renal failure must be excluded by careful history, physical examination, urine examination, and ultrasound study before the diagnosis of HRS can be considered. The absence of shock or gastrointestinal bleeding and excess gastrointestinal, peritoneal, or renal fluid loss also must be documented. Prerenal AKI must be excluded by withdrawal of diuretics and fluid challenge either with 1.5 liters of normal saline or preferably with albumin 1 g/kg body weight per day up to the maximum of 100 g/day for 2 days. Absence of microhematuria and proteinuria of less than 500 mg/day helps exclude significant coexisting glomerular or tubulointerstitial disease leading to renal failure and support the diagnosis of HRS.

The diagnostic criteria for HRS were established by the International Ascites Club in 1996[1] and were revised in 2007.[10] The main changes in the more recent criteria include the exclusion of creatinine clearance as a measure of renal function because of the difficulty in obtaining accurate urine collection data, the removal of ongoing bacterial infection as an exclusion criterion so that treatment of HRS is not delayed in these patients, the substitution of saline with albumin as the preferred fluid for plasma volume expansion, and the removal of the minor criteria. Another relevant change in the diagnostic criteria for HRS is the removal of a fixed cut-off value of serum creatinine (>1.5 mg/dl [132 µmol/l], >2.5 mg/dl [220 µmol/l] in cases of type 1 HRS). The remaining criteria are maintained (Box 73.2).[11] Consequently, patients with initial AKI stage 2 or 3 or with progression of the initial stage of AKI despite appropriate medical therapy fulfilling all other diagnostic criteria of HRS can be treated with vasoconstrictors plus albumin, irrespective of the value of serum creatinine. The potential advantage of the new diagnostic algorithm is that it may allow earlier treatments of type-1 HRS, and possibly better outcomes.

Serum creatinine concentration and blood urea nitrogen (BUN) are poor markers of GFR in cirrhosis.[3] Patients with cirrhosis may have significant renal impairment despite normal serum creatinine or BUN concentration values because they are frequently malnourished, with reduced lean body mass, and often have a low urea generation rate because of liver failure and low protein intake. Severe hyperbilirubinemia, which is often present in patients with HRS, interferes with the Jaffe reaction (picric acid) for creatinine quantification and may cause falsely low results. Enzymatic creatinine assays are less susceptible to high bilirubin levels. In cases of uncertainty, GFR may be assessed with use of iodine-125–iothalamate or chromium-51–labeled ethylenediaminetetraacetic acid (^{51}Cr-labeled EDTA). Small studies suggest that serum cystatin C could be an accurate GFR marker in the cirrhotic population.[12] However, the utility of serum cystatin C for assessing GFR in cirrhosis needs to be confirmed.

BOX 73.2 Diagnostic Criteria Hepatorenal Syndrome According to the International Club of Ascites

- Cirrhosis with ascites
- Diagnosis of acute kidney injury (AKI) according to the ICA-AKI criteria
- No improvement in serum creatinine after at least 2 days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs (nonsteroidal antiinflammatory drugs, aminoglycosides, iodinated contrast media, etc.)
- Absence of structural kidney injury as indicated by proteinuria greater than 500 mg/day, microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasound findings.

From reference 11.
ICA, International Club of Ascites.

The most important differential diagnosis for renal failure in cirrhosis is between type 1 HRS and “true” AKI with tubular damage (acute tubular necrosis [ATN]) because they require rapid therapeutic decisions with different treatments. The parameters traditionally used to differentiate ATN from functional renal failure (urinary sodium excretion and urinary-plasma osmolality ratio) are of no value in patients with cirrhosis and ascites.[3] Granular casts may be found in the urinary sediment in both HRS and ATN. Recent data suggest that the determination of the neutrophil gelatinase–associated lipocalin (NGAL) level, a urinary biomarker of tubular damage, could be of help to differentiate these two entities.[13] However, further studies are needed to confirm this finding because these biomarkers also can be increased in prerenal acute injury[14] and HRS can progress to ATN.

NATURAL HISTORY

Without treatment, the median survival rate for type 1 HRS is about 2 weeks; that of type 2 HRS is about 4 to 6 months.[3,8] Patients with type 1 HRS usually die in the setting of multiple organ failure and are now considered to have ACLF, a syndrome recently redefined and characterized by the presence not only of organ failure(s) and high mortality rate but also of systemic inflammation.[7] Severe hepatic encephalopathy, gastrointestinal bleeding, and sepsis are common final events in these patients. Patients with type 2 HRS are at higher risk for type 1 HRS after the development of a precipitating event.[3]

PREVENTION AND TREATMENT

General Principles in the Prevention of AKI

In patients with cirrhosis and ascites, excessive diuretic therapy results in volume contraction and AKI. To avoid the latter, a stepwise approach to the treatment of ascites is recommended. All patients are advised to have bed rest and follow a low-sodium diet (60 to 90 mmol/day, equivalent to about 1.5 to 2 g of salt per day). After this, spironolactone is prescribed at increasing doses (100 mg/day as initial dose; if there is no response within 4 days, 200 mg/day). If required, furosemide is then added at increasing doses every 2 days of 40 to 80 mg/day. Maximum doses of spironolactone and furosemide are 400 and 160 mg/day, respectively. In patients with diuretic resistance, therapeutic paracentesis is indicated but must be combined with plasma volume expansion with use of albumin (8 g/l of ascites removed) to decrease the incidence of circulatory dysfunction after treatment and to prevent development of HRS. The use of renin-angiotensin system blockers as well as potentially nephrotoxic agents, including NSAIDs, aminoglycosides, and radiocontrast media, should be avoided as much as possible.[2,3] β-Blockers, used for primary or secondary prophylaxis of variceal bleeding, reduce MAP and GFR and must be used cautiously in patients with cirrhosis and ascites. Renal function should be closely monitored, especially in patients with refractory ascites. β-Blockers may increase short-term mortality in this specific cirrhotic subpopulation and should therefore be replaced by band ligation of varices.[15]

Preventive Measures

Accepting the hypothesis that HRS represents one end of the spectrum of the homeostatic abnormalities in liver failure and portal hypertension and that it is precipitated by clinical events as volume contraction or bacterial infection, it follows that a major focus of treatment must be to prevent such events and to treat them promptly when they occur. There should be a low threshold for antibiotic therapy for suspected infection in cirrhosis. Spontaneous bacterial peritonitis must be excluded by regular examination of ascites whenever a patient is admitted to the hospital or clinically deteriorates. This infection must be treated not only with broad-spectrum antibiotics but also with albumin infusion (1.5 g/kg at diagnosis and 1 g/kg at day 3) because the latter prevents the subsequent development of HRS and improves short-term survival.[16] Primary prophylaxis with norfloxacin has been shown to prevent SBP, delay the development of HRS, and improve survival in cirrhotic patients at high risk for complications (low ascitic protein level <15 g/l; advanced liver failure with Child-Pugh score ≥9 and serum bilirubin ≥3 mg/dl or impaired renal function with serum creatinine ≥1.2 mg/dl or serum sodium ≤130 mmol/l).[17] Norfloxacin is thought to exert its renoprotective effect by reducing the subclinical translocation of viable bacteria and bacterial products from the intestine, systemic inflammation, and NO generation, which in turn leads to improved hemodynamics. Prophylactic use of pentoxifylline 400 mg orally three times per day also prevents the development of HRS in patients with acute alcoholic hepatitis, probably by inhibiting the synthesis of tumor necrosis factor-α.[18]

General Approach to Treatment

In patients with preexisting liver failure, portal hypertension, and renal failure, nephrotoxic agents must be stopped. The absence of shock or gastrointestinal bleeding, as well as excess gastrointestinal, peritoneal, or renal fluid loss must be documented. Prerenal AKI must be excluded by withdrawal of diuretics and fluid challenge either with normal saline or preferably with albumin. Absence of microhematuria and proteinuria also should be confirmed.

Once HRS has been diagnosed, patients should be assessed for orthotopic liver transplantation (OLT). Suitable candidates should be placed on the waiting list for deceased donor or, if possible, living donor liver transplantation. Bridge treatments are also needed. Pharmacotherapy (see later), transjugular intrahepatic portosystemic shunt, extracorporeal liver support therapy, and (in patients with advanced uremia) renal replacement therapy should be considered, to improve renal function and potentially survival.

Pharmacotherapy

The most promising pharmacotherapy appears to be vasoconstrictors in combination with albumin, targeted at reversal of splanchnic arteriolar vasodilation and restoration of the effective arterial blood volume (Box 73.3). Vasodilators (aiming to reverse renal vasoconstriction) are contraindicated in HRS because they are ineffective and can induce marked hypotension.

Vasopressin analogues exhibit preferential vasoconstrictor action on the splanchnic versus the renal vascular bed. Terlipressin (triglycyllysine vasopressin) is a synthetic analogue of vasopressin that, in addition to having a greater effect on the vascular vasopressin receptors (V_1) than the renal vasopressin receptors (V_2), is a prodrug requiring transformation to the active form, lysine vasopressin. Because of this, terlipressin has a prolonged half-life and can be given as an intravenous bolus or as continuous intravenous infusion. Continuous administration improves the tolerability of the treatment (lower incidence of systemic ischemic side effects) and improves its effectiveness (treatment is effective at lower doses).[3,19] Long-term prospective studies[20-22] and a large retrospective study[23] in patients with type 1 and type 2 HRS have shown that terlipressin combined with daily albumin infusion improved renal function in 60% of the treated patients, with 37% surviving beyond 1 month (60% of them without OLT). Reversal of HRS was associated with improved survival.[21,23] The efficacy of terlipressin in the treatment of HRS has been confirmed in four randomized trials (Table 73.2).[24-27] Terlipressin was given at a starting dose of 2 to 6 mg/day, and in two studies the dose was titrated upward on the basis of response to a maximum dose of 12 mg/day. Both treated patients and controls were given daily albumin infusion of 20 to 40 g/day. Reversal of HRS was associated with improved survival in only one study.[26] The inclusion of patients with more severe renal failure in the treated group[25] and the unexpected high response and survival rates in controls[27] may explain the inability of some of these studies to show a survival benefit of treatment despite success in reversing HRS. The latter is likely a result of the more aggressive use of

BOX 73.3 Pharmacologic Options in the Treatment of Hepatorenal Syndrome

Terlipressin + albumin*: Terlipressin—1 mg/4-6 h to start,[†] increasing to a maximum of 2 mg/4-6 h if serum creatinine decreases less than 25% at day 3. Treatment is maintained until serum creatinine has decreased below 1.5 mg/dl (133 μmol/l). Maximum duration of treatment: 14 days.

Norepinephrine + albumin*: Norepinephrine—: IV infusion at 0.5 mg/h to start, increasing the dose by 0.25 to 0.5 mg/h every 4 hours up to a maximum of 3 mg/h to achieve an increase in MAP of at least 10 mm Hg. Maximum duration of treatment: 14 days.

Vasopressin + albumin*: Vasopressin—IV infusion at 0.01 U/min to start, increasing the dose upward to a maximum of 0.8 U/min to achieve an increase in MAP of at least 10 mm Hg. Maximum duration of treatment: 11 days.

Midodrine + octreotide + albumin*: Oral midodrine—2.5 to 7.5 mg/8 h + subcutaneous octreotide 100 mcg/8 h to start, increasing midodrine dose to a maximum of 12.5 mg/8 h and octreotide dose to a maximum of 200 mcg/8 h to achieve an increase in MAP of at least 15 mm Hg. Maximum duration: 14 days

*Albumin dose: 1 g/kg on day 1 (up to 100 g) followed by 20 to 40 g/day. Central venous pressure monitoring is advised (but not mandatory) to achieve a value of 10 to 15 mm Hg.

[†]Terlipressin also can be administered as continuous infusion (initially 3 mg/24 h; maximum dose 12 mg/24 h).

IV, Intravenous; *MAP,* mean arterial pressure.

TABLE 73.2 Randomized Controlled Trials of Terlipressin or Norepinephrine in Hepatorenal Syndrome

Reference	Treatment	Vasoconstrictor Dose	Patients (n)*	Reversal of HRS[†] (%)	Survival at 3 Months (%)	Survival at 6 Months (%)
Solanki et al., 2003[24]	Terlipressin + albumin	1 mg/12 h	12 (0)	42[‡]	NA	NA
	Placebo	—	12 (0)	0	0	0
Sanyal et al., 2008[25]	Terlipressin + albumin	1-2 mg/6 h	56 (0)	34[†]	NA	43
	Placebo	—	56 (0)	13	NA	38
Neri et al., 2008[26]	Terlipressin + albumin	0.5-1 mg/8 h	26 (0)	80[†]	54[†]	42
	Albumin	—	26 (0)	19	19	15
Martín-Llahí et al., 2008[27]	Terlipressin + albumin	1-2 mg/4 h	23 (6)	39[†]	26	NA
	Albumin	—	23 (5)	4	17	NA
Alessandria et al., 2007[32]	Terlipressin + albumin	1-2 mg/4 h	12 (7)	83	67	67
	Norepinephrine + albumin	0.1-0.7 mcg/kg/min	10 (6)	70	70	70
Sharma et al., 2008[33]	Terlipressin + albumin	0.5-2 mg/6 h	20 (0)	50	NA	NA
	Norepinephrine + albumin	0.5-3 mg/h	20 (0)	50	NA	NA

*Number of patients with type 2 hepatorenal syndrome in parentheses.
[†] Serum creatinine ≤1.5 mg/dl.
[‡] *P* <.05 versus placebo or control.

albumin infusion in these studies because such an approach has been shown to reverse HRS in a high proportion of patients. A meta-analysis confirms that terlipressin plus albumin prolongs short-term survival in patients with type-1 HRS.[28] Response to therapy is characterized by a slow and sustained reduction in serum creatinine and improvement in systemic hemodynamics (marked suppression of the plasma levels of renin and norepinephrine, increase in MAP), urine volume, and serum sodium concentration. Median time to reversal of HRS is 7 days and depends on pretreatment serum creatinine.[3]

Recurrence of HRS after successful treatment tends to be more common in type 2 (around 50%) than in type 1 HRS (20%).[20,21,22,25,27] Retreatment with terlipressin is successful in most patients.[21,25] Younger age,[23,26] lower baseline serum creatinine level,[27] Child-Pugh score of 12 or lower,[23,26] administration of albumin,[21] serum bilirubin below 10 mg/dl, and increase in MAP over 5 mm Hg after initiation of terlipressin[29] are independent predictors of a successful response to treatment. In patients with severe alcoholic hepatitis, the absence of underlying cirrhosis increases the probability of response to treatment. Child-Pugh score (<12)[21,23,25,26] and MELD score[27] are independent predictors for survival. Transient abdominal pain and diarrhea after the first dose of terlipressin treatment are common. Significant ischemic side effects attributed to terlipressin occurred in an average of 4% to 12% of patients.[20-27]

Intravenous vasopressin has been used as an alternative to terlipressin in the treatment of HRS in countries where this drug is not available and was successful in reversing type 1 and type 2 HRS in 42% of patients in a retrospective study.[30] Responders had significantly lower mortality and a higher liver transplantation rate than nonresponders. No adverse effect related to therapy was observed.

Intravenous norepinephrine combined with intravenous albumin and furosemide reversed type 1 HRS in 10 of 12 patients; 3 survived with OLT, and 4 survived for a median of 332 days without OLT.[31] With use of a similar dosage regimen, two randomized comparative studies showed that norepinephrine is as effective as terlipressin in the treatment of type 1 and type 2 HRS (see Table 73.2).[32,33] All recurrences were successfully retreated with the original regimen. Significant treatment-related side effects were low, and the cost of treatment with norepinephrine was 3 and 15 times lower, respectively, than with terlipressin.

Administration of midodrine (an oral vasoconstrictor with α-adrenergic effect), subcutaneous octreotide, and albumin infusion has been demonstrated to be less effective in improving renal function in patients with HRS than the combination of terlipressin plus albumin. In a recent randomized controlled trial (RCT), reversal of HRS was achieved in 56% of patients receiving terlipressin plus albumin in comparison to only 5% in those receiving octreotide plus midodrine and albumin.[34] If these results are confirmed by other groups, octreotide plus midodrine and albumin should be considered a third-line treatment of patients with type 1 HRS.

In the United States and in countries where terlipressin is not available, patients with type 1 HRS should be treated with α-adrenergic drugs (intravenous norepinephrine or oral midodrine plus subcutaneous octreotide) administered with albumin.

Transjugular Intrahepatic Portosystemic Shunt

Portal hypertension is central in the pathogenesis of the homeostatic abnormalities in HRS. The high operative mortality precludes side-to-side portacaval shunts in HRS patients. The transjugular intrahepatic portosystemic shunt (TIPS) creates a parenchymal tract between branches of the hepatic and portal vein (Fig. 73.4). In experienced hands, operative mortality rates are 1% to 2%, and the morbidity rate is 10%. Procedure-related complications include intraabdominal bleeding, cardiac arrhythmia, shunt migration and thrombosis, hemolytic anemia, fever, infection, and reactions to radiocontrast media (including nephrotoxicity). The resultant diversion of portal blood flow from the liver to the systemic circulation may result in transient deterioration of liver function. Shunt stenosis and hepatic encephalopathy are the main long-term complications of TIPS. Exceptionally, TIPS induces disabling encephalopathy. In these cases, closure of the shunt should be performed.[35] In an earlier study, TIPS improved renal function in 6 of 7 HRS patients (all with Child-Pugh score <12) and achieved a mean survival of 4.7 (0.3 to 17) months.[36] A long-term study of 31 cirrhotic patients with HRS (14 type 1 and 17 type 2) who were not transplant candidates and did not have severe liver failure confirmed that TIPS improved renal function and survival compared with controls.[37] Shunt stenosis and occlusion occurred in 7 patients (treated in 6 by balloon dilation or stent prolongation), and 11 developed hepatic encephalopathy during follow-up. TIPS therefore could be an alternative treatment of type 1 HRS in patients without response to terlipressin/norepinephrine plus albumin.

Transjugular Intrahepatic Portosystemic Stent-Shunt

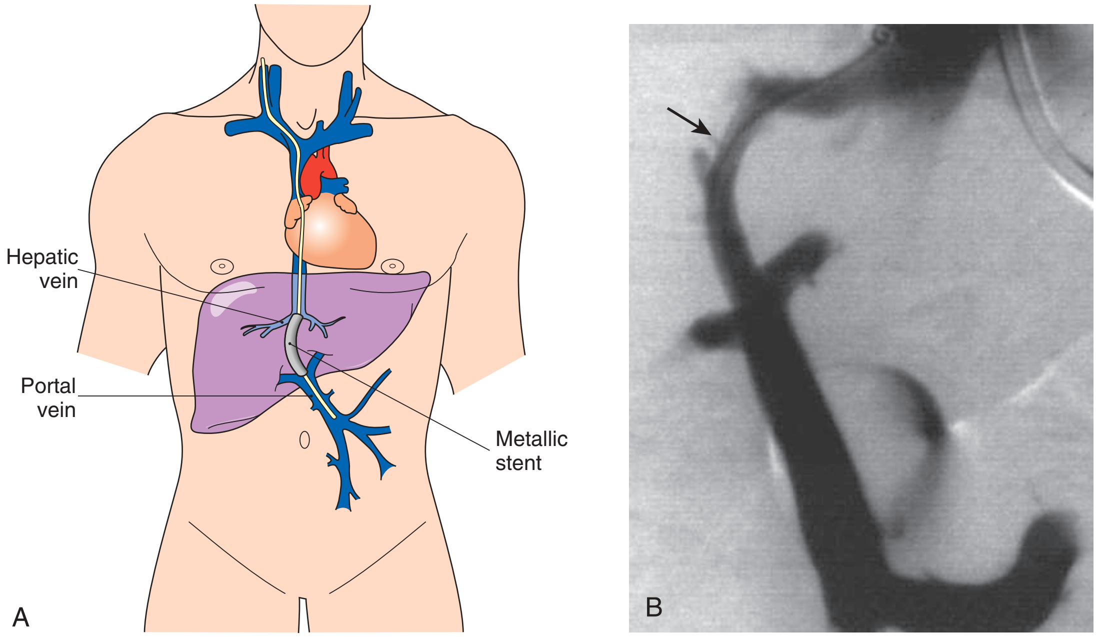

Fig. 73.4 **Transjugular intrahepatic portosystemic shunt.** (A) An intrahepatic tract has been created between the hepatic vein and the right portal vein. (B) The tract is dilated *(arrow)* and stented, creating a shunt as demonstrated on shuntogram. (Courtesy Dr. W. K. Tso, Queen Mary Hospital, Hong Kong.)

Combined TIPS and intravenous terlipressin therapy was performed in nine patients with type 2 HRS.[22] All seven patients who responded to terlipressin and relapsed after treatment cessation responded to TIPS. In another study, TIPS was performed in five patients with type 1 HRS after successful treatment with midodrine, octreotide, and albumin.[38] Complete normalization of renal function was observed in all patients at 12 months after TIPS. In both studies, improvement or elimination of ascites was an added benefit.

Extracorporeal Liver Support Therapy

Extracorporeal liver support therapy, as a bridge to OLT, relies on biologic (hepatocytes from human or animal source in an ex vivo perfusion system) or nonbiologic methods, including plasma exchange and albumin dialysis systems. Numerous studies have suggested that albumin dialysis (molecular adsorbent recirculating system [MARS] or fractionated plasma separation and adsorption [FPSA]) may have beneficial effects in patients with type 1 HRS. In a small RCT, a mean of five treatments with MARS effectively removed albumin-bound toxic metabolites (i.e., bilirubin and bile acids), improved renal function, and prolonged survival in eight patients (mean survival, 25 ± 5 days) with type 1 HRS and severe liver failure compared with five control patients treated only with hemodiafiltration (mean survival, 5 ± 2 days).[39] In another study of eight encephalopathic patients with acute alcoholic hepatitis (five with type 1 and two with type 2 HRS), MARS improved renal function, bilirubin, prothrombin time, grade of encephalopathy, MAP, systemic vascular resistance, and cardiac output, with four patients still alive without OLT at 3 months.[40] Three large RCTs have so far been performed evaluating albumin dialysis in patients with ACLF.[41-43] In the first study, albumin dialysis with MARS was found to be more effective than standard medical therapy in the management of patients with grade 3 or 4 hepatic encephalopathy. Most patients had HRS, and the treatment was found to be safe.[41] The two other trials compared albumin dialysis with standard medical therapy in patients with type 1 HRS (MARS) or with type 1 and 2 HRS (FPSA). A significant beneficial effect on hepatic encephalopathy was observed in the MARS study but not on survival.[42] In the FPSA trial no effect on survival was observed in the whole group or in patients with type 1 HRS, but a significant improvement was observed in patients with high MELD score (>30 points). The administered dosage of dialysis was very low in both studies (six sessions of 6 hours in 21 days). In these studies, therapy was well tolerated.[42,43] Further studies are clearly needed to ascertain the potential role of albumin dialysis in type 1 HRS. Patients with type 2 HRS are usually treated by total paracentesis or TIPS.

Renal Replacement Therapy

Hemodialysis and peritoneal dialysis in HRS patients with advancing uremia are both difficult. Conventional hemodialysis is hampered by the invariable systemic hypotension, and the efficacy and safety of peritoneal dialysis have not been well evaluated in these patients. Continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodiafiltration (CVVHDF) has been advocated for the treatment of advancing uremia in HRS.[44] This is particularly true for patients with fulminant hepatic failure in whom intermittent dialysis can increase intracranial pressure. Anticoagulation should be minimized or avoided (especially in patients with severe coagulopathy) by giving the replacement fluid in the predilutional mode. When anticoagulation is needed, conventional heparin is generally recommended. Regional citrate anticoagulation is not recommended in advanced cirrhosis because the liver plays a significant role in its metabolism. If used, dose adaptation and close metabolic monitoring would be required, especially after prolonged use. Close serum calcium monitoring is mandatory because hypocalcemia is common because of impaired citrate clearance. Bicarbonate should be used instead of lactate as the buffer for the replacement solution to minimize metabolic acidosis. MARS may be combined with either CVVH or hemodialysis for the treatment of HRS, especially in patients with severe hepatic encephalopathy.

Liver Transplantation

Liver transplantation is the treatment of choice in patients with advanced cirrhosis, including those with type 1 and type 2 HRS.[2,3,45,46] The hemodynamic and neurohormonal abnormalities associated with HRS disappear within the first month after liver transplantation. For this reason, calcineurin inhibitors should be withheld in the first few days after OLT to give the ischemic kidneys a chance to recover. Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than transplantation patients without HRS. The long-term survival of patients with HRS who undergo liver transplantation, however, is good (3-year survival 60%) compared with transplantation in patients without HRS (70% to 80%).[45] Although renal function improves after transplantation in HRS patients, it never reaches that observed in non-HRS patients.[47] The incidence of end-stage renal disease in patients with HRS is slightly higher than that observed in transplantation recipients without HRS (7% vs. 2%). Thus OLT is associated with comparable liver outcome but inferior renal outcome in patients with HRS. This problem cannot be overcome by performing combined kidney and liver transplantation in HRS, which overall produces outcomes no better than with OLT alone.[48] However, in the rare subgroup of patients with HRS who required prolonged pretransplant dialysis for more than 2 months, combined kidney and liver transplantation did confer an advantage in patient survival and use of hospital resources. These infrequent patients usually have normal kidney size and morphology on ultrasound but develop some additional indications of organic nephropathy during follow-up (mild proteinuria or microhematuria).[49]

The main problem with liver transplantation in type 1 HRS is that most patients die before transplantation. The introduction of the MELD score for listing has partially solved the problem because patients with HRS are prioritized for transplantation. As mentioned earlier, treatment of HRS with vasoconstrictors and albumin improves survival in the group of patients with response to treatment, increasing the number of patients reaching liver transplantation. In addition, reversal of HRS before transplantation may decrease early morbidity and mortality after transplantation and prolong survival.[46]

Therapeutic Algorithm

Fig. 73.5 shows the recommended algorithm for the management of HRS. Recent recommendations have been published by the International Club of Ascites.[11,50] OLT is undoubtedly the treatment of choice for patients with HRS, but other treatments described earlier must be used as a bridge to OLT and they may improve the renal outcome after

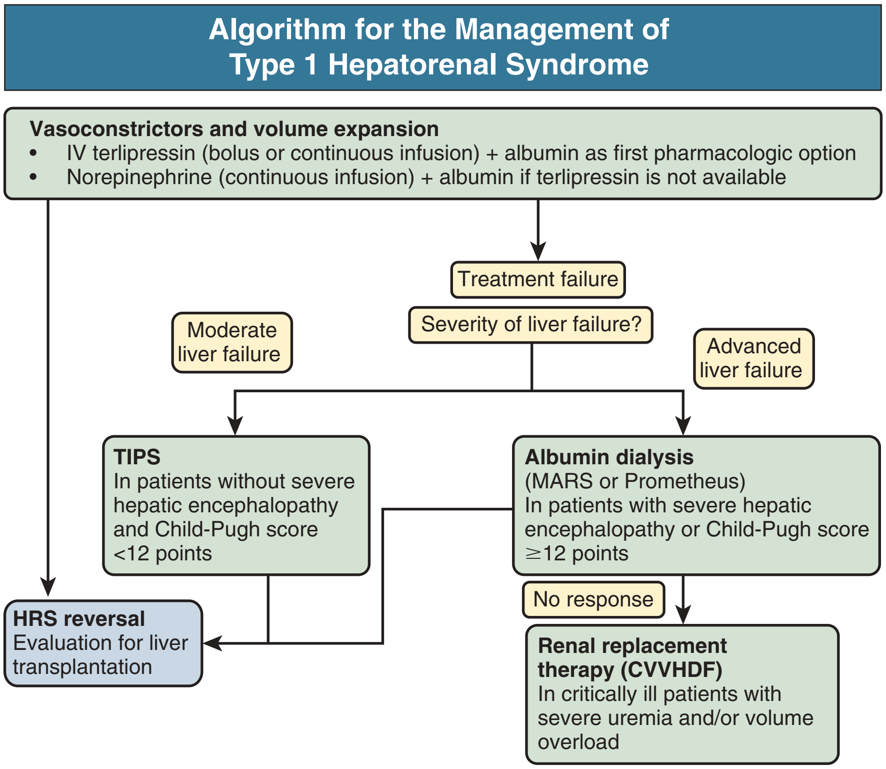
Algorithm for the Management of Type 1 Hepatorenal Syndrome
Vasoconstrictors and volume expansion
• IV terlipressin (bolus or continuous infusion) + albumin as first pharmacologic option
• Norepinephrine (continuous infusion) + albumin if terlipressin is not available
Treatment failure
Severity of liver failure?
Moderate liver failure
Advanced liver failure
TIPS
In patients without severe hepatic encephalopathy and Child-Pugh score <12 points
Albumin dialysis
(MARS or Prometheus)
In patients with severe hepatic encephalopathy or Child-Pugh score ≥12 points
No response
HRS reversal
Evaluation for liver transplantation
Renal replacement therapy (CVVHDF)
In critically ill patients with severe uremia and/or volume overload

Fig. 73.5 Algorithm for the management of type 1 hepatorenal syndrome *(HRS).* Initial treatment is based on the use of vasoconstrictor therapies plus albumin. Intravenous terlipressin is the most established and is the preferred therapy.[50] If terlipressin is not available, continuous intravenous norepinephrine should be used. Patients with history of significant atherosclerotic or cardiovascular disease should be treated with norepinephrine. If pharmacologic therapy fails, the severity of liver failure should be assessed. In patients with less severe liver dysfunction (bilirubin <5 mg/dl or 85.5 µmol/l and Child-Pugh score <12) without severe hepatic encephalopathy (grade ≤2) or history of recurrent encephalopathy, transjugular intrahepatic portosystemic shunt *(TIPS)* should be considered.[3] In patients with more severe liver failure (Child-Pugh score ≥12) and/or severe hepatic encephalopathy (grade >2), albumin dialysis (molecular adsorbent recirculating system *[MARS]* or fractionated plasma separation and adsorption [FPSA]) should be considered. In critically ill cirrhotic patients with advancing renal failure, continuous venovenous hemodiafiltration *(CVVHDF)* is the treatment of choice.

successful OLT. In patients who are not transplantation candidates, these treatments are their only chance for increased survival and in some cases may improve their condition to an extent that may allow them to be reconsidered for transplantation. The choice of therapeutic modalities depends on the availability of resources and expertise on the one hand and the severity of underlying renal and liver failure and the general condition of the patient on the other. All patients should be considered for vasoconstrictor therapy combined with albumin infusion. Among the vasoconstrictor therapies, intravenous terlipressin, combined with daily albumin infusion, is most established and is the preferred therapy.[2,3,50] In countries where terlipressin is not available, continuous intravenous norepinephrine or vasopressin may be used as alternative. Patients with a history of significant atherosclerotic or cardiovascular disease should be treated with norepinephrine plus albumin. Oral midodrine combined with subcutaneous octreotide and albumin is another alternative in the treatment of HRS, especially in patients with type 2 HRS. In patients with relatively well-preserved liver function (serum bilirubin <5 mg/dl or 85.5 μmol/l and Child-Pugh score <12) without severe hepatic encephalopathy (grade ≤2) or history of recurrent encephalopathy, concurrent severe bacterial infection, or serious cardiovascular or pulmonary disease, TIPS should be considered, especially in patients with recurrence after vasoconstrictor therapy, a situation more commonly observed in HRS type 2 patients.[3] In these patients, TIPS may have the added benefit of relieving refractory ascites. TIPS also appears to achieve complete normalization of renal function in selected patients after an initial successful response to vasoconstrictor therapy. In patients with severe liver failure (Child-Pugh score ≥12) and severe hepatic encephalopathy (grade >2), MARS should be considered. In critically ill cirrhotic patients with advancing renal failure, CVVH is the treatment of choice and may be combined with other therapeutic modalities, especially MARS or FPSA.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following pathogenic events are observed in patients with hepatorenal syndrome (HRS)?
   - **A.** Splanchnic vasodilation
   - **B.** Cardiac dysfunction
   - **C.** Systemic inflammation
   - **D.** Tubular and glomerular lesions
2. Diagnosis of HRS is established by:
   - **A.** Liver biopsy
   - **B.** Renal biopsy
   - **C.** Measurement of plasma renin activity
   - **D.** It is a clinical diagnosis and is established by exclusion
3. Which affirmation(s) is/are incorrect in patients with hepatorenal syndrome?
   - **A.** It occurs in patients with subacute or chronic liver failure and portal hypertension.
   - **B.** Patients are normally hypertensive.
   - **C.** Plasma renin activity is usually high.
   - **D.** It can be observed in patients with and without ascites.
   - **E.** Patients can be infected.
4. Which affirmation(s) is/are incorrect regarding the treatment of patients with HRS?
   - **A.** The combination of terlipressin and albumin is the preferred treatment.
   - **B.** TIPS is an alternative treatment.
   - **C.** Patients must undergo early dialysis.
   - **D.** Albumin dialysis can be used in patients in whom pharmacologic treatment has failed.
   - **E.** The combination of midodrine, octreotide, and albumin is a good pharmacologic option.
5. Which affirmation(s) is/are correct in the prophylaxis of hepatorenal syndrome?
   - **A.** Norfloxacin prevents the development of HRS in patients with advanced cirrhosis and low-protein ascites.
   - **B.** Albumin infusion (1.5 g/kg at diagnosis and 1 g/kg at day 3) prevents the development of HRS and improves short-term survival in patients with SBP.
   - **C.** Albumin infusion prevents HRS in patients with infections other than spontaneous bacterial peritonitis.
   - **D.** Oral midodrine prevents HRS.

74

Principles of Drug Therapy, Dosing, and Prescribing in Chronic Kidney Disease and Renal Replacement Therapy

Matthew J. Cervelli, Graeme R. Russ

Renal impairment can alter drug pharmacokinetics and pharmacodynamics, and consequently patients with renal impairment are at risk for adverse effects. In addition, these patients take multiple drugs and are at high risk for drug interactions and drug-related problems.[1] To prescribe safely and effectively, clinicians should be familiar with the pharmacokinetics of drugs in varying stages of renal impairment and renal replacement therapy (RRT) and ideally rely on data from these populations. Unfortunately, such information is not always available, and exclusion of these patients from clinical studies can lead to restrictive licensed recommendations. This chapter describes pharmacokinetic principles and highlights common prescribing issues in patients with renal impairment, dialysis, and transplantation. Specific dose recommendations and pharmacokinetic data are not included but can be obtained elsewhere.[2-5]

PHARMACOKINETIC PRINCIPLES

Pharmacokinetics describes the behavior of a drug (or metabolite) in terms of its absorption, distribution, metabolism, and elimination (Fig. 74.1 and Table 74.1).[6,7]

Absorption: Bioavailability

Bioavailability *(F)* is the portion of a drug dose that appears in the systemic circulation after administration by a nonintravenous route. Drugs given intravenously have 100% bioavailability, whereas drugs given by alternative routes pass through a series of biologic membranes before entering the systemic circulation so that only a fraction may reach the circulation.

After oral administration, the liver can metabolize a drug during "first pass" when it is absorbed or later when it is delivered through systemic blood flow. First-pass metabolism can significantly reduce absorption. The gastrointestinal (GI) mucosa also acts as a barrier to absorption by metabolizing drugs or retarding absorption.[8] Renal impairment can influence absorption, although effects are difficult to quantify and clinical examples are limited. GI edema can limit oral drug absorption (e.g., oral furosemide in nephrotic syndrome). Nausea and vomiting from uremia can impair absorption and contact time between a drug and GI mucosa. In patients with advanced uremia, the alkalinizing effect of salivary urea may decrease absorption of drugs optimally absorbed in an acid milieu. Commonly prescribed metallic ion phosphate binders can decrease drug absorption by forming nonabsorbable complexes with drugs (Table 74.2).[9] Changes in cardiac output in renal failure can reduce the rate and extent of absorption for drugs with significant first-pass metabolism. Increased absorption in patients with renal impairment from reduced first-pass metabolism is seen with some β-blockers, dextropropoxyphene, and dihydrocodeine. Comorbidities in renal patients also can have an effect; for example, absorption can be erratic because of diabetic GI neuropathy.

Distribution

Volume of Distribution

After absorption, drugs may distribute from plasma to an extravascular compartment. Each drug has a characteristic volume of distribution (V_D), which is really an apparent V_D because it does not correspond to an anatomic space but instead relates the amount of drug in the body to its plasma concentration. V_D is used to calculate the loading dose to achieve a desired plasma concentration (V_D = dose/[plasma]). Water-soluble drugs tend to be restricted to the extracellular fluid space and have a relatively small V_D. Lipid-soluble drugs penetrate body tissues and have a large V_D. Increased V_D can occur with edema, ascites, or infection, particularly for water-soluble drugs; if usual doses are given, low concentrations result. Conversely, muscle wasting or volume depletion can decrease the V_D of water-soluble drugs and usual doses produce high concentrations.

Plasma Protein Binding

Drugs can bind extensively to plasma proteins.[10] The free (unbound) fraction of a drug is usually the portion that exerts a pharmacologic effect. If protein binding is reduced, a greater free fraction is available for any given total drug concentration, which may increase drug activity. Organic acids usually have a single binding site on albumin, whereas organic bases have multiple binding sites on glycoproteins. Protein binding can be altered in patients with renal impairment, especially when serum albumin is low (e.g., nephrotic syndrome) or when uremic toxins displace drugs from binding sites (Table 74.3). Predicting the effect of changes in protein binding is difficult. For example, a decrease in protein binding means more free drug is available at the site of action, but also that more is available for metabolism or renal excretion.

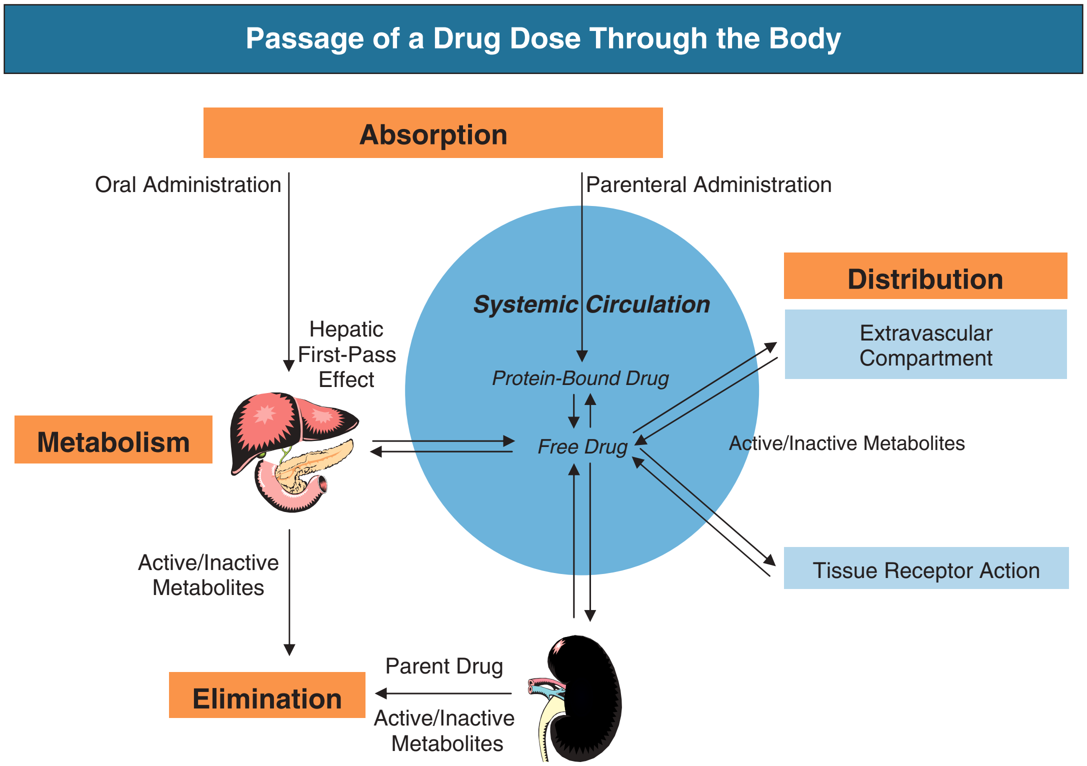
Passage of a Drug Dose Through the Body
Absorption
Oral Administration
Parenteral Administration
Systemic Circulation
Distribution
Extravascular Compartment
Hepatic First-Pass Effect
Protein-Bound Drug
Metabolism
Free Drug
Active/Inactive Metabolites
Tissue Receptor Action
Active/Inactive Metabolites
Parent Drug
Elimination
Active/Inactive Metabolites

Fig. 74.1 Passage of a drug dose through the body.

TABLE 74.1 Pharmacokinetic Parameters

Parameter	Definition	Application
Bioavailability *(F)*	Percentage of a dose that appears in the systemic circulation after administration by a nonintravenous route	Determines the amount of drug reaching the systemic circulation
Volume of distribution (V_D)	Proportionality constant relating the amount of drug in the body at a given time to a simultaneously occurring drug concentration in plasma, blood, or other reference fluid at an identical time	Determines the size of loading doses
Clearance	Proportionality constant between rate of drug elimination from the body (mass/unit time) and the concentration of the drug in plasma or blood at the same point in time	Determines the maintenance dose
Half-life ($t_{1/2}$)	Time taken for the drug concentration in plasma to fall to half its current value	Determines frequency of administration and time to steady state

TABLE 74.2 Effect of Food and Phosphate Binders on Oral Drug Absorption

Drug	Effect of Food
Captopril	Decreases serum drug levels
Bisphosphonates (oral)	Significantly reduces drug absorption
Cinacalcet	Significantly increases drug absorption
Iron (oral)	Decreases absorption
Ketoconazole or itraconazole	Increases absorption with reduced pH
Sirolimus	High-fat meals increase absorption
Tacrolimus	Reduces drug absorption
Drug	**Effect of Metallic Phosphate Binders**
Bisphosphonates (oral)	Calcium-containing binders significantly reduce absorption
Fluoroquinolones	Reduction in absorption
Tetracycline	Reduction in absorption
Thyroid hormones	Reduction in absorption

Thus lower plasma concentrations can occur and drug half-life may decrease rather than increase. Phenytoin, for example, has marked decreases in protein binding in patients with renal impairment, and toxicity can occur despite normal or low total plasma concentrations because of an increase in free fraction. With albuminuria, bound drug also may be lost, which may partially explain the refractoriness of nephrotic patients to diuretics. In patients with chronic kidney disease (CKD), high plasma levels of α_1-acid glycoprotein are induced in acute and chronic inflammation, which can increase drug binding.

Metabolism

Drug metabolism is primarily a hepatic function by which drugs are converted to more water-soluble entities, which promotes elimination by the kidneys and bile. Despite the assumption that nonrenal clearance is

TABLE 74.3 **Protein Binding of Drugs in Renal Disease**

Major Effects	Minor Effects
Albumin: Binding Sites for Acidic Compounds	
Barbiturates (↓)	Ascorbic acid (↑)
Benzodiazepine (↑)	Valproate (↓)
Carbamazepine (↑)	Fatty acids (↑)
Fibrates (↑)	Nafcillin (↑)
Furosemide (↓)	Phenylbutazone (↓)
Mycophenolate mofetil (↑)	Probenecid (↑)
Penicillins (↑)	Thiopental (↓)
Phenytoin (↓)	Warfarin (↓)
Sulfonamides (↓)	Thyroxine (↓)
Globulins: Binding Site for Basic Compounds	
Digoxin (↓)	Adenosine (↑)
Methadone (↑)	Amitriptyline (↑)
Propranolol (↑)	Chloramphenicol (↑)

↓, Indicates reduced protein binding in renal impairment; ↑, indicates increased protein binding in renal impairment. However, the therapeutic effect is not easily predicted (see text).

BOX 74.1 **Mathematics of Drug Elimination**

Total body clearance = Drug dose/AUC

Renal clearance = Total amount of drug in urine/plasma drug concentration

Total amount of drug in urine = Drug × volume of the sample collected in a fixed time

Drug half-life $(t_{1/2}) = V_D \times 0.693/\text{Clearance}$

AUC, Area under the concentration-time curve; V_D, volume of distribution (dose/blood concentration).

unchanged, renal impairment can alter and slow drug metabolism.[11] It is important to note that some drugs have active or toxic metabolites that are renally cleared; although insignificant with normal renal function, such metabolites can accumulate in patients with renal impairment.

Elimination

The kidney is the most important organ for drug and metabolite elimination. Terms to describe drug clearance are shown in Box 74.1. Total drug clearance equals the apparent volume of blood or plasma from which the drug is cleared per unit of time and is expressed as the dose divided by the area under the drug concentration curve (AUC). *Half-life* describes the time taken for plasma concentrations to halve and is related to V_D and clearance. Quantitation of drug elimination by the kidney is expressed as renal clearance, which depends on renal blood flow and the ability of the kidney to remove the drug. Renal drug clearance is the balance of its glomerular filtration rate (GFR), renal tubular secretion, and tubular reabsorption. Glomerular filtration depends on molecular size (<10 kDa), charge, and protein binding (increased when binding decreases). Secretion of drugs eliminated by tubular transport may change with renal disease, but measurement of tubular function is difficult. Practically, as GFR decreases, drugs dependent on tubular secretion are also excreted more slowly. Assuming no change in nonrenal clearance, as GFR falls, clearance of drugs (and metabolites) eliminated by the kidney decreases and their half-life is prolonged.

PRESCRIBING PRINCIPLES FOR CHRONIC KIDNEY DISEASE AND RENAL REPLACEMENT THERAPY

Ideally, dose modification recommendations should be made by comparing the pharmacokinetics of a drug at varying stages of renal impairment relative to normal function. However, lack of reliable data and individual patient factors limit such generalities and clinical judgment about a patient's ability to handle a drug is vital.[12] Dose nomograms, tables, and computer recommendations are helpful but not necessarily associated with better outcomes. Physicians should use clinical judgment to evaluate every situation individually, choose a dosage regimen based on factors in that patient, and continually reevaluate the response to therapy.

Initial Assessment and Laboratory Data

A targeted history is important in assessing dose in patients with renal impairment. Previous drug efficacy or toxicity should be determined and the current prescribed medications reviewed for potential interactions or nephrotoxins. Physical and laboratory parameters indicate volume status, height, weight, and extrarenal disease (e.g., liver).

Estimating Renal Function for Drug Dosage

Estimating renal function is essential in renal drug dosing. The greater the degree of renal impairment, the greater is the potential need for dose modification. With exceptions, dose modification usually is not clinically necessary until GFR is below 30 ml/min. Assessment of renal function to assist drug dosing is not a precise science. What is essential for clinical decision making is awareness that renal function is impaired, and approximately to what extent, rather than knowledge of the precise GFR.[13] For drug prescribing, renal impairment is usually graded as mild (30 to 60 ml/min), moderate (10 to 30 ml/min), or severe (<10 ml/min or on dialysis). For drug dosage calculation, estimating GFR is usually sufficient (see Chapter 3). The Cockcroft-Gault equation has been the most widely used and accepted method for drug dosage calculation. The Modification of Diet in Renal Disease (MDRD) formula and Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) formula, if not corrected for body surface area, can lead to recommendations different from those obtained by the Cockcroft-Gault equation. An important limitation of all renal function estimates is inaccuracy of single-point estimates when renal function is rapidly changing. This may lead to overestimation or underestimation of renal function and underdosing or overdosing. In patients with severe acute kidney injury (AKI), the decline in GFR is so rapid that patients should receive dosages appropriate for GFR below 10 ml/min. The opposite is true in rapidly improving renal function after AKI or early posttransplant.

Activity and Toxicity of Metabolites

It is essential to consider the activity (or toxicity) of drug metabolites in addition to that of the parent drug itself. Renally cleared metabolites can accumulate, leading to enhanced drug action or toxicity (Table 74.4).

Fraction of Active Drug (and Active or Toxic Metabolite) Excreted Unchanged in Urine

The greater the fraction of active drug or metabolite excreted unchanged by the kidneys (fe), the greater is the need for dose modification. It is usually clinically necessary to modify doses only if the fe is greater than 25% to 50%. The reported fe is often determined from studies that do not distinguish between parent drug and metabolites. The contribution

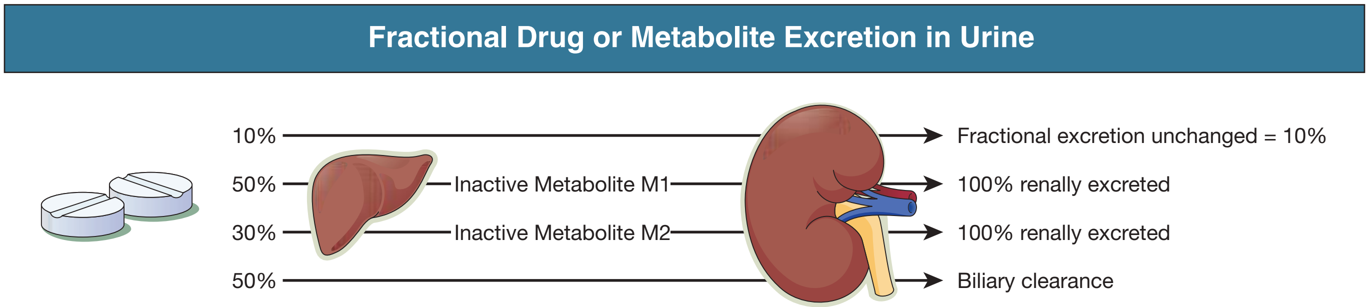
Fractional Drug or Metabolite Excretion in Urine
10%
50%
30%
50%
Inactive Metabolite M1
Inactive Metabolite M2
Fractional excretion unchanged = 10%
100% renally excreted
100% renally excreted
Biliary clearance

Fig. 74.2 **Fraction of drug or metabolite excreted in urine.** In this hypothetical example, 10% of the dose is excreted unchanged in urine (fe = 10%); 50% of the dose is metabolized to inactive metabolite M1, which is then all renally excreted; 30% of the dose is metabolized to inactive metabolite M2, which is all renally excreted; and the remaining 10% is excreted unchanged in bile. For this drug, the total excretion of drug dose in urine is 90%. However, this 90% comprises 10% as parent drug and 80% as inactive metabolites, and dose modification is probably not essential even in severe renal impairment. Total renal excretion of the dose is 90%; however, the clinically significant fraction of active drug excreted in urine is 10%.

TABLE 74.4 Drugs With Renally Cleared Active or Toxic Metabolites That Accumulate in Patients With Reduced Glomerular Filtration Rate

Drug	Active Metabolite	Consequence
Allopurinol	Oxypurinol	
Cefotaxime	Desacetyl cefotaxime	
Glyburide	4-*trans*-Hydroxyglibenclamide 3-*cis*-Hydroxyglibenclamide	Hypoglycemia
Morphine	Morphine-6-glucuronide	CNS side effects
Tramadol	*O*-Desmethyltramadol	CNS side effects
Venlafaxine	*O*-Desmethylvenlafaxine	CNS and cardiovascular side effects
Drug	**Toxic Metabolite**	**Consequence**
Dapsone	Monoacetylated metabolite	
Meperidine (pethidine)	Normeperidine (norpethidine)	CNS (seizures)
Nitroprusside	Thiocyanate	Cyanide toxicity
Procainamide	*N*-Acetylprocainamide (NAPA)	Arrhythmia
Propoxyphene	Norpropoxyphene	Cardiac toxicity

CNS, Central nervous system.

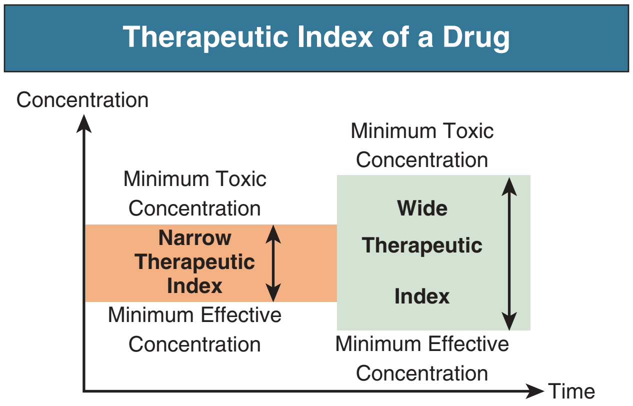
Therapeutic Index of a Drug
Concentration
Minimum Toxic Concentration
Narrow Therapeutic Index
Minimum Effective Concentration
Minimum Toxic Concentration
Wide Therapeutic Index
Minimum Effective Concentration
Time

Fig. 74.3 **Therapeutic index of a drug.** Two examples of drugs with, on the left, a narrow therapeutic index, and on the right, a wide therapeutic index.

of inactive nontoxic metabolites to overall renal drug elimination may exaggerate the potential for harm. Active or toxic metabolites should be assessed separately for their dependence on renal elimination in the same way as the parent drug (Fig. 74.2).

Therapeutic Index of the Drug or Metabolites

The decision to modify dosage in patients with renal impairment is influenced by the therapeutic window or index of the drug. The therapeutic window is the range of plasma drug concentrations spanning the minimum concentration for clinical efficacy and toxicity. The therapeutic index is the ratio of these concentrations (Fig. 74.3). If the therapeutic window is wide (e.g., many penicillins), there may be no clinical need for dose modification despite significant renal elimination and or renal impairment. If the therapeutic window is narrow (e.g., digoxin), dose modification is more critical. Clinicians should judge the clinical relevance of increased exposure to drug or metabolites.

Avoiding Nephrotoxic Drugs

A wide range of drugs can cause nephrotoxicity (Table 74.5). Idiosyncratic nephrotoxicity (e.g., interstitial nephritis) is unpredictable and independent of dose. Predictable hemodynamic-related nephrotoxicity can occur with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), nonsteroidal antiinflammatory drugs (NSAIDs), diuretics, antihypertensives, and laxatives. Direct tubular nephrotoxins include aminoglycosides, vancomycin, amphotericin, cisplatin, calcineurin inhibitors (CNIs), and radiographic contrast media. Obstructive uropathy can occur with tubular crystallization of acyclovir, statin-induced rhabdomyolysis, or tricyclic antidepressant use. In dialysis patients with no significant residual renal function, use of nephrotoxic drugs may be acceptable. Drug nephrotoxicity is discussed further in Chapter 66.

Drugs That Aggravate the Metabolic Effects of Renal Impairment

Some drugs have no direct adverse effect on renal function but when used in patients with renal impairment can aggravate the metabolic consequences of renal failure. Hyperkalemia is exacerbated by potassium

TABLE 74.5 Some Examples of Nephrotoxic Drugs

Examples	Mechanism	Prevention and Management
ACE inhibitors, ARBs	Impairment of angiotensin II–mediated afferent arteriole dilation during renal hypoperfusion	Withdraw in renal hypoperfusion
Aminoglycosides Amikacin Gentamicin Tobramycin	In proximal tubules, aminoglycosides bind to anionic phospholipid, are delivered to megalin, are taken up into the cell, accumulate, and cause direct toxicity	Alternative if possible Monitor drug concentrations Avoid multiple daily doses Withdraw if creatinine rises
Antifungals Amphotericin	Afferent vasoconstriction and direct action to reduce GFR Distal tubular injury via creation of pores that increase membrane permeability leading to hypokalemia, hypomagnesemia, metabolic acidosis caused by tubular acidosis, polyuria from nephrogenic diabetes insipidus	Avoid use Administer slowly with hydration Use liposomal preparation
Antivirals		
Acyclovir	Deposition of drug crystals → intratubular obstruction and foci of interstitial inflammation	Avoid bolus dose Reduce dose in renal impairment Hydrate during therapy
Cidofovir	Induces apoptosis in proximal tubule → tubular dysfunction, diabetes insipidus, renal failure	Oral probenecid and hydration
Foscarnet	Direct tubular toxicity → acute tubular necrosis, nephrogenic diabetes insipidus Crystals in glomerular capillary lumen and proximal tubular lumen	Hydration
Indinavir	Crystal neuropathy, nephrolithiasis → obstructive AKI	Hydration
Calcineurin inhibitors Cyclosporine Tacrolimus	↓ PG and ↑ 20-HETE acid production → vasoconstriction, generation of H_2O_2 resulting in depleted glutathione → decreased GFR, ischemic collapse or scarring of the glomeruli, vacuolization of the tubules, and focal areas of tubular atrophy and interstitial fibrosis	Measure plasma concentrations Avoid interacting drugs Withdraw drug (switch to mTOR inhibitor)
Chemotherapeutics		
Cisplatin	*Cis* chloride replaced by H_2O → highly reactive OH radical → DNA injury, tubular cell death Nephrogenic diabetes insipidus, hypomagnesemia (may be persistent)	Forced diuresis and hydration
Ifosfamide	Direct tubular injury and mitochondrial damage → renal tubular acidosis, Fanconi-like syndrome, nephrogenic diabetes insipidus hypokalemia	
Intravenous immunoglobulin (sucrose-containing products)	Accumulation of sucrose in proximal convoluted tubules, ↑ osmolarity → cell swelling, vacuolization, and tubular luminal occlusion	Infusion rate <3 mg sucrose/kg/min Avoid radiocontrast Avoid sucrose-containing product Hydration
Lithium	Impairment of collecting duct concentrating ability → diabetes insipidus Chronic tubulointerstitial nephropathy (tubular atrophy and interstitial fibrosis)	Measure plasma concentrations Prevent dehydration Avoid thiazides
NSAIDs	Hemodynamically induced AKI caused by vasoconstriction via reduced prostaglandin production Recruitment and activation of lymphocytes → acute and chronic tubulointerstitial nephritis, with or without nephrotic syndrome	Avoid use Withdraw during hypoperfusion Withdraw (add corticosteroids)
Proton pump inhibitors	Interstitial nephritis	Withdraw (add corticosteroids)
Radiocontrast media	High osmolarity, medullary vasoconstriction, ↑ active transport in thick ascending loop of Henle → ↑ O_2 demand	Hydration preprocedure and postprocedure Acetylcysteine
Sulfonamides	Intrarenal precipitation → kidney stone formation	Fluid intake >3 l/day; monitor urine for crystals Alkalinize urine to pH >7.15 if crystal seen

ACE, Angiotensin-converting enzyme; *AKI,* acute kidney injury; *ARBs,* angiotensin receptor blockers; *GFR,* glomerular filtration rate; *20-HETE acid,* 20-hydroxyeicosatetraenoic acid; H_2O_2; hydrogen peroxide; *mTOR,* mammalian target of rapamycin; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PG,* prostaglandin.

supplements, potassium-sparing diuretics, aldosterone antagonists, and blockers of the renin-angiotensin system. The catabolic effects of tetracycline can exacerbate uremia. Sodium-containing drugs and those that promote sodium and water retention should be used cautiously because they may provoke fluid overload and hypertension.

Effect of Renal Impairment on Pharmacodynamic or Physiologic Mechanisms

Renal disease may alter a pharmacodynamic response or physiologic process, which in turn affects clinical response. For example, the inability of impaired kidneys to activate vitamin D precursors means that vitamins D_2 and D_3 may be less effective. Patients with renal impairment often have a coagulopathy from the effects of uremia on platelet function and may be more prone to the bleeding complications of anticoagulant and antiplatelet therapy.

Effect of Renal Impairment on the Concentration of Drug at the Site of Action

Renal impairment can alter drug concentration at the site of action. Some diuretics and antibiotics become ineffective in patients with renal impairment because they do not achieve adequate concentrations at their site of action in the renal tubules or bladder. This may preclude the use of drugs such as thiazide diuretics and nitrofurantoin or may require increased doses of others (e.g., loop diuretics).

Location of Drug Action

Drugs that have negligible bioavailability and that are used for a local or topical effect may be given safely at normal dose despite toxicity with systemic doses. These include topical NSAIDs, nebulized gentamicin, and oral vancomycin.

Method of Administration

In fluid-restricted patients, administration of intravenous drug infusions with approved fluid volumes may be undesirable. When administration exceeds daily fluid restrictions, consider alternative drugs or more concentrated solutions provided that physiochemical parameters allow. Similarly, oral drug administration with large fluid volumes (e.g., bisphosphonates) may not be advisable. In patients with severe nausea and vomiting, essential immunosuppressants should be administered intravenously.

Drug Interactions

Pharmacokinetic drug interactions are frequently problematic, and awareness of clinically significant interactions is essential, especially with regard to patients receiving transplant immunosuppressants. The most important of these are cyclosporine, tacrolimus, everolimus, and sirolimus, which are substrates of both the cytochrome P450 (3A4) drug metabolizing enzyme system and P-glycoprotein drug efflux system expressed in GI mucosa and liver (Fig. 74.4).[14] Coprescription of drugs that inhibit these systems (e.g., some azole antifungals, calcium channel blockers, macrolides, and grapefruit juice) can increase absorption and reduce metabolism of the immunosuppressant, causing toxicity. Conversely, drugs that induce these systems (e.g., barbiturates, phenytoin, carbamazepine, rifampin, and St. John's wort *[Hypericum]*) can reduce absorption and increase metabolism and therefore increase the risk for rejection (see Fig. 74.4 and Table 74.6). All drug changes in patients receiving transplant immunosuppression should be considered for their potential to interact, and appropriate dose modifications or alternatives used.

TABLE 74.6 Therapeutic Drug Monitoring in Renal Impairment

Drug	Therapeutic Range and When to Draw Sample
Aminoglycosides	Peak (30 min after a 30-min infusion)
(24-h dosing)	Trough (6-12 h after dose)
Gentamicin	Peak: >10 mg/l
	Trough: Depends on time after dose 0.5-2 mg/l
Tobramycin	Peak: >10 mg/l
	Trough: Depends on time after dose 0.5-2 mg/l
Amikacin	Peak: >30 mg/l
	Trough: depends on time after dose 1.5-6 mg/l
Immunosuppressants	
Cyclosporine	C_0 (trough): 150-250 μg/ml
	C_2 (2 h after dose): 1200-1500 μg/ml
	AUC_{0-4} >4400 μg/ml/h
Tacrolimus	C_0 (trough): 4-12 μg/ml
Sirolimus	C_0 (trough): 5-15 μg/ml
Antiarrhythmics	
Digoxin	0.8-2.0 μg/ml (trough at least 6 h after dose)
Lidocaine	1-5 μg/ml 8 h after IV infusion starts or is changed
Antipsychotics	
Lithium	Acute: 0.8-1.2 mmol/l (trough)
	Chronic: 0.6-0.8 mmol/l (trough)
Antiepileptics	
Carbamazepine	4-12 μg/ml (trough before administration)
Phenytoin	10-20 μg/ml (trough before administration)
Free phenytoin	1-2 μg/ml (trough before administration)
Phenobarbital	15-40 μg/ml (trough before administration)
Valproic acid	40-100 μg/ml (trough before administration)
Vancomycin	Trough: 10-20 mg/l

Target levels are dependent on assay methodology and clinical context.
IV, Intravenous.

Clinical Condition of the Patient

The patient's welfare should override theoretical concerns. Higher than recommended doses may be appropriate when there is a strong clinical indication. For example, excessive reduction in initial antibiotic doses based on renal function may be inappropriate in patients with life-threatening infection when the consequences of failed therapy are greater than those of potential toxicity.

METHODS OF DOSE REDUCTION

Loading Doses

For most drugs, steady-state concentrations are achieved after five drug half-lives. Hence, for some drugs, a loading dose is given to reduce time to steady state. Because renal impairment may prolong the half-life, simply reducing drug doses could be a therapeutic error because this would further delay achievement of steady state. The loading dose (milligram/kilogram) is equal to the product of the desired plasma concentration (milligram/milliliter) and V_D (milliliter/kilogram) and is independent of clearance. Provided the desired concentration and V_D are unchanged, loading doses do not require modification in patients with renal impairment. If V_D is altered, especially with hypoproteinemia or fluid overload, the loading dose of drugs with a narrow therapeutic

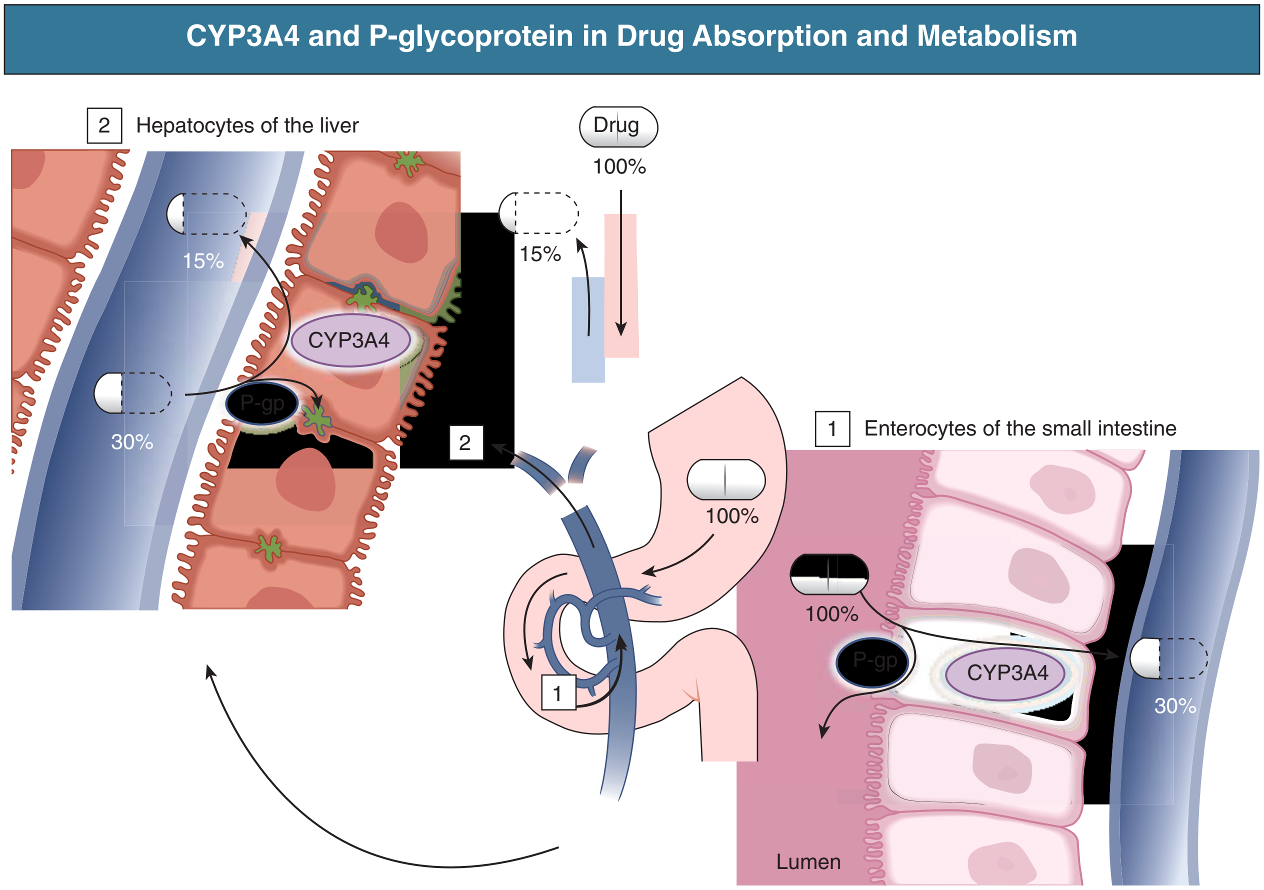
CYP3A4 and P-glycoprotein in Drug Absorption and Metabolism
2 Hepatocytes of the liver
Drug
100%
15%
15%
CYP3A4
P-gp
30%
2
1 Enterocytes of the small intestine
100%
100%
P-gp
CYP3A4
30%
1
Lumen

Fig. 74.4 *CYP3A4* **and P-glycoprotein** *(P-gp)* **in drug absorption and metabolism.** Schema for absorption and metabolism of drugs that are substrates for CYP3A4 and P-gp. Overall, approximately 15% of ingested drug reaches the systemic circulation. *(1)* Enterocyte: P-gp on the apical surface of enterocytes prevents drug absorption, maintaining drug in the gastrointestinal lumen; CYP3A4 in enterocytes metabolizes drug. The net effect is that approximately 30% of ingested drug reaches the portal circulation. *(2)* Hepatocyte: P-gp on the cell surface prevents drug entry into hepatocytes; CYP3A4 in hepatocytes metabolizes the drug. The net effect is that drug entry to the systemic circulation is further reduced.

index such as digoxin may be increased. Aminoglycoside doses may need to be increased in patients with fluid overload or sepsis who have an increased V_D.

Maintenance Doses

When specific pharmacokinetic information is not available, and assuming no change in nonrenal clearance, maintenance doses should be reduced in proportion to the extent of renal impairment and renal drug elimination. For example, if renal function is 50% of normal and the drug is 100% renally excreted, a maintenance dose of 50% is required. If the drug is 50% renally cleared and the patient has 20% renal function, the dose should be 60% of normal. The dose reduction factor is estimated from first principles or the following formula:

$$\text{Fraction of normal renal function dose to use in renal impairment} = 1 - fe(1 - \text{fraction of normal renal function})$$

where *fe* = the fraction of active drug excreted unchanged in urine.

Once a dose reduction factor has been determined, the clinician must decide on a dose reduction method. Two methods are used, either alone or in combination (Fig. 74.5).

Interval Method

Because drug clearance is reduced, a reduction in delivered dose is achieved by administering the same dose less frequently. This method is particularly useful when the size of the dose and peak blood concentrations are important for efficacy (e.g., aminoglycosides). If this method is used, practical dose intervals should be recommended rather than inconvenient or complex intervals.

Dose Method

An alternative method is to administer a smaller dose at the usual interval. This method is common, especially when the size of a dose and peak concentrations are less critical for efficacy. If this method is used, clinicians should consider the availability of smaller dose formulations and the ability of the patient to accurately and safely divide available dosage forms.

Combination Method

Sometimes, especially for drugs with a narrow therapeutic index, for which tight control of concentrations is required (e.g., digoxin), a combination of the dose and interval methods is used.

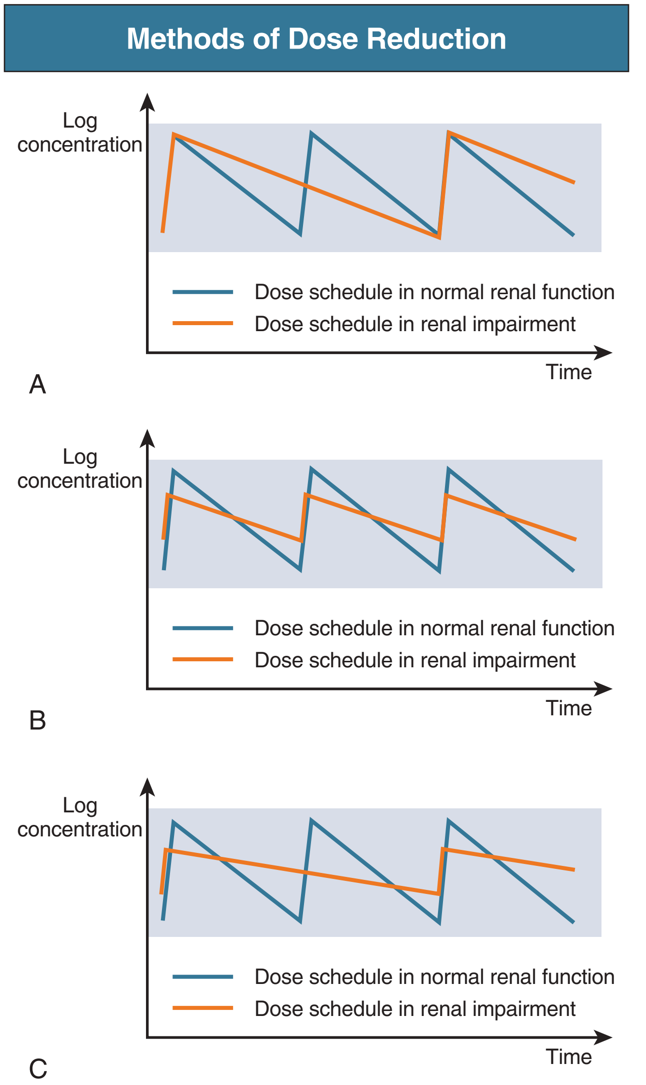

Fig. 74.5 **Methods of dose reduction.** (A) Interval method. (B) Dose method. (C) Combination method.

Ongoing Assessment

Even with appropriate dose modification in patients with renal impairment, clinicians should always remain vigilant and closely monitor the response to therapy to guide dose titration.

Therapeutic Drug Monitoring

Therapeutic drug monitoring can provide objective information to guide dosage calculation and is valuable for drugs such as aminoglycosides, glycopeptides, digoxin, lithium, antiepileptics, and immunosuppressants (see Table 74.1). Assays usually measure total blood concentrations and may significantly underestimate plasma levels of the active or free form of the drug.

Clinical Response

Ultimately, clinical response should influence the need to modify doses. Doses should be carefully titrated according to response and adverse effects. Exemplar measures of response include blood pressure for antihypertensives, blood glucose concentration and hemoglobin A_{1c} (HbA_{1c}) for oral hypoglycemics, and renal function for toxicity from CNIs, ACE inhibitors, and ARBs.

EXTRACORPOREAL DRUG LOSSES

Failure to consider dialysis drug clearance may significantly reduce drug efficacy.[5,7] Alternatively, dialysis may be used in overdose to assist drug removal (see Chapter 98). Studies of drug clearance with RRT modalities have often used variations in dialysis technique that make it difficult to compare results. Many studies before the 1990s report data from standard hemodialysis (HD) with low-flux membranes, which are less efficient at drug removal than the high-flux membranes now widely used. Many recommendations report the need for supplemental doses. Clinically, supplemental doses are rarely used, especially if less than 30% of the drug is cleared or the drug has a wide therapeutic index. Rather, drugs known to be significantly cleared by dialysis should be administered after dialysis (Table 74.7). When drugs are given in multiple daily doses, at least one of the daily doses should be administered soon after the completion of dialysis.

Hemodialysis

HD drug clearance occurs mainly by passive diffusion along a concentration gradient but also by convectional movement of soluble drug with ultrafiltrated plasma water.[7,15] The efficiency of drug removal depends on physiochemical drug properties. As molecular size decreases (<500 d) and water solubility increases, drug removal increases. Conversely, as protein binding and V_D increase, dialysis clearance decreases. HD factors influencing drug removal include membrane type and surface area, blood flow rates, and dialysis frequency and duration. HD can remove drug from plasma faster than it can redistribute from tissue, so drug concentrations determined from samples drawn soon after beginning or completion of HD may be low. Samples should preferably be drawn before dialysis or about 1 to 2 hours after to allow drug redistribution.

Peritoneal Dialysis

Many drug properties that affect removal by HD also apply to peritoneal dialysis (PD), but PD is usually less efficient.[16] For significant removal by peritoneal PD, the drug must have a very low V_D and low protein binding. For most drugs, there is little evidence of significant removal during chronic PD. A few studies have examined drug clearance from automated PD that uses large volumes of short dwells at night, often accompanied by one or more longer daytime dwells. Clearance of some drugs on automated PD is increased because of the increased drug concentration gradient between blood and dialysate. Increased drug dialyzability may occur with increased peritoneal dialysate flow rates or during peritonitis.

Continuous Renal Replacement Therapy

Drug clearance by continuous RRT (CRRT) with hemofiltration, HD, or hemodiafiltration differs from that by intermittent HD.[17] Relying on continuous ultrafiltration of plasma water, CRRT can remove large quantities of ultrafilterable drug. CRRT generally uses membranes with larger pore sizes and involves convective transport of solute. Hence, CRRT allows the passage of larger molecules (up to 5000 d). A large V_D and protein binding still prevents removal by CRRT. Protein binding and the device filtration rate determine the rate of removal. A series of sieving coefficients is available that allows calculation of the amount of drug actually lost if the ultrafiltration flow rate is known.[5] The sieving coefficient is the ratio of drug concentration in the ultrafiltrate to the prefilter plasma water drug concentration. The closer the sieving coefficient is to 1.0, the more it passes across the filter. There are few detailed studies of drug clearance with use of these methods, and clinicians must rely on estimates from HD, known physiochemical properties, and clinical response.

TABLE 74.7 **Dialysis Clearance of Drugs**

Drugs Significantly Cleared by Hemodialysis That Require Administration After Dialysis or a Supplement After Dialysis	Drugs Not Significantly Cleared by Hemodialysis and That Do Not Require Administration After Dialysis or a Supplement After Dialysis or That Must Be Administered at Specific Times Independent of Hemodialysis	Drugs Significantly Cleared by Hemodialysis That Require Administration After Dialysis or a Supplement After Dialysis	Drugs Not Significantly Cleared by Hemodialysis and That Do Not Require Administration After Dialysis or a Supplement After Dialysis or That Must Be Administered at Specific Times Independent of Hemodialysis
Analgesics Morphine 6-glucuronide (in toxicity) Aspirin, high dose (contraindicated) **Antibiotics** Aminoglycosides Amikacin Gentamicin Tobramycin Cephalosporins Cefotaxime Cefazolin Ceftazidime Carbapenems Imipenem Meropenem Metronidazole Penicillins Amoxicillin Ticarcillin Piperacillin Fluoroquinolones Ciprofloxacin Glycopeptides Vancomycin (high-flux dialyzers) Teicoplanin Miscellaneous antibiotics Ethambutol Cotrimoxazole **Antifungal** Fluconazole	**Anemia** Erythropoietins Iron **Analgesics** Paracetamol Fentanyl Oxycodone NSAIDs **Antibiotics** Penicillins Amoxicillin Flucloxacillin Fluoroquinolones Moxifloxacin Rifamycins Rifampin Rifabutin Glycopeptides Vancomycin (oral or "low flux") Tetracyclines Tetracycline Doxycycline Minocycline **Antifungals** Amphotericin Voriconazole Ketoconazole Itraconazole **Antiviral** Amphotericin **Antiepileptic** Carbamazepine	**Antivirals** Acyclovir Cidofovir Famciclovir Foscarnet Ganciclovir Ribavirin Valganciclovir Zidovudine **Antineoplastics** Cyclophosphamide Methotrexate **Anticoagulant** Lepirudin **Antiepileptics** Gabapentin Pregabalin Levetiracetam **Cardiovascular Agent** Sotalol **Antidiabetic** Metformin (in overdose) **Vitamins** Water-soluble B, C, and folate **Psychotropic** Lithium	**Cardiovascular Agents** Amiodarone Perhexiline Nitrates **Anticoagulants** Heparin Warfarin LMWHs **Antiplatelet Drugs** Low-dose aspirin Clopidogrel Dipyridamole **Immunosuppressants** Azathioprine Cyclosporine and tacrolimus Mycophenolate Prednisolone Sirolimus and everolimus T cell–depleting antibodies Rituximab Anti-CD25 antibodies **Antidiabetics** Sulfonylureas **Musculoskeletal Agents** Bisphosphonates **Antiepileptics** Sodium valproate Carbamazepine **Antidepressants** SSRIs (administer in morning) **Vitamins** Fat-soluble vitamins A, D, E, K

LMWHs, Low molecular weight heparins; *NSAIDs,* nonsteroidal antiinflammatory drugs; *SSRIs,* selective serotonin reuptake inhibitors.

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SELF-ASSESSMENT QUESTIONS

1. What percentage of the dose in normal renal function should be given for a hypothetical drug that is 80% renally cleared unchanged in urine to a person with 25% of normal renal function?
   - **A.** 20%
   - **B.** 30%
   - **C.** 40%
   - **D.** 60%
   - **E.** 80%
2. Which of the following factors or drug characteristics does *not* increase the likelihood of drug removal by hemodialysis?
   - **A.** High-flux membranes
   - **B.** Low protein binding
   - **C.** Low volume of distribution
   - **D.** Large molecular weight
3. Which of the following drugs do not require clinically relevant dose modification in renal impairment?
   - **A.** Amoxycillin
   - **B.** Ribavirin
   - **C.** Digoxin
   - **D.** Sotalol
   - **E.** Enoxaparin
4. Which of the following drug combinations are *least* likely to cause clinically significant drug interactions?
   - **A.** Adding clarithromycin to the regimen of a patient on sirolimus
   - **B.** Adding phenytoin to the regimen of a patient on prednisolone
   - **C.** Adding fluconazole to the regimen of a patient on tacrolimus
   - **D.** Adding roxithromycin to the regimen of a patient on cyclosporin
   - **E.** Adding verapamil to the regimen of a patient on everolimus

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Common Issues in Prescribing in Kidney Disease and Renal Replacement Therapy

Matthew J. Cervelli, Graeme R. Russ

Appropriate prescribing for people with kidney disease is underpinned by the principles discussed in Chapter 74. Even experienced physicians will frequently need to check reference sources to be sure of the correct prescribing approach to medications with which they are less familiar. Up-to-date reference databases should be used to inform prescribing in patients with renal impairment, those on dialysis, and after renal transplantation.[1-4] In this chapter, common prescribing issues in such patients are discussed.

ANALGESICS

Various analgesics undergo renal excretion, and dose modification or avoidance is required in people with impaired kidney function.[5] Fear of adverse effects often prevents use of sufficient doses. Adequate initial doses should be followed by careful assessment and dose titration.

Acetaminophen (Paracetamol)

Despite suggestions that acetaminophen is nephrotoxic and is relatively ineffective for pain relief, its lack of platelet inhibition and gastrointestinal effects make it a safer base analgesic in chronic kidney disease (CKD) and renal replacement therapy than nonsteroidal antiinflammatory drugs (NSAIDs) and opioids. Acetaminophen is hepatically metabolized and does not require dose adjustment.

Opioid Analgesics

Opioids have metabolites with variable activity and dependence on renal excretion.[6] Metabolite accumulation prolongs drug action and predisposes to central nervous system (CNS) toxicity (sedation, respiratory depression, confusion, hallucinations, and seizures). Regular opioid use in fluid-restricted renal patients can exacerbate constipation. Opioids should be used cautiously in renal impairment, with adequate doses given to establish control and titrated to the smallest effective dose. Morphine is metabolized to two renally cleared active metabolites (morphine 3-glucuronide and morphine 6-glucuronide) that can accumulate in renal impairment, causing CNS toxicity, respiratory depression, and sedation. Meperidine (pethidine) should be avoided in moderate to severe renal impairment because it is metabolized to a renally cleared metabolite (normeperidine) that can cause CNS toxicity (seizures, myoclonus, opisthotonus, mental state changes, respiratory depression, and psychosis).[7] It should be avoided in moderate to severe renal impairment. Dextropropoxyphene should be avoided because it is metabolized to the renally cleared metabolite norpropoxyphene, which can cause cardiac toxicity. Hydromorphone is metabolized to hydromorphone 3-glucuronide, which has minor activity and does not accumulate substantially. Buprenorphine is metabolized to relatively inactive metabolites, which are excreted in bile, and is relatively safe. Weaker opioids (codeine, dihydrocodeine, and hydrocodone) can still cause CNS and respiratory depression. They should be used cautiously in severe renal impairment. With appropriate titration, alfentanil, fentanyl, sufentanil, methadone, and oxycodone are relatively safer choices because they do not have significantly active metabolites. The partial opioid tramadol is metabolized to a renally cleared active metabolite, *O*-desmethyltramadol whose half-life doubles in renal impairment and predisposes to seizures, respiratory depression, and other CNS adverse effects. In opioid intoxication, naloxone may be used at normal dose for reversal.

Nonsteroidal Antiinflammatory Drugs

The most frequent nephrotoxic effect of NSAIDs is to cause acute renal impairment by preventing renal prostaglandin-mediated afferent arteriolar vasodilation (see Chapter 66). In healthy individuals, cyclooxygenase (COX) inhibition has little effect on renal function. Nephrotoxicity is more likely in those with a high renin state or renal hypoperfusion in whom renal prostaglandins are upregulated and play a supportive role in maintaining glomerular filtration. Combinations of NSAIDs with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, or other antihypertensives increase the potential for nephrotoxicity, and such combinations should be prescribed cautiously. If required, in stable patients with CKD, NSAIDs should be used at the lowest effective dose for the shortest period with monitoring of renal function. Increases in serum potassium and sodium, as well as fluid retention also may occur. NSAIDs (especially fenoprofen) can cause rare idiosyncratic reaction that may present with acute interstitial nephritis or nephrotic syndrome with a glomerular lesion resembling minimal change disease. Because COX-2 is expressed in the kidney, COX-2–selective agents offer no advantage in renal toxicity over nonselective inhibitors.[8] The potential for cardiovascular complications of COX-2 inhibitors is also undesirable in renal patients at high risk for cardiovascular disease.

Drugs for Neuropathic Pain

Low-dose tricyclic antidepressants are used at normal doses, although renal patients may be more sensitive to anticholinergic side effects. Low-dose valproate and carbamazepine are used at normal doses. Extreme caution and dose reductions are required with gabapentin[9] and pregabalin[10] because they are extensively renally cleared and can cause significant CNS adverse effects (somnolence, lethargy, dizziness, myoclonus, and ataxia) and falls.

ANTIMICROBIAL AGENTS

The kidneys excrete many antiinfective agents, and dose reduction is often required in patients with severe renal impairment or who are undergoing extended therapy.[11] However, many other antiinfectives have a wide therapeutic index and dose adjustment is clinically unnecessary despite their reliance on renal excretion. An important principle of antiinfective therapy is to initiate effective drugs at sufficient doses rather than use conservative dose reductions that fail to achieve effective drug concentrations. Normal doses or doses larger than expected based on renal function may be appropriate when treating less susceptible organisms or when drug distribution to the site of infection is reduced (e.g., in meningitis). Severe infection, particularly in severely immunocompromised patients, may require extended therapy. In patients with urinary tract infection (UTI), if glomerular filtration rate GFR is below 30 ml/min and the drug does not undergo tubular secretion, inadequate renal tract concentrations may result and systemic accumulation could lead to toxicity (e.g., nitrofurantoin).

Antibacterials

Aminoglycosides

Aminoglycosides are excreted unchanged by the kidneys and can cause nephrotoxicity and irreversible vestibular and ototoxicity.[12] When use is essential, the total daily dose should be reduced, treatment courses kept to a minimum, and serum concentrations and renal function monitored. Because aminoglycosides undergo tubular secretion, high urine concentrations are achieved even in advanced renal impairment, and lower doses may be appropriate for uncomplicated UTIs.

Aminoglycoside dosage schedules. Despite short half-lives (2 to 3 hours with normal renal function), aminoglycosides are usually given once daily rather than in divided daily doses. This is based on data showing that their action depends on peak concentration and that once-daily regimens have reduced toxicity. The required dose regimen depends on volume of distribution (V_D) and renal clearance. Dosage calculation in renal impairment involves reducing the normal daily dose of 5 to 7 mg/kg for gentamicin and tobramycin or 15 mg/kg for amikacin according to renal function (e.g., with 25% remaining renal function, reduce the total daily dose to 25% of normal). Aminoglycosides should be administered at a minimum effective dose (≥2.5 mg/kg for gentamicin and tobramycin; ≥7.5 mg/kg for amikacin) to achieve target peak serum concentrations (>10 μg/ml for gentamicin and tobramycin; >30 μg/ml for amikacin). The calculated reduced normal daily dose might be lower than the minimum individual dose required to achieve target peak concentrations. If so (e.g., moderate to severe renal impairment), it may be necessary to administer the minimally effective dose at an extended interval (e.g., every 36 or 48 hours) rather than reducing the size of the individual dose.

Aminoglycoside concentration monitoring. Because of toxicity and pharmacokinetic variability in patients with infection and renal impairment, monitoring is essential to guide aminoglycoside dosing particularly when therapy is initiated or significant changes occur in renal function or clinical condition. Routine monitoring is not required for short treatment (<48 hours). Graphic methods using a single-point concentration 6 to 14 hours after administration are valid only with relatively normal renal function. They do not provide information on attainment of peak concentrations and are not recommended in patients with renal impairment. Trough concentrations can be measured but must be interpreted in the context of the time after the dose when the sample was drawn. Trough monitoring does not provide information on the attainment of peak concentrations. Some patients, especially those with severe sepsis and renal impairment, may have altered (usually higher) V_D, which results in lower peak concentrations. Measuring peak concentrations (30 minutes after dosing) is the only certain way to determine dose adequacy. Combining peak and trough monitoring provides information on both V_D and clearance and can therefore be used to determine both the size of individual doses and the administration interval. Provided the relationship between the time of administration and blood sampling is known, simple dose modifications are made on first principle estimates (see Chapter 74). Peak and trough target levels for aminoglycosides are shown in Table 74.6.

Carbapenems. Ertapenem, doripenem, imipenem, and meropenem are significantly excreted in urine but with appropriate dose modification can be used safely. Imipenem can cause significant neurotoxicity (myoclonic activity, seizures, and confusion), especially in high doses in those with underlying CNS disorders or renal impairment. Imipenem is inactivated by renal dehydropeptidase 1 and is combined with cilastatin to prevent this.

Cephalosporins. Although most cephalosporins are predominantly renally cleared, their relative safety means that normal doses are used for most short-course therapies even in dialysis patients (e.g., ceftriaxone, cefaclor, and cephalexin). High-dose parenteral therapy and prolonged courses of some agents require dose reduction in severe impairment (e.g., cefepime, cefotaxime, ceftazidime, cefoxitin, and cefazolin). Therapeutic concentrations of cefazolin are maintained after doses of 20 mg/kg after dialysis three times weekly.[13] Some cephalosporins (e.g., cefoxitin) cause a creatinine-like reaction in assays based on the picrate method, which can falsely elevate serum creatinine.[14]

Fluoroquinolones. Renal excretion is significant with ciprofloxacin, norfloxacin, and gatifloxacin, and doses are reduced if GFR is below 30 ml/min.[15] Moxifloxacin is 20% renally excreted, and dose reduction is not required. Norfloxacin is well secreted by kidneys and useful in UTIs. Quinolones are generally well tolerated but can cause CNS effects (headache, dizziness, insomnia, depression, restlessness, and tremors), interstitial nephritis, musculoskeletal effects (tendonitis and arthralgias), and crystalluria. Quinolones should be administered at least 1 hour before or 2 hours after meals and metallic phosphate binders, which reduce absorption.

Glycopeptides. Glycopeptides (vancomycin and teicoplanin) have extensive renal excretion. Because of potential nephrotoxicity and ototoxicity, dose modification is essential even in mild to moderate impairment. Nephrotoxicity is greater in those with renal impairment, prolonged therapy, high doses (typically vancomycin trough levels >40 μg/ml), and concomitant nephrotoxins. Ototoxicity may involve sensorineural deafness and tinnitus and is more likely with previous auditory compromise or impaired renal function. Rapid infusion also can cause an erythematous anaphylactoid-like reaction involving the upper body (red man syndrome) that resolves with slowing of the infusion and administration of antihistamine agents. If glycopeptide use is essential, duration of therapy should be minimized with regular monitoring of serum concentrations and renal function. Glycopeptides demonstrate time-dependent antibacterial activity, so doses should be repeated once serum concentrations have fallen below minimum inhibitory concentrations. In dialysis patients, single doses (e.g., 1 g) of vancomycin can maintain therapeutic concentrations (>15 μg/ml) for 3 to 5 days.[16] Vancomycin is removed more extensively with high-flux than with low-flux dialysis membranes.

Lincosamides. Lincosamides (e.g., clindamycin and lincomycin) are relatively safe and are not significantly excreted by the kidneys.

Macrolides. Macrolides are mostly hepatically cleared, and dose modifications are usually not required even in end-stage renal disease. Dose reduction is required with high-dose or intravenous erythromycin, which may prolong QT interval and cause ototoxicity. Various macrolides are potent inhibitors of cytochrome P450 (CYP)3A4 and P-glycoprotein, so there may be major interactions with and increased exposure to coadministered drugs that rely on CYP3A4- or P-glycoprotein–mediated absorption and metabolism (cyclosporine, tacrolimus, sirolimus, everolimus, and statins). Erythromycin and clarithromycin are the most potent inhibitors. Roxithromycin is a much weaker inhibitor causing few or no significant interactions. Azithromycin does not significantly inhibit CYP3A4 or P-glycoprotein.

Penicillins. Most penicillins have a short half-life and are rapidly eliminated by renal filtration and secretion. Most have a relatively wide therapeutic window and are used at normal doses for short courses of oral therapy (e.g., amoxicillin). High-dose parenteral therapy or prolonged high-dose oral therapy may require dose reduction to prevent electrolyte disturbances and neurotoxicity in advanced renal failure. Because most penicillins exert little or no postantibiotic effect, the amount of time above the minimum inhibitory concentration is more important than the maximum concentration. Severe reductions in frequency of administration are not advised. Dose reduction of ticarcillin-clavulanate and piperacillin is advised.

Rifamycins. Rifamycins are mainly hepatically metabolized and used at normal doses. Orange-red coloration of body fluids (e.g., urine and peritoneal dialysis [PD] fluid) is common. Infrequently, these agents cause hepatotoxicity and blood dyscrasias. Rifampin is a potent enzyme inducer and significantly increases metabolism of drugs, including immunosuppressants such as corticosteroids. Rifabutin does not induce CYP450 enzymes to the same extent.

Tetracyclines. Tetracycline depends more on renal excretion than doxycycline or minocycline. In renal impairment, tetracycline should be avoided because it is catabolic causing uremia, hyperphosphatemia, and metabolic acidosis; it also may aggravate preexisting renal failure.[17] Doxycycline, minocycline, and tigecycline may be used as usual. Outdated (degraded) tetracycline (anhydro-4-epitetracycline) may result in renal tubular damage and a Fanconi-like syndrome.

Sulfonamides and trimethoprim. Sulfonamides are eliminated by acetylation followed by renal excretion. Acetylated metabolites may cause crystalluria and tubular damage. Sulfamethoxazole and trimethoprim display similar renal excretion except at extremes of urine pH. Alkaline urine promotes sulfamethoxazole excretion, whereas acidic urine promotes trimethoprim excretion. Both accumulate in renal impairment, and dose reduction is advisable except perhaps in the initial treatment of *Pneumocystis jiroveci* infection, in which the risk for toxicity is balanced against the seriousness of infection. Trimethoprim inhibits tubular secretion of creatinine, resulting in a reversible increase in serum creatinine[18] that can be misinterpreted as nephrotoxicity.

Other antibiotics. Linezolid is used at a normal dose. Metronidazole has a partially active, renally cleared metabolite, although only 15% of the parent drug is renally cleared. It is usually given in usual doses or reduced to twice-daily doses with dialysis.

Antimycobacterials

Antimycobacterial treatment (see also Chapter 52) requires dose modification according to renal function and avoidance of drug interactions.[19] Dose reduction with ethambutol (80% renally cleared) is essential to avoid visual toxicity. Isoniazid, pyrazinamide, and rifampin-rifabutin can be given in usual doses. Rifampin causes induction of hepatic enzymes and severe drug interactions with transplant immunosuppressants. Amikacin, kanamycin, streptomycin, capreomycin, and gatifloxacin have extensive renal clearance, are nephrotoxic, and require significant dose reduction.

Antifungals

Amphotericin. Amphotericin use is limited by nephrotoxicity (see Chapter 53). Nephrotoxicity with crystalline amphotericin may be minimized with prehydration and administration by continuous infusion. Liposomal formulations have fewer infusion-related problems and are less nephrotoxic but more expensive. Oral amphotericin is not absorbed and does not contribute to nephrotoxicity.

Azole antifungals. Most azole antifungals (ketoconazole, itraconazole, and voriconazole) are extensively metabolized and do not require dose reduction. Fluconazole is renally excreted; after an adequate loading dose, maintenance doses should be reduced in moderate to severe renal impairment, and it should be given after dialysis. Fluconazole is significantly excreted in urine and preferred for fungal UTIs. The manufacturer recommends avoiding intravenous voriconazole in severe renal impairment because of possible accumulation of the intravenous vehicle (sulfobutyl betadex sodium). Voriconazole, ketoconazole, and itraconazole are potent inhibitors of CYP3A4 and P-glycoprotein that are involved in the metabolism and absorption of a variety of drugs, including cyclosporine, tacrolimus, sirolimus, everolimus, and statins. A 2- to 10-fold reduction of the concomitant drug may be required with drug monitoring. Interactions between ketoconazole and calcineurin inhibitors (CNIs) or mammalian target of rapamycin (mTOR) inhibitors have been exploited as a cost-reducing immunosuppressant-sparing strategy. Increased exposure to statins (except pravastatin) increases the risk for rhabdomyolysis-induced renal impairment. Fluconazole is a weak enzyme inhibitor, and although caution should be exercised, the need for preemptive dose reduction of concomitant drugs is less certain. Topical azoles, including bifonazole, clotrimazole, econazole, ketoconazole, tinidazole, and miconazole, are minimally absorbed and do not cause interactions.

Other antifungals. Absorption of nystatin from topical and oral preparations is minimal and safe in renal impairment. Terbinafine is hepatotoxic, and a 50% dose reduction is suggested in moderate to severe renal impairment. Griseofulvin and caspofungin can be given in usual doses. Flucytosine has extensive renal clearance and requires significant dose reduction.

ANTIVIRALS

Many antivirals (or their active metabolites) have extensive renal excretion and can cause nephrotoxicity (see also Chapter 66).

Guanine Analogues

Acyclovir, its prodrug valacyclovir, and famciclovir have extensive renal clearance and can crystallize in tubules, causing obstructive nephropathy, especially when given intravenously. High concentrations cause severe CNS toxicity (cerebral irritation, ataxia, and myoclonus). Ganciclovir and its prodrug valganciclovir have extensive renal clearance,[20] and accumulation leads to severe bone marrow toxicity. Dose reduction based on renal function is essential, even in mild renal impairment. These agents are freely dialyzed and should be given after hemodialysis (HD).

Hepatitis B and C

Pegylated interferon alfa-2a has a larger metabolic clearance than pegylated interferon alfa-2b, which has higher renal clearance and requires dose reduction in renal impairment. Interferons can upregulate cell surface expression of class II histocompatibility antigens, which increases the potential for transplant rejection. Ribavirin and its metabolites rely on renal excretion; accumulation causes severe anemia, making it contraindicated if GFR is below 50 ml/min; significantly reduced doses are sometimes used in lower levels of GFR. Newer direct-acting antivirals for hepatitis C (boceprevir, daclatasvir, ledipasvir, sofosbuvir, ombitasvir, partitaprevir, ritonavir, dasabuvir, simeprevir, telaprevir) are less dependent on renal excretion and may be preferable in patients with renal impairment. Adefovir, entecavir, lamivudine, and telbivudine have extensive renal excretion, and significant dose reduction is essential.

Neuraminidase Inhibitors

Oseltamivir is converted by hepatic esterases to its active metabolite, oseltamivir carboxylate, which is extensively (99%) renally cleared through filtration and secretion.[21] The area under the curve (AUC) is increased 10-fold in severe renal impairment, and, although the drug is well tolerated, dose reduction is recommended. Despite intravenous doses showing significant reliance of zanamivir on renal clearance, dose modification is not necessary because bioavailability from inhaled doses is approximately 2% and high intravenous doses are well tolerated.

Other Antivirals

Cidofovir and foscarnet have extensive renal clearance and require dose reduction in renal impairment. Both are nephrotoxic, require close monitoring of renal function, and should be administered with hydration. Cidofovir is often administered with probenecid to slow renal secretion and minimize nephrotoxicity. Agents active against HIV infection are also discussed in Chapter 56.

IMMUNOSUPPRESSANTS

Dosing of immunosuppressive agents used in renal transplantation as well as adverse effects are discussed in Chapter 102. Initial and maintenance doses in individuals are highly variable and depend on local protocol, concomitant therapy, rejection risk, drug concentrations, and response. Immunosuppression is required for the life of the transplant and should never be withheld except in exceptional circumstances (life-threatening infection or malignancy). Regimens should preferably be limited to convenient twice-daily schedules. In practice, the precise timing of doses or intake relative to time and food is not as important as consistency in relation to time and food because doses can be titrated to levels and response. Most immunosuppressants are hepatically metabolized and do not require dose modification based on altered excretion in renal impairment.

Immunosuppressants are prone to a range of significant drug interactions, which should be considered whenever a patient receiving these agents has a change in drug regimen. Significant interactions also can occur with "natural" or "herbal" medicines (e.g., St John's wort; see also Chapter 76). If these products are deemed essential, it is advisable to monitor response, renal function, blood counts, and serum drug concentrations regularly. Therapeutic monitoring is recommended for several immunosuppressants[22] (tacrolimus, cyclosporine, everolimus, sirolimus, and mycophenolate). Target levels should be interpreted in the context of patient response, immunosuppressive regimen, time after transplantation, and assay methodology.[23]

Calcineurin Inhibitors

CNIs are extensively metabolized to inactive metabolites. A major adverse effect of CNIs is nephrotoxicity (acute and chronic),[24] and regular assessment of renal function is essential. Nephrotoxicity may increase with concurrent use of mTOR inhibitors. Early detection of CNI nephrotoxicity on biopsy assists in planning maintenance therapy (see Chapters 102 and 105). Lower doses or temporary withdrawal may be used when CNIs have caused or are likely to cause nephrotoxicity (e.g., delayed graft function). Calcium channel blockers (CCBs) and blockade of the renin-angiotensin system may both reduce CNI nephrotoxicity. CNIs are substrates of P-glycoprotein and CYP3A4. Drugs that inhibit or compete as substrates for these enzymes can increase absorption and reduce metabolism of CNIs, causing increased serum concentrations and adverse effects. Drugs that induce these enzymes can reduce absorption and increase metabolism of CNIs, causing reduced serum concentrations, and increase the risk for rejection (Table 75.1). Tacrolimus trough concentrations (C_0) show good correlation with drug exposure (AUC) and are used to monitor therapy. Clinically, a combination of C_0 (trough), C_2 (concentration 2 hours after dose), and $AUC_{0\text{-}4}$ (multipoint AUC, 0 to 4 hours) is used to measure cyclosporin. Different assay methodologies (high-performance liquid chromatography [HPLC] and immunoassays) have differing abilities to detect parent compound from metabolites. Specific HPLC methods are recommended, and results from different laboratories may not be interchangeable.

Corticosteroids

Corticosteroids are predominantly cleared by hepatic metabolism to inactive metabolites. Dose modification based on renal function is not required.

Antiproliferative and Cytotoxic Agents

Various antiproliferative and cytotoxic agents are used to prevent rejection (azathioprine and mycophenolate) and in patients with autoimmune and inflammatory renal disorders (azathioprine, cyclophosphamide, chlorambucil, methotrexate, and mycophenolate). Their primary dose-limiting toxicity is bone marrow suppression, which is exacerbated by combined use with other bone marrow suppressants (e.g., ganciclovir, cotrimoxazole, and mTOR inhibitors). Regular blood monitoring is needed to guide dosage. Methotrexate relies on renal clearance and should be avoided or used cautiously at a reduced dose. Renal clearance is significant with cyclophosphamide (which also causes hemorrhagic cystitis) and chlorambucil, and dose modifications are required. Allopurinol significantly interferes with metabolism of the active metabolite of azathioprine (6-mercaptopurine), and coprescription can lead to life-threatening bone marrow suppression. The combination should be avoided by exchanging azathioprine with mycophenolate or by significant (75%) dose reduction of azathioprine or mercaptopurine.

mTOR Inhibitors

Although not nephrotoxic when used alone, mTOR inhibitors (sirolimus, everolimus) can potentiate the nephrotoxicity of CNIs. mTOR inhibitors are almost entirely hepatically metabolized to essentially inactive metabolites. Dosage is independent of renal function and based on response, serum drug levels, and specific toxicities (especially hematologic and lipids). mTOR inhibitors are substrates of CYP3A4 and P-glycoprotein and susceptible to the same drug interactions as CNIs (Table 75.2). Bone marrow toxicity (neutropenia, anemia, and thrombocytopenia) is increased when they are used in combination with other myelosuppressants (azathioprine, mycophenolate, ganciclovir, and cotrimoxazole). Trough levels show good correlation with drug exposure (AUC) and are used to monitor therapy. Different assay methodologies (HPLC vs. immunoassays) vary in their ability to detect parent drug from metabolites. Specific HPLC methods are recommended, and results from different laboratories or methods may not be interchangeable.

Immunosuppressant Antibodies

Antibodies used for immunosuppression include T cell–depleting antibodies (antithymocyte globulin, anti–interleukin-2 receptor (CD25) antibodies (basiliximab and daclizumab), and B cell–depleting antibodies (rituximab) (see Chapter 102). Dosage is independent of renal function, and these agents should be administered after plasma exchange[25] to avoid drug removal. They are not removed by HD.

ANTICOAGULANTS, ANTIPLATELET AGENTS, THROMBOLYTICS, AND HEMOSTATICS

The risk for bleeding with anticoagulants, antiplatelet agents, thrombolytics, and hemostatics is generally increased in patients with CKD.[26]

Unfractionated Heparin

Unfractionated heparin (UFH) clearance occurs by a rapid saturable mechanism of the endothelium and reticuloendothelial system and a slower nonsaturable mechanism through the kidneys. Half-life is slightly prolonged (1.5-fold) in renal impairment, especially at higher doses.

TABLE 75.1 Common Drug Dosing Recommendations in Renal Impairment and Transplant

	PREDOMINANT ELIMINATION PATHWAY			
Drugs	**Hepatic**	**Renal**	**Dosing Recommendations**	**Comments**
Analgesics				
Simple analgesics	Acetaminophen		Normal dosing	
Opioids		Morphine	Avoid/dose reduction	Renally cleared metabolites
		Pethidine	Avoid	Renally cleared metabolites
	Fentanyl		Cautious normal doses	
	Oxycodone		Cautious normal doses	
	Hydromorphone		Cautious normal doses	
	Methadone		Cautious normal doses	
	Tramadol	Tramadol	Cautious dose reduction	
NSAIDs			Avoid if possible	Potential Nephrotoxicity
Neuropathic pain		Gabapentin	Significant dose reduction	CNS adverse effects
		Pregabalin	Significant dose reduction	CNS adverse effects
	Low-dose TCAs		Normal dose	
	Carbamazepine		Normal dose	
	Valproate		Normal dose	
Anti-infectives				
Aminoglycosides		Amikacin	Avoid/dose reduction	Nephrotoxicity
		Gentamicin	Avoid/dose reduction	Nephrotoxicity
		Tobramycin	Avoid/dose reduction	Nephrotoxicity
Carbapenems		Ertapenem	Dose reduction	
		Doripenem	Dose reduction	
		Imipenem	Dose reduce	
Cephalosporins		Cephalexin	Normal dose	
		Cefotaxime	Dose reduction	
		Ceftazidime	Dose reduction	
	Ceftriaxone		Normal dose	
Fluoroquinolones		Ciprofloxacin	Dose reduction in severe impairment	PO_4 binders may impair absorption
		Norfloxacin	Dose reduction in severe impairment	PO_4 binders may impair absorption
	Moxifloxacin		Normal dose	
Glycopeptides		Vancomycin	Avoid/dose reduction	Nephrotoxicity and ototoxicity
		Teicoplanin	Avoid/dose reduction	Nephrotoxicity and ototoxicity
Macrolides	Azithromycin		Normal dose	
	Roxithromycin		Normal dose	
	Clarithromycin		Normal dose	Significant CYP3A4 interactions
		Erythromycin	Dose reduction	Significant CYP3A4 interactions
Penicillins		Amoxycillin	Normal dose	
Sulfonamides and trimethoprim			Reduce high doses	Falsely elevates creatinine
Tetracyclines		Tetracycline	Avoid	
	Doxycycline		Normal dose	
	Minocycline		Normal dose	
Antimycobacterials		Ethambutol	Dose reduction	
	Isoniazid		Normal dose	
	Pyrazinamide		Normal dose	
	Rifampicin		Normal dose	Significant CYP3A4 interactions
Azole antifungals		Fluconazole	Reduce maintenance doses	
	Ketoconazole		Normal dose	Significant CYP3A4 interactions
	Itraconazole		Normal dose	Significant CYP3A4 interactions
	Voriconazole		Normal dose	Significant CYP3A4 interactions
Other antifungals		Terbinafine	Dose reduction maintenance doses	
	Griseofulvin		Normal dose	
	Caspofungin		Normal dose	

TABLE 75.1 Common Drug Dosing Recommendations in Renal Impairment and Transplant—cont'd

	PREDOMINANT ELIMINATION PATHWAY			
Drugs	**Hepatic**	**Renal**	**Dosing Recommendations**	**Comments**
Guanine analogues		Acyclovir	Dose reduction	CNS and nephrotoxicity
		Famciclovir	Dose reduction	CNS and nephrotoxicity
		Valaciclovir	Dose reduction	CNS and nephrotoxicity
		Ganciclovir	Dose reduction	Hematologic toxicity
Other antivirals		Ribavirin	Avoid/dose reduction	Hematologic toxicity
		Entecavir	Avoid/dose reduction	
Neuraminidase inhibitors		Oseltamivir	Dose reduction	
Other Antivirals		Cidofovir	Significant dose reduction	Nephrotoxic
		Foscarnet	Significant dose reduction	Nephrotoxic
Immunosuppressants				
Calcineurin inhibitors	Cyclosporin		Normal dose	Nephrotoxic
	Tacrolimus		Normal dose	Nephrotoxic
mTOR Inhibitors	Sirolimus		Normal dose	
	Everolimus		Normal dose	
Antiproliferatives	Azathioprine		Normal dose	
	Mycophenolate		Normal dose	Hematologic toxicity
		Cyclophosphamide	Dose reduction	
Anticoagulants, Antiplatelet Agents, Thrombolytics, and Hemostatics				
Unfractionated heparin (UFH)	UFH	UFH	Dose reduction	
Low molecular weight heparins		Enoxaparin	Dose reduction	Bleeding risk
		Dalteparin	Dose reduction	
Anticoagulants	Warfarin		Avoid/normal dose	May promote vascular calcification
		Bivalirudin	Avoid/dose reduction	Bleeding risk
		Danaparoid	Avoid/dose reduction	
		Fondaparinux	Avoid/dose reduction	
		Lepirudin	Avoid/dose reduction	
		Ximelagatran	Avoid/dose reduction	
		Melagatran	Avoid/dose reduction	
Antiplatelets		Aspirin	Normal dose	
		Clopidogrel	Normal dose	
		Dipyridamole	Normal dose	
Cardiovascular Drugs				
Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers			Titrate according to renal function and serum potassium	Potential nephrotoxicity Potential hyperkalemia
β-Blockers		Atenolol	Dose reduction	
		Sotalol	Dose reduction	
	Carvedilol		Normal dose	
	Labetalol		Normal dose	
	Metoprolol		Normal dose	
	Pindolol		Normal dose	
	Propranolol		Normal dose	
Calcium channel blockers	Amlodipine		Normal dose	
	Nifedipine		Normal dose	
	Lercanidipine		Normal dose	
	Verapamil		Normal dose	Significant CYP3A4 interactions
	Diltiazem		Normal dose	Significant CYP3A4 interactions

Continued

TABLE 75.1 Common Drug Dosing Recommendations in Renal Impairment and Transplant—cont'd

	PREDOMINANT ELIMINATION PATHWAY			
Drugs	**Hepatic**	**Renal**	**Dosing Recommendations**	**Comments**
Antianginals	Nitrates		Normal dose	
	Nicorandil		Normal dose	
	Perhexiline		Normal dose	
Statins	Atorvastatin		Normal dose	
	Rosuvastatin		Normal dose	
	Simvastatin		Normal dose	
		Pravastatin	Normal dose	
Fibrates		Fenofibrate	Dose reduction	
Antiarrythmics		Digoxin	Reduce dose with monitoring	Bradycardia
		Disopyramide	Dose reduction	
		Procainamide	Dose reduction	
	Amiodarone		Normal dose	
	Flecainide		Normal dose	
	Mexiletine		Normal dose	
Diuretics		Furosemide	Dose increase	
		Spironolactone	Avoid	Hyperkalemia
Diabetes				
Insulins		Insulin	Cautious dose titrations	
Biguanides		Metformin	Avoid	Lactic acidosis
Sulfonylureas	Gliclazide		Normal doses	
	Glibenclamide		Avoid/dose reduction	Active metabolites
	Glipizide		Avoid/dose reduction	Active metabolites
Thiazolidinediones	Pioglitazone		Avoid	
	Rosiglitazone		Avoid	
Gastrointestinal				
H_2-Antagonists		Ranitidine	Normal dose	
	Cimetidine		Avoid	Significant drug interactions
Proton Pump Inhibitors	Lansoprazole		Normal dose	Acute interstitial nephritis may occur (see Chapter 60)
	Esomeprazole		Normal dose	
	Pantoprazole		Normal dose	
	Omeprazole		Normal dose	
Dopamine antagonists	Domperidone		Normal dose	Extrapyramidal and CNS effects at high dose with renal impairment
	Metoclopramide		Normal dose	
	Prochlorperazine		Normal dose	
5-HT_3 antagonists	Ondansetron		Normal dose	
	Dolasetron		Normal dose	
	Tropisetron		Normal dose	
Aperients and laxatives	Low potency:			Fluid and electrolyte disturbances
	Docusate		Normal dose	
	Bisacodyl		Normal dose	
	Lactulose		Normal dose	
	Sorbitol		Normal dose	
	High potency, including phosphate containing		Avoid	
Antidiarrheal agents	Loperamide		Normal dose	
	Diphenoxylate		Normal dose	
	Atropine		Normal dose	

TABLE 75.1 Common Drug Dosing Recommendations in Renal Impairment and Transplant—cont'd

	PREDOMINANT ELIMINATION PATHWAY			
Drugs	**Hepatic**	**Renal**	**Dosing Recommendations**	**Comments**
Musculoskeletal				
Gout		Allopurinol	Reduce dose	Active metabolite
	Febuxostat		Normal dose	
Bisphosphonates		Alendronate	Normal or reduced dose	Avoid in adynamic bone disease
		Risedronate	Normal or reduced dose	
		Pamidronate	Normal or reduced dose	Rapid IV doses may be nephrotoxic
Central Nervous System–Acting Drugs				
Antiepileptics		Levetiracetam	Reduce dose	
	Valproate		Normal dose	
	Phenytoin		Normal dose with monitoring	Significant CYP3A4 interactions
	Carbamazepine		Normal dose	Significant CYP3A4 interactions
Selective serotonin uptake inhibitors	Citalopram		Normal dose	
	Paroxetine		Normal dose	
	Venlafaxine		Normal dose	
Antipsychotics	Olanzapine		Normal dose	
	Risperidone		Normal dose	
	Clozapine		Normal dose	
Benzodiazepines	Oxazepam		Normal dose	Enhanced CNS toxicity
	Clonazepam		Normal dose	Enhanced CNS toxicity
	Temazepam		Normal dose	Enhanced CNS toxicity
	Diazepam		Normal dose	Enhanced CNS toxicity

CNS, Central nervous system; *TCAs,* tricyclic antidepressants.

However, UFH is used at normal dose with titration based on activated partial thromboplastin time monitoring. In some centers, UFH is preferred in severe renal impairment because its effect is shorter and more easily measured and reversed.

Low Molecular Weight Heparins

Low molecular weight heparins (LMWHs) rely more on renal clearance than UFH and in moderate to severe renal impairment they accumulate, increasing the risk for serious bleeding. Consideration should be given to the use of UFH in this setting. If prolonged treatment doses of LMWHs are used, doses should be reduced and, if possible, anti-Xa activity measured to guide therapy.

Other Parenteral Anticoagulants

Other parenteral anticoagulants that accumulate in renal impairment and that should be avoided or used with significant dose reduction include bivalirudin, danaparoid, fondaparinux, lepirudin, ximelagatran, and melagatran. Argatroban may be used at normal dose. Prostacyclin, used to prevent platelet aggregation in HD circuits, is rapidly hydrolyzed and not affected by renal impairment.

Oral Anticoagulants

The liver extensively metabolizes warfarin, and in renal impairment it is usually commenced at normal dose and titrated according to the international normalized ratio. Warfarin is highly protein bound, and with hypoalbuminemia there may be increased sensitivity to warfarin. Similarly, hepatic metabolism may be altered with renal impairment increasing sensitivity. Warfarin promotes vascular calcification and should be avoided in patients with advanced CKD unless absolutely necessary (e.g., those with a mechanical heart valve). Newer oral anticoagulants (rivaroxaban, dabigatran, and to a lesser extent apixaban) are partially dependent on renal clearance. Dose modifications are recommended in moderate renal impairment and contraindicated by the manufacturer in dialysis patients.

Antiplatelet Drugs

Commonly prescribed doses of oral antiplatelet drugs (aspirin, clopidogrel, and dipyridamole) do not require adjustment, although patients are often more prone to bleeding. Despite their efficacy in patients with reduced renal function, eptifibatide and tirofiban are renally excreted and have been associated with bleeding in this setting. Abciximab is cleared by platelet binding and is not associated with increased bleeding risk in patients with renal impairment.

Thrombolytics

Streptokinase, anistreplase, and alteplase are used as normal, but the high risk for hemorrhage should be considered. Urokinase is also used to unclot dialysis catheters.

Hemostatics

Tranexamic acid requires dose reduction in moderate to severe renal impairment. Protamine and vitamin K are used as normal, as are fresh-frozen plasma and whole blood with critical bleeding.

DIURETICS

Diuretics must reach the renal tubule lumen unbound to exert an effect.[27] Pharmacokinetic and pharmacodynamic properties of diuretics can

TABLE 75.2 Common CYP3A4/P-gp–Mediated Interactions With Transplant Immunosuppressants (Cyclosporine, Tacrolimus, Sirolimus, and Everolimus)

Drug Class	Examples	Relative Potency
Drugs That Inhibit CYP3A4 and P-gp		
Macrolide antibiotics	Azithromycin	–
	Clarithromycin	+++
	Erythromycin	+++
	Roxithromycin	+
Azole antifungals	Fluconazole	+/–
	Itraconazole	++
	Ketoconazole	+++
	Voriconazole	+++
Calcium channel blockers	Amlodipine	+
	Nifedipine	+/–
	Felodipine	+/–
	Diltiazem	++
	Verapamil	+++
Herbals, foods	Grapefruit juice	++
Drugs That Induce CYP3A4 and P-gp		
Antiepileptics	Carbamazepine	++
	Phenytoin	+++
	Phenobarbitone	++
Antibiotics	Rifampin	+++
Herbals, foods	St John's wort	+++

P-gp, P-glycoprotein.

change with proteinuria or renal impairment, usually causing a resistance to their effect. Diuretics in the immediate posttransplant setting may increase urine flow in native kidneys, giving a false appearance of transplant function.

Thiazide Diuretics

Thiazide diuretics (chlorthalidone, hydrochlorothiazide, and indapamide) generally become ineffective as diuretics when GFR is below 30 ml/min, although they may augment the effectiveness of a loop diuretic and retain their antihypertensive effects. Metolazone can maintain efficacy at a lower GFR.

Loop Diuretics

Loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) remain effective at low GFR and are generally preferred in patients with renal impairment, although higher doses are usually required.

Potassium-Sparing Diuretics

Potassium-sparing diuretics are the least effective diuretics and should be used cautiously in moderate to severe renal impairment because of the risk for hyperkalemia.

ANTIHYPERTENSIVES

Antihypertensives should be used cautiously to avoid renal hypoperfusion.[28] Hypotension during HD may require that doses be withheld or delayed on dialysis days.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Although various ARBs and the active metabolites of ACE inhibitors are renally excreted, they can be used effectively in CKD if initiated at moderate doses and titrated to response, renal function, and serum potassium level. An increase in serum creatinine (up to 20% to 30% in the first 2 months) may be associated with blood pressure response. All ACE inhibitors and ARBs can cause acute renal impairment by inhibiting angiotensin II–mediated homeostatic vasoconstriction of the efferent renal arteriole during renal hypoperfusion (e.g., with dehydration, hypotension, blood loss, and infection) or preexisting renal impairment (see also Chapter 66). Nephrotoxicity is more likely with coadministration of drugs that reduce renal perfusion, including diuretics, antihypertensives, and NSAIDs.[29] Hyperkalemia is more likely in those with renal impairment and those taking potassium-sparing diuretics or supplements. ACE inhibitors or ARBs also can worsen anemia by reducing erythropoietin production.

β-Blockers

Most β-blockers (carvedilol, labetalol, metoprolol, pindolol, and propranolol) are hepatically metabolized and used at normal doses. Sotalol and atenolol rely on renal clearance, and dose reductions are generally required. β-Blockers may slightly elevate serum potassium.

Calcium Channel Blockers

Pharmacokinetics of CCBs are essentially unaltered in renal impairment. These drugs are generally well tolerated and used in normal doses. Dihydropyridine CCBs can cause significant edema, which can aggravate the edema of renal impairment. To varying extents, CCBs inhibit CYP3A4 and P-glycoprotein, causing increased absorption and reduced elimination of various substrate drugs, including CNIs and mTORs. Verapamil and diltiazem are moderately potent inhibitors, and dose modification of the concomitant drug is required. This interaction has been exploited so that diltiazem and often other CYP3A4 and P-glycoprotein inhibitors are used as immunosuppressant-sparing agents.[30] Other CCBs do not usually cause clinically significant interactions.

Other Antihypertensives

Methyldopa, clonidine, prazosin, terazosin, doxazosin, and minoxidil are renally cleared but can be initiated and titrated at conventional dosage. They are often associated with a higher incidence of adverse effects in patients with renal impairment. In particular, minoxidil is relatively contraindicated in CKD because it can lead to volume expansion with the development of pericardial and pleural effusions; when used, additional diuretic therapy may be required. α-Blockers cause profound orthostatic hypotension. Nitroprusside must be used cautiously because the toxic metabolite thiocyanate may accumulate with renal impairment but is hemodialyzable.

ANTIANGINAL AGENTS

Most antianginals (nitrates, CCBs, nicorandil, and perhexiline) can be used as normal.

ANTIARRHYTHMICS

Various antiarrhythmics (digoxin, flecainide, disopyramide, procainamide, and sotalol) rely on renal excretion and require dose modification. Digoxin has significant renal excretion and a narrow therapeutic window, so dose reduction is essential even in mild renal impairment. Because of reduced tissue protein binding and V_D, some physicians use a smaller loading dose of digoxin than in patients with normal renal function. Cautious monitoring and titration can prevent accumulation and toxicity. When possible, monitoring of antiarrhythmic drug concentrations and the electrocardiogram is recommended. Other agents (amiodarone, flecainide, metoprolol, mexiletine, and verapamil) are used at normal doses.

LIPID-LOWERING AGENTS

Bile Acid–Binding Resins

Bile acid–binding resins are now rarely used, and the large fluid volumes required to administer them limit their use in patients with kidney failure. They can interfere with absorption and enterohepatic recirculation of various drugs, including mycophenolate.

Statins

Most statins (hydroxymethylglutaryl–acetyl CoA [HMG-CoA] reductase inhibitors) are extensively metabolized and can be used effectively at normal doses in renal impairment and those who have undergone transplantation.[31] Rhabdomyolysis with acute kidney injury can occur, although the risk does not appear to be greatly increased with chronic renal impairment. The risk increases with use of fibrates and drugs that inhibit the CYP3A4 metabolism of statins. Patients commencing therapy should have lipids, renal function, and creatine kinase monitored regularly.

Fibrates

Fenofibrate but not gemfibrozil has extensive renal clearance, and dose reduction is required. Combination of statins and fibrates significantly increases the risk for rhabdomyolysis and should be used only when benefits outweigh risks and with monitoring for muscle symptoms, creatine kinase, and alanine aminotransferase.

DIABETES

The kidney plays an important role in insulin metabolism, and thus renal function influences glycemic control. Diabetes is also common after transplantation because of resumed insulin metabolism by the functioning transplant and also the effect of tacrolimus and corticosteroids. Patients with renal impairment are at increased risk for hypoglycemia, and drugs should be initiated and titrated cautiously.[32] Various antidiabetic drugs depend on renal excretion, and accumulation in renal impairment can cause adverse effects.[33] Management of diabetes in CKD is discussed in Chapter 32.

Diabetes Management in Peritoneal Dialysis

Patients receiving PD may have higher antihyperglycemic requirements because of the glucose load in PD fluid. If intraperitoneal insulin is used, dosages may vary from intravenous requirements. Icodextrin solutions can significantly interfere with blood glucose monitoring because of metabolites (maltose, maltotriose, or maltotetraose) that falsely elevate blood glucose readings when monitors use the enzyme glucose dehydrogenase pyrroloquinoline quinone. This may lead to administration of insulin and the development of life-threatening hypoglycemia. A glucose-specific test strip is required to avoid interference.

Biguanides

Metformin is excreted almost entirely unchanged in urine and accumulation can contribute to severe or fatal lactic acidosis (see Chapter 32).[34] Metformin should be temporarily discontinued in situations known to increase the risk for lactic acidosis or reduce renal function (e.g., acute tissue hypoxia, dehydration, serious infection or trauma) and 24 to 48 hours before anticipated surgery or use of iodinated radiocontrast media. Metformin is not usually recommended if GFR is below 60 ml/min and certainly below 30 ml/min. Nevertheless, a patient with renal impairment established on low-dose metformin is still at risk for lactic acidosis, and any acute deterioration in renal function can reduced drug clearance at any time. Patients on this regimen should be advised to seek early medical advice in any cases of acute deterioration in health.

Insulins

As renal function decreases, insulin clearance decreases. Uremia, however, can cause peripheral resistance to insulin, requiring increased doses. Most insulin regimens can be used in patients with CKD or transplantation with cautious titration and monitoring.

Meglitinides

The nonsulfonylurea insulin secretagogues repaglinide and nateglinide can be used in patients with renal failure without dose adjustment.

Sulfonylureas

Sulfonylureas are metabolized and some (glibenclamide and glimepiride) have active, renally excreted metabolites. In moderate to severe renal impairment, hypoglycemic risk is increased.[35] These agents should be initiated at low dose and titrated to response. Gliclazide and glipizide are preferable because they do not have active metabolites. Regardless of which agent is used, the effect of sulfonylureas still may be increased because the insulin they release will itself have a prolonged action in renal impairment.

SGLT2 Inhibitors

SGLT2 inhibitors (e.g. dapagliflozin) depend on adequate renal function to lower blood glucose levels and may be less effective at achieving this in moderate or severe renal impairment although they may have additional and independent benefits in delaying diabetic kidney disease.[36]

DPP-4 Inhibitors

Many DPP-4 inhibitors (sitagliptin, vildagliptin) rely on renal excretion and require significant dose reduction in renal impairment.

Thiazolidinediones

Thiazolidinediones are extensively metabolized and excreted in bile. Their pharmacokinetics are not significantly altered by renal impairment and in fact show reduced exposure, possibly because of reduced protein binding. However, they can cause fluid retention and edema, exacerbating the difficulties of fluid management and heart failure and are generally best avoided in renal impairment. Thiazolidinediones have been associated with dilutional anemia because of an increase in plasma volume, which may complicate management of renal anemia.

DRUGS FOR THYROID DISORDERS

Thyroid hormones generally do not require dose alteration in CKD.[37] Doses should be initiated and titrated to thyroid-stimulating hormone levels and clinical effect. In circulation, thyroxine (T_4) is 99.98% protein bound (0.02% free) and triiodothyronine (T_3) is 99.8% bound (0.2% free). T_3 and T_4 bind partially, in slightly different proportions, to three different plasma proteins: thyroid-binding globulin, thyroid-binding prealbumin, and albumin. In protein-deficient states (e.g., nephrotic syndrome), there is the possibility of transient or permanent changes in thyroid hormone protein binding that may alter the free fraction of T_3 and T_4, leading to transient toxicity. Uremic toxins can inhibit enzymes associated with conversion of T_4 to T_3. Oral absorption of thyroid hormones is affected by coadministration with metallic phosphate binders and iron. Euthyroid patients with CKD may have abnormal thyroid function test results, possibly because of decreased peripheral conversion of T_4 to T_3, decreased clearance of reverse T_3 generated from T_4, or decreased binding of thyroid hormones to proteins. Antithyroid drugs can be used at usual doses.

MINERAL AND BONE DISORDERS

Prescribing for these disorders is further discussed in Chapter 84.

Phosphate Binders

Phosphate binders should be taken with meals for maximal efficacy. Patients can be instructed to tailor phosphate binder intake to the phosphorus content and frequency of meals. Doses are not affected by renal function except that reducing function increases the need for phosphate binders. Dosage is based on phosphate levels and the need to avoid biochemical abnormalities. Acid suppression may reduce the effectiveness of phosphate binders by inhibiting hydrolysis of metallic ions in the gut. Phosphate binders also may reduce gastrointestinal absorption of drugs, including thyroid hormones, fluoroquinolones, tetracyclines, digoxin, and immunosuppressants.

Vitamin D

In patients with renal impairment, inability of the kidneys to activate 25-hydroxycholecalciferol to calcitriol may produce relative vitamin D deficiency and hypocalcemia, which requires treatment with the active vitamin D preparations calcitriol or alfacalcidol.

Calcimimetics

Cinacalcet dosage is independent of renal function except that progressive renal impairment exacerbates secondary hyperparathyroidism. When possible, cinacalcet should be administered with the evening meal to improve absorption and minimize side effects. Similarly, morning blood samples for parathyroid hormone levels should be drawn at least 12 hours after administration. Cinacalcet and etelcalcetide usage is further discussed in Chapter 84.

DYSPEPSIA, GASTROESOPHAGEAL REFLUX DISEASE, AND PEPTIC ULCERS

Proton pump inhibitors, histamine-2 (H_2) receptor blockers, and antacids are commonly used in patients with CKD (see Chapter 86).

Antacids

Alginates, magnesium trisilicate, and sodium bicarbonate are useful for symptom control but have high sodium content, which exacerbates hypertension and fluid status. Magnesium and aluminum salts can reduce the absorption of mycophenolate. Aluminum salts are often avoided in patients with advanced CKD.

Histamine-2 Antagonists

Most H_2 antagonists are renally cleared but relatively safe, so dose reduction is usually not required.[38] Protein binding and V_D are unaltered; however, the bioavailability of nizatidine is reduced in renal impairment. Cimetidine should be avoided because accumulation produces CNS effects and it causes significant interactions through the CYP450 system and falsely elevates serum creatinine levels.

Proton Pump Inhibitors

Proton pump inhibitors are generally safe and well tolerated even at normal dose, although they have rarely been associated with interstitial nephritis and there is increasing concern that their use may be associated with the development of CKD, although evidence is not definitive.

ANTIEMETICS

Dopamine Antagonists

Domperidone, metoclopramide, and prochlorperazine are not significantly renally cleared; however, extrapyramidal and CNS effects may occur in CKD, especially at high doses. Domperidone does not cross the blood-brain barrier and may be preferable for long-term management. Metoclopramide and domperidone increase gastric emptying, which may alter drug pharmacokinetics.

5-HT_3 Antagonists

Most 5-HT_3 antagonists are minimally excreted in urine and have a wide therapeutic window. Dolasetron, granisetron, ondansetron, and tropisetron are safe, and dose modification is not required.

APERIENTS AND LAXATIVES

Common low-potency agents including docusate, bisacodyl, glycerin, lactulose, liquid paraffin, senna, and sorbitol may be used for acute or chronic constipation. Normal doses should be titrated to effect while avoiding significant dehydration, fluid shifts, or electrolyte disturbances. High-potency laxatives and bowel preparations should be used cautiously. They can cause significant fluid and electrolyte disturbances, especially in susceptible renal patients. Preparations containing high amounts of phosphate should be avoided. Despite the large fluid volumes required for administration, isoosmotic laxatives may be used for bowel preparation in patients with renal impairment and dialysis.

ANTIDIARRHEALS

Opioids or their derivatives should be used with the same caution as when they are used as analgesics. Loperamide and diphenoxylate-atropine can be given in usual doses.

DRUGS FOR ERECTILE DYSFUNCTION

Phosphodiesterase-5 Inhibitors

The AUCs of sildenafil (twofold), tadalafil (fourfold), and vardenafil (20% to 30%) are increased in patients with severe renal impairment despite minimal dependence on renal excretion. However, provided that relevant cardiovascular and drug contraindications are excluded, they can be used safely. They should be initiated at low doses and titrated to response. Shorter acting agents (sildenafil and vardenafil) may be preferable. Vardenafil can prolong the QT interval.

Intracavernosal Therapy

Drugs given directly by intracavernosal injection do not achieve significant concentrations in the systemic circulation and can be used in patients with renal impairment.

MUSCULOSKELETAL DRUGS

Nonsteroidal Antiinflammatory Drugs

NSAIDs can cause significant nephrotoxicity and should be avoided or used with extreme caution in patients with CKD.

Miscellaneous Arthritis Drugs

Gold salts and penicillamine are now rarely used for rheumatoid arthritis. Both were associated with nephrotic syndrome caused by membranous nephropathy. Glucosamine and fish oil can be used safely.

Gout and Hyperuricemia

Gout is highly prevalent in patients with renal impairment. In acute therapy, short courses of oral corticosteroids are safe and preferable to NSAIDs. Colchicine accumulation in renal impairment may cause diarrhea and hypoperfusion-induced renal impairment, as well as myelosuppression. In maintenance therapy, allopurinol is effective but the dose should initially be reduced in moderate to severe renal impairment because of its renally cleared active metabolite (oxypurinol).[39] Despite this, some patients with end-stage renal disease tolerate normal doses. Allopurinol significantly interacts with azathioprine with a risk for severe myelosuppression. If the combination is unavoidable the azathioprine dose should be reduced by 75% and blood counts monitored carefully. Uricosuric agents (e.g., probenecid) inhibit secretion of acids in the proximal tubule and prevent reabsorption of uric acid from the tubular lumen. They often become ineffective with diminishing renal function and are best avoided if the GFR is below 40 ml/min. Probenecid also interferes with the tubular secretion of many drugs, causing interactions.

Bisphosphonates

Bisphosphonates are extensively excreted in urine. The fraction not excreted is incorporated into bone, from which it slowly dissociates. In renal impairment, impaired clearance of absorbed drug may increase the fraction available for incorporation into bone. The long terminal elimination half-life of these agents reflects rate-limiting dissociation from bone and may not be significantly altered in patients with renal impairment. Oral bisphosphonates appear to be safe in CKD stages 2 and 3. Their safety in CKD stages 4 and 5 is less well established, and they are contraindicated in adynamic bone disease. Rapid administration of intravenous bisphosphonates (pamidronate and zoledronic acid) without hydration has been associated with acute nephrotoxicity. Intravenous preparations should be administered slowly with hydration, and renal function assessed regularly. Oral bisphosphonate administration may be complicated by the volumes of fluid recommended. In addition, many patients with renal impairment are taking calcium-based phosphate binders or supplements that impair the absorption of oral bisphosphonates.

ANTIEPILEPTICS

Patients with CKD may be more prone to seizures (e.g., uremic encephalopathy and dialysis disequilibrium syndrome) and to the CNS effects of antiepileptics. Some antiepileptics rely on renal excretion, and dose modification is essential. Some antiepileptics (barbiturates, phenytoin, and carbamazepine) are strong inducers of drug-metabolizing enzymes. Coadministration with drugs reliant on hepatic metabolism (e.g., immunosuppressants) can reduce exposure and efficacy of the concomitant drug. Therapeutic drug monitoring is available for many antiepileptics and should be used to guide dosage.

Benzodiazepines

See the later discussion of psychotropic drugs.

Carbamazepine

Carbamazepine is administered as normal and titrated to response and blood concentrations. It is a potent enzyme inducer, and care must be taken to account for important drug interactions.

Phenytoin

Caution should be exercised with phenytoin in renal impairment because of its erratic absorption, saturable metabolism, nonlinear pharmacokinetics, reduced protein binding, and increased V_D. The concentration of free drug may be higher than in normal renal function. Because most laboratories measure total drug concentration, a low serum total phenytoin level in renal impairment should not be mistaken as subtherapeutic. Nystagmus, cerebellar ataxia, and seizures can occur in overdose, and small dose increases may result in disproportionate increases in serum concentrations. Cautious titration based on effect and monitoring of free plasma concentration is advised. Phenytoin is a potent enzyme-inducing agent, and care must be taken to account for drug interactions.

Other Antiepileptics

Levetiracetam, topiramate, and vigabatrin undergo significant renal excretion, and dose modification is required. Valproate and lamotrigine are not significantly renally excreted and do not cause enzyme induction or inhibition. Protein binding changes can increase the free fraction of valproic acid, predisposing to increased responsiveness.

ANTIPARKINSONIAN DRUGS

In addition to their use for Parkinson disease and hyperprolactinemia disorders, dopaminergic drugs are used to treat restless legs and other limb movement disorders in patients with renal impairment. Most are hepatically cleared and safe, although dopaminergic agents may exacerbate postural hypotension. Amantadine is highly dependent on renal excretion, and dose modification is essential.

ANTIMIGRAINE DRUGS

Simple analgesics (acetaminophen) are used as normal, although aspirin should be avoided at therapeutic doses and opioids used cautiously (see discussion of analgesics). NSAIDs are best avoided because of potential nephrotoxicity. 5-HT_1 agonists are effective in patients with renal impairment and transplantation. Naratriptan relies the most on renal excretion (50%), and a lower maximum dose is recommended. Sumatriptan and zolmitriptan are preferred because they are less dependent on renal excretion.

PSYCHOTROPIC DRUGS

Most psychotropics are fat soluble and nondialyzable, undergo significant hepatic metabolism, and are excreted as inactive compounds. Even so, renal patients are often more susceptible to common adverse effects (especially CNS effects).[40] Slow titration and dose modifications are required. Adverse effects are not easily distinguished from symptoms of uremia. Despite being metabolized extensively by CYP450 enzymes, very few psychotropics cause clinically significant inhibition or induction of CYP3A4.

Selective Serotonin Reuptake Inhibitors

Most selective serotonin reuptake inhibitors (SSRIs) are extensively metabolized to compounds without significant SSRI activity.[41] Normal doses of citalopram, fluvoxamine, paroxetine, and sertraline can be used with cautious dose titration. Fluoxetine is metabolized to an active metabolite (norfluoxetine), but single- and multiple-dose studies have shown little change in pharmacokinetics even in dialysis patients. Patients with renal impairment may be more prone to the CNS toxicity of SSRIs and serotonin syndrome. SSRIs can cause the syndrome of inappropriate antidiuretic hormone secretion and platelet aggregation or hemorrhagic complications, which may increase the risk for bleeding in uremic patients who are already prone to bleeding complications. Although most SSRIs have some inhibitory effect on CYP3A4, this is usually not significant.

Fluoxetine and fluvoxamine are more likely to interact than citalopram and sertraline, but all can be used in patients taking immunosuppressants. Cinacalcet can cause significant inhibition of CYP2D6-mediated metabolism of SSRIs and perhexiline. This may increase the possibility of serotonin syndrome or perhexiline toxicity.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are now infrequently used for depression but more for neuropathic pain, and their anticholinergic properties in urinary tract disorders. They are predominantly metabolized to metabolites with varying activity. Patients with renal impairment may be more prone to the common anticholinergic adverse effects, particularly urinary retention, orthostatic hypotension, confusion, and sedation.[42] Obstructive uropathy can occur from the anticholinergic properties. Cautious initial doses and titration of TCAs are recommended. Depending on response, many agents can be used at up to normal or maximal doses.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors are extensively metabolized by the liver. Although they are now rarely used, normal doses of reversible monoamine oxidase inhibitors (moclobemide) are preferred and can be titrated cautiously to full doses. Monoamine oxidase inhibitors can cause peripheral edema, which is not usually associated with fluid retention and is unresponsive to diuretics. Prostatic hypertrophy and urinary retention also may occur.

Other Antidepressants

Venlafaxine dose should be initially reduced in patients with severe renal impairment because of reduced clearance of the active metabolite *O*-desmethylvenlafaxine and the potential for hypertension. Nefazodone is used at a normal dose.

Antipsychotics

Conventional antipsychotics cause a variety of side effects to which patients with renal impairment may be susceptible (sedation, confusion, and postural hypotension). Caution is advised for atypical antipsychotics that prolong the QT interval (e.g., pimozide, thioridazine, mesoridazine, droperidol, and ziprasidone). Newer atypical agents are more commonly used and better tolerated. Clozapine, olanzapine, quetiapine, and aripiprazole are commenced at normal doses and titrated to response. Risperidone and its active metabolite 9-hydroxyrisperidone are renally excreted, and clearance is reduced by 60% in severe renal impairment. Lithium is filtered and reabsorbed mainly in the proximal tubule. It has extensive renal clearance and accumulates even in mild renal impairment, causing toxicity, and should be avoided if possible. If use is essential, the dose must be reduced with monitoring of plasma concentrations. In hyponatremic patients, tubular reabsorption of lithium is increased, leading to increased plasma concentrations and toxicity. NSAID coprescription also may increase toxicity. HD is efficient in removal of lithium and can be used in overdose; however, multiple dialysis treatments are usually required because plasma concentrations rebound soon after HD. Chronic lithium nephrotoxicity is discussed further in Chapter 62.

Benzodiazepines

Benzodiazepines are extensively metabolized by the liver to a range of active and inactive metabolites. Enhanced CNS toxicity, especially sedation, is the main concern in renal patients. Because of the potential for accumulation, chronic use should be discouraged. Short-acting benzodiazepines are preferred, and the dose should be titrated cautiously according to response. The dose of midazolam should be reduced because of changes in plasma protein binding. Hemoperfusion and dialysis are not useful in patients with benzodiazepine intoxication. Flumazenil may be used as an antidote in patients with overdose, at doses similar to those with normal renal function.

ANEMIA DRUGS

Erythropoiesis-Stimulating Proteins

The pharmacokinetics of erythropoiesis-stimulating agents (ESAs) are not affected by renal function per se. However, as renal function decreases, dose requirements may increase to account for reduced endogenous erythropoietin production. Use of ESAs is discussed in detail in Chapter 82.

Iron Therapy

Oral supplements may be sufficient in early-stage CKD or PD patients who do not have the same degree of regular blood loss as HD patients. Maximum absorption of oral iron occurs with frequent administration of small doses away from food, although gastrointestinal intolerance limits therapy. Patients with severe iron deficiency and those on HD often require intravenous supplementation (see Chapter 82).

ANTIHISTAMINES

Normal doses of sedating antihistamines generally can be used. They should be used cautiously in patients with bladder outflow obstruction because they may cause or aggravate urinary frequency or retention. Newer, less sedating antihistamines are better tolerated and have a wider therapeutic index, and accumulation rarely causes significant complications. Cetirizine relies more on renal clearance, and dose reduction is suggested. Loratadine and desloratadine have active metabolites but are safe. Fexofenadine is safe; however, terfenadine should be avoided because of the risk for arrhythmias.

VACCINES

Live vaccines (BCG [bacillus Calmette-Guerin], oral poliovirus, rubella, typhoid, yellow fever, and varicella) in immunosuppressed patients are contraindicated because of the potential for causing disease. Attenuated vaccines (diphtheria-tetanus, hepatitis B, influenza, meningococcal, and pneumococcal) may be used, but impaired response in immunocompromised individuals may lead to inadequate protection (see Chapter 83). Hepatitis B may need more doses for seroconversion to be achieved in patients on HD. Immunization should preferably occur at least 1 month before initiation of immunosuppression. After transplantation, the immune response may be inadequate for at least 6 to 8 months, meaning that vaccination should be withheld until then.[43]

VITAMIN SUPPLEMENTATION

Patients with renal impairment may become vitamin deficient as a result of poor dietary intake and the effect of dialysis on removal of water-soluble vitamins. Administration of vitamin supplements (B, C, and folic acid) is recommended after dialysis.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following drug require(s) clinically significant dose modification in patients with significant renal impairment. (More than one answer is possible.)
   - **A.** Enoxaparin
   - **B.** Gabapentin
   - **C.** Amoxicillin
   - **D.** Amlodipine
   - **E.** Famciclovir
2. Which of the following drug is(are) the *most* likely to cause clinically significant drug interactions with calcineurin inhibitors (CNIs). (More than one answer is possible.)
   - **A.** Fluconazole
   - **B.** Clarithromycin
   - **C.** Vancomycin
   - **D.** Acyclovir
   - **E.** Roxithromycin
3. Which of the following drug require(s) dose modifications in renal impairment because of a renally cleared metabolite. (More than one answer is possible.)
   - **A.** Olanzapine
   - **B.** Allopurinol
   - **C.** Atenolol
   - **D.** Amlodipine
   - **E.** Pethidine
4. Which of the following drugs is(are) likely to be removed by hemodialysis and should therefore be dosed after dialysis? (More than one answer is possible.)
   - **A.** Pregabalin
   - **B.** Amiodarone
   - **C.** Levetiracetam
   - **D.** Pantoprazole
   - **E.** Acyclovir

76

Herbal and Over-the-Counter Medicines and the Kidney

Mark S. Segal, Xueqing Yu

The use of herbal medicines and dietary supplements continues to increase globally. An estimated one third of adults in developed countries and more than 80% of the population in many low and middle income countries use herbal and folk medicines to promote health and manage a number of common maladies, such as colds, hay fever, indigestion, and constipation, as well as liver cirrhosis, cancer, heart disease, AIDS, and diabetes.[1] In Africa, up to 80% of the population depends on traditional medicine for primary health care; in China, herbal preparations account for up to 50% of the total consumption of pharmaceutical agents; and there has been a surge in the popularity of herbal medicine in the West. For instance, the U.S. herbal medicine market increased from $1.6 billion in 1994 to $6.4 billion in 2014[1,2]; complementary and alternative medicines, including Chinese herbal medicines and herbal plants, have been used by about 50% of Australians.[1]

Germany and France are the leaders in sales of over-the-counter (OTC) herbal medicines in Europe and also have large markets for prescription herbal preparations (Fig. 76.1).[3] The European Union has taken steps to regulate herbal remedies with the Traditional Herbal Medicinal Products Directive (also known as Directive 2004/24/EC), implemented in May, 2011. This mandates all herbal medicinal products obtain an authorization to market within the European Union and that herbal medicines be manufactured under Good Manufacturing Practice.

There are at least 11,000 species of plants for medicinal use, and about 500 of them are commonly used by various ethnic groups.[1,4] These herbal plants may be used either in their primary forms or in mixtures. However, the source and composition of botanical medicines vary depending on the prevalent local practices. Herbal remedies are not tested for efficacy and safety, their ingredients are largely unknown, and there is no standardization of dosage and route of administration. Organ toxicity caused by traditional medicines is directly related to a combination of poor education, poverty, lack of medical facilities, weak or absent legislation, and widespread belief in indigenous systems of medicine in rural areas. Problems related to herbal medicines arise as a result of intrinsic toxicity, adulteration, contamination, substitution, misidentification, mistaken labeling, and unfavorable herb-drug interactions.[1,4] Increasing evidence for both adverse drug reactions and poisoning events associated with the use of herbal medicines has been reported worldwide. Herbal medicines have been found to be adulterated with synthetic drugs and other potentially toxic compounds. On the other hand, coadministration of herbal medicines with conventional drugs raises the potential for herb-drug interactions, which may cause altered drug elimination, undertreatment, and/or toxicity.[1,4,5]

HERBAL MEDICATIONS AND THE KIDNEY

The kidneys are particularly vulnerable to toxic injury because of their high blood flow rate, large endothelial surface area, high metabolic activity, active uptake by tubular cells, medullary interstitial concentration, and low urine pH. Renal tubules are involved in active transport and urinary concentration, and therefore the local concentration of these toxins is potentially high, leading to direct injury to tubular cells. Herbal medicines may be nephrotoxic via one or more common pathogenic mechanisms, including alterations in intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. Furthermore, potentially nephrotoxic exogenous substances such as paint thinners, turpentine, chloroxylenol, ginger, pepper, soap, vinegar, copper sulfate, and potassium permanganate, are often added to herbal compounds. Drug-related nephrotoxicity is becoming more common, as more people have multiple comorbidities that require multiple medications and more diagnostic and therapeutic procedures, all with the potential to harm kidney function. Patient-related risk factors for drug-induced nephrotoxicity include age older than 60 years, underlying renal impairment with glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2, volume depletion, diabetes, heart failure, and sepsis.[6] These same risk factors also may make individuals susceptible to renal toxicity from herbal medicines.

An overview of the potential renal side effects of herbal medicines is shown in Table 76.1.

ARISTOLOCHIC ACID NEPHROPATHY

Aristolochic Acids

Aristolochic acids (AAs) are a family of structurally related nitrophenanthrene carboxylic acids found in herbal medicines such as *Aristolochia* spp., including *Aristolochia fangchi, Aristolochia clematitis,* and *Aristolochia manshuriensis* (Table 76.2). The predominant AAs are AAI (8-methoxy-6-nitro-phenanthro-[3,4-*d*]-1,3-dioxolo-5-carboxylic acid) and AAII (6-nitro-phenanthro-[3,4-*d*]-1,3-dioxolo-5-carboxylic acid). AAs are activated by human NAD(P)H:quinone oxidoreductase (NQO1)[7] and react with DNA to form covalent 7-(deoxyadenosin-N^6-yl)aristolactam I (dA-AA) and 7-(deoxyguanosin-N^2-yl)aristolactam(dG-AA) adducts. These aristolactam adducts are mutagenic.[8] After even a single dose, AAI is stably detected in the kidneys. Human aristolochic acid nephropathy (AAN) is reproducible in rodents with AA intoxication, resulting in tubular atrophy and interstitial fibrosis, leading to renal failure.[9] The progressive tubular atrophy is related to impaired regeneration and apoptosis of proximal tubular epithelial cells, which is considered a possible mechanism of tubular epithelial cell deletion. The resident fibroblast activation plays a critical role in the process of renal fibrosis during AA toxicity.[10] The nephrotoxic and carcinogenic effects of AAs have been reported in animals, exposure to AA causes a progressive renal interstitial fibrosis associated with urothelial malignancy. Similar toxicities are observed in humans.

Aristolochic Acid Nephropathy

The association of kidney disease with long-term consumption of *A. fangchi* was first reported in Belgium in nine young women taking slimming preparations.[11] Since then there have been case reports and series from around the world (Fig. 76.2).[12] Even though this disease may affect millions worldwide, high-quality epidemiologic data on the incidence and prevalence of AAN are lacking because of the absence of internationally agreed diagnostic criteria and global low awareness of the disease.[12] Increasing evidence supports that it is the AAs in the herbs that are responsible for their renal toxicity (Figs. 76.3 and 76.4).[9] The renal syndrome was initially referred to as *Chinese herb nephropathy* and is now known by the more specific, mechanistic name AAN.[14] The renal toxicity of AA depends on the dosage and the duration of administration.[15] It is now clear that Balkan endemic nephropathy, a condition known for several decades without a known cause, is another manifestation of AAN, in which there is contamination of wheat (flour) by *A. clematitis*.[9]

There is no evidence that AA is a causative agent more widely for chronic kidney disease (CKD) in other specific cohorts, and this is unlikely to be overlooked because no other known endemic nephropathy shares the association with urothelial malignancy, so characteristic of AA toxicity.

Definition

AAN is characterized by tubulointerstitial nephritis that progresses to fibrosis with deterioration of renal function, ultimately leading to end-stage renal disease (ESRD), sometimes within months after first exposure. There is a high associated risk for uroepithelial malignancy.

Epidemiology

Soon after its initial description, AAN was recognized as a global health problem.[9,11,12,15,16] Since the publication of the index cases, new cases of AAN have been reported, not only in Belgium but also worldwide[9-13] (see Fig. 76.2). The true incidence of AAN remains unknown and is probably underestimated because numerous ingredients known or suspected to contain AA are used in traditional medicine in China, Japan, and India (see Fig. 76.3).[9] Balkan endemic nephropathy (BEN) affects thousands of people living in discreet areas in Bulgaria, Bosnia, Croatia, Romania, and Serbia along the Danube River basin (Fig. 76.5).[16,17] BEN typically presents in the fourth or fifth decade of life and is only rarely seen in individuals younger than 20 years, presumably reflecting low-grade chronic exposure to AA.

Clinical Manifestations

The initial presentation of AAN is usually silent, and the renal disease only discovered by routine blood testing. Occasional patients present with Fanconi syndrome or with acute kidney injury (AKI) caused by acute tubular necrosis.[18] The urinary sediment is unremarkable, and the urinalysis is initially negative for albuminuria. However, urinary excretion of low molecular weight proteins (e.g., β_2-microglobulin, cystatin C) is markedly increased, and the ratio of urinary low molecular weight protein to albumin is higher than in glomerular diseases.[19] When there is prospective monitoring in endemic areas, tubular proteinuria

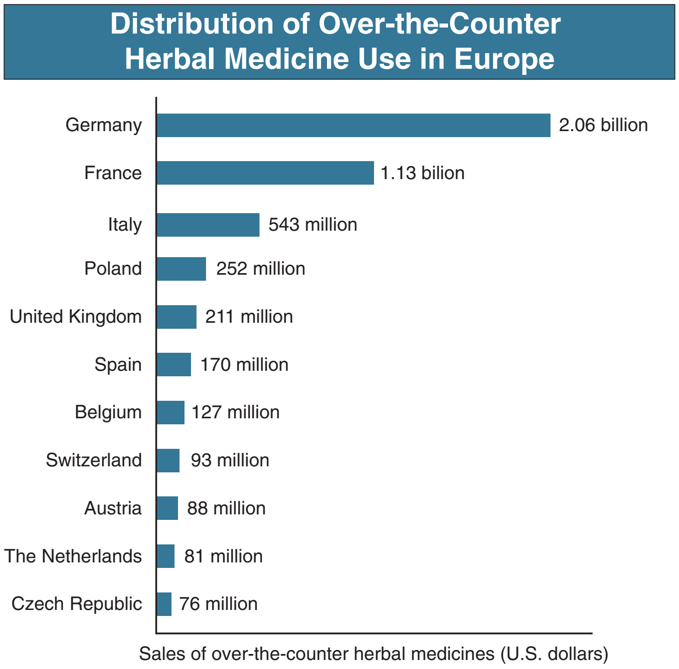

Fig. 76.1 Distribution of the $4.96 billion European market for over-the-counter herbal medicines in 2003. (Based on date from reference 3.)

TABLE 76.1 Kidney Syndromes Induced by Herbal Medicines

Syndrome	Herbal Medicine
Hypertension	*Glycyrrhiza* spp. (Chinese herbal teas, gancao, boui-ougi-tou) *Ephedra* spp. (ma huang)
Acute tubular necrosis	Traditional African medicine: Toxic plants (*Securidaca longepedunculata, Euphoria matabelensis, Callilepis laureola,* Cape aloes), or adulteration by dichromate Chinese medicine: *Taxus celebica* Morocco: *Takaout roumia* (paraphenylenediamine)
Acute interstitial nephritis	Peruvian medicine *(Uno degatta)* Tung Shueh pills (adulterated by mefenamic acid)
Fanconi syndrome	Chinese herbs containing AAs (*Akebia* spp., boui-ougi-tou, Mokutsu) Chinese herbs adulterated by cadmium
Papillary necrosis	Chinese herbs adulterated by phenylbutazone
Chronic interstitial renal fibrosis	Chinese herbs or Kampo containing AAs (*Aristolochia* spp., *Akebia* spp., Mu Tong, Boui, Mokutsu)
Urinary retention	*Datura* spp., *Rhododendron molle* (atropine, scopolamine)
Kidney stones	Ma huang (ephedrine) Cranberry juice (oxalate)
Urinary tract carcinoma	Chinese herbs containing AAs

From reference 6.
AA, Aristolochic acids.

TABLE 76.2 **Botanicals Known or Suspected to Contain Aristolochic Acid and Their Common Names**

Botanical Name	Common or Other Names
Aristolochia spp.	Aristolochia, Guan Mu tong, Guang Mu tong
Aristolochia acuminata (syn. *Aristolochia tagala*)	Oval leaf Dutchman's pipe
Aristolochia bracteata	Ukulwe
Aristolochia clematitis	Birthwort
Aristolochia contorta	Ma Dou Ling (fruit), Bei Ma Dou Ling (root), Tian Xian Teng (herb)
Aristolochia cymbifera	Mil homens
Aristolochia debilis (syn. *Aristolochia longa, Aristolochia recurvilabra, Aristolochia sinarum)*	Ma Dou Ling (fruit), Tian Xian Teng (herb), Qing Mu Xiang (root), Sei-Mokkou (Japanese), Birthwort, Long birthwort, Slender Dutchman's pipe
Aristolochia fangchi	Guang Fang ji (root), Fang ji, Fang chi, Makuboi (Japanese), Kou-boui (Japanese), Kwangbanggi (Korean)
Aristolochia heterophylla	Han Fang Ji
Aristolochia indica	Indian birthwort (root), Yin Du Ma Dou Ling
Aristolochia kaempferi (syn. *Aristolochia chrysops, Aristolochia feddei, Aristolochia heterophylla, Aristolochia mollis, Aristolochia setchuenensis, Aristolochia shimadai, Aristolochia thibetica, Isotrema chrysops, Isotrema heterophylla, Isotrema lasiops*)	Yellowmouth Dutchman's pipe, Zhu Sha Lian
Aristolochia macrophylla (syn. *Aristolochia sipho*)	Dutchman's pipe
Aristolochia manshuriensis (syn. *Hocquartia manshuriensis, Isotrema manshuriensis*)	Manchurian birthwort, Manchurian Dutchman's pipe (stem), Guan Mutong (stem), Kan-Mokutsu (Japanese), Mokubai (Japanese), Kwangbanggi (Korean)
Aristolochia maxima (syn. *Howardia hoffmannii*)	Maxima Dutchman's pipe, Da Ma Dou Ling
Aristolochia mollissima	Wooly Dutchman's pipe, Mian Mao Ma Dou Ling
Aristolochia moupinensis	Moupin Dutchman's pipe, Huai Tong
Aristolochia sarpentaria (syn. *Aristolochia serpentaria*)	Virginia snakeroot, Serpentaria, Virginia serpentary
Aristolochia triangularis	Triangular Dutchman's pipe, San Jiao Ma Dou Ling
Aristolochia tuberosa	Tuberous Dutchman's pipe, Kuai Jing Ma Dou Ling
Aristolochia tubiflora	Tubeflower, Dutchman's pipe, Guan Hua Ma Dou Ling
Aristolochia versicolar	Versicoloraus Dutchman's pipe, Bian Se Ma Dou Ling
Asarum canodense (syn. *Asarum acuminatum, Asarum ambiguum, Asarum canadense, Asarum furcatum, Asarum medium, Asarum parvifolium, Asarum reflexum, Asarum rubrocinctum*)	Wild ginger, Indian ginger, Canada snakeroot, false coltsfoot, colic root, heart snakeroot, Vermont snakeroot, Southern snakeroot, Jia Na Da Xi Xin
Asarum himalai(y)cum	Tanyou-saishin (Japanese)
Asarum splendens	Do-saishin (Japanese)

From reference 16.

is usually the first manifestation of BEN. Other manifestations of tubular dysfunction include impaired acidification, decreased ammonia, increased uric acid excretion, and urine-concentrating defects with renal salt wasting, which may precede the decrease in GFR. The disease progresses to ESRD. Other hallmarks are that the severity of the anemia is disproportionate to the degree of renal impairment whereas the blood pressure is usually in the normal range until the development of ESRD.

Distinctive for AA exposure is the increased incidence of uroepithelial carcinomas. A case series with a 15-year follow-up identified upper tract urothelial carcinoma as a potent risk factor for the subsequent development of bladder urothelial carcinoma after kidney transplantation for AAN.[20]

Pathology

AAN is characterized by extensive renal interstitial fibrosis and tubular atrophy, which generally decreases in severity from the outer to the inner cortex (see Fig. 76.4). Early in the disease, the glomeruli are relatively spared, although at later stages there is some collapse of the capillaries and wrinkling of the basement membrane. There is endothelial cell swelling with consequent thickening of interlobular and afferent arterioles.[9,21] There are no immune deposits.

Pathogenesis

The striking association between AA exposure and uroepithelial abnormalities was first noted in nephroureterectomy specimens from individuals with AAN removed at the time of transplantation, demonstrating moderate atypia and atypical hyperplasia (see Fig. 76.4).[9,22] An early and massive interstitial inflammation characterized by activated monocytes and macrophages and cytotoxic $CD8^+/CD103^+$ T lymphocytes seen in experimental AAN[23,24] suggests that the pathophysiology includes an immunologic element. The persistence of AA-DNA adducts in renal tissues of the Belgian women cohort is consistent with their postulated role of DNA adducts in urothelial cancer. Of AAN patients, 40% to 45% develop multifocal high-grade transitional cell carcinomas, mainly

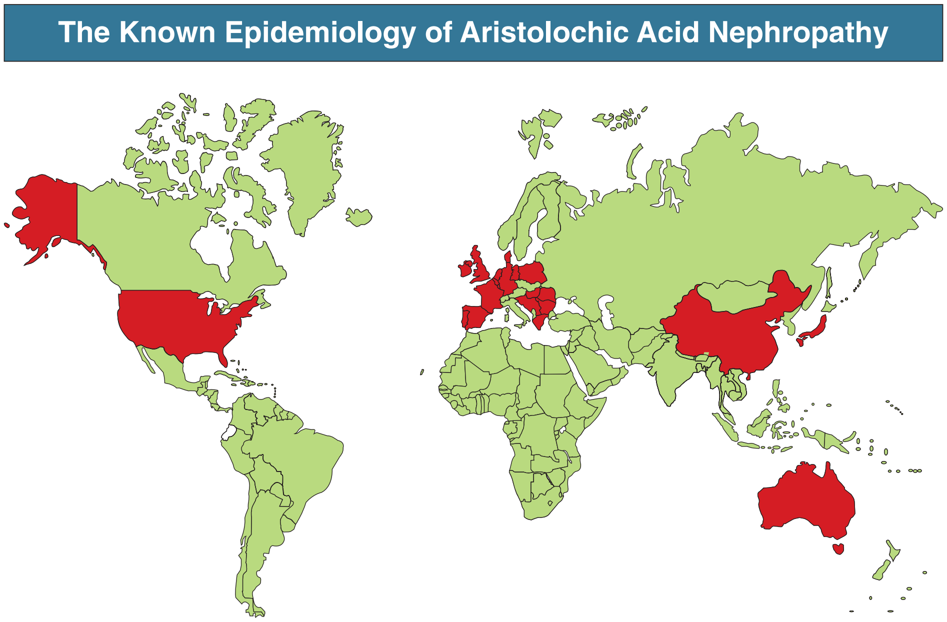

Fig. 76.2 The known epidemiology of aristolochic acid (AA) nephropathy. Countries in which cases of AA nephropathy or Balkan endemic nephropathy have been reported. It is likely that the true worldwide distribution of the diseases extends beyond the countries highlighted, especially in East and South Asia. (From reference 12.)

Fig. 76.3 Traditional Chinese pharmacy. A pharmacy selling traditional herbal remedies including Fang Chi and Mu Tong. The true incidence of aristolochic acid nephropathy (AA) is largely unknown and probably underestimated because numerous ingredients known or suspected to contain AA are used in traditional medicine in India and Eastern Asia. (From reference 9.)

in the upper urinary tract.[13] There is a strong association between DNA adduct formation, mutation pattern, and tumor development. In animal models, oral ingestion of AA is followed by extensive formation of AA-DNA adducts in the forestomach, accompanied by the development of tumors.[20] A genome-wide search in a series of cancers from Taiwan (where a significant fraction of the population is prescribed herbal medicines containing AA) demonstrated the presence of AA-DNA adducts and other DNA signatures of AA exposure in cancers of the upper urinary tract. Of additional concern was the presence of AA-DNA adducts in cancers of the liver and kidney.[25] Transitional cell cancers from patients with BEN contain AA and a characteristic pattern of tumor protein 53 (TP53) mutations, 89% occurring at A:T pairs and 78% of these being A:T to T:A transversions. These types of transversions are not seen in transitional cell carcinomas of the renal pelvis in the absence of AA exposure. Molecular epidemiologic evidence relates urothelial carcinoma in patients with BEN to dietary exposure to AA.[26]

There is now strong evidence for the role of AA in the pathogenesis of BEN. In endemic regions, bread is a dietary staple and is traditionally prepared from flour made from locally grown wheat. The seeds of *A. clematitis*, a plant native to the region, are found interspersed with the harvested wheat grain. dA-aristolactam and dG-aristolactam DNA adducts are found in the renal cortex of patients with BEN but not in those with other chronic renal diseases.[26,27] Aristolactam-DNA adducts have been found in 70% of people in endemic areas with dietary exposure to AA and in 94% of patients with specific A:T to T:A mutations in *TP53*. Neither aristolactam-DNA adducts nor specific mutations were detected in tissues of those from nonendemic regions. Because BEN occurs only in a fraction of those individuals exposed to AA, there is assumed to be a genetic susceptibility that puts individuals with a dietary exposure to AA at risk for BEN and its resultant urothelial carcinomas.[9,12]

Diagnosis

Diagnostic criteria for AAN and in endemic areas for BEN are shown in Box 76.1. An analysis of 182 patients in Serbia showed that proteinuria, urine α_1-microglobulin, and kidney size are significant predictors of BEN, whereas renal failure as well as several tubular disorders (urine specific gravity, fractional sodium excretion, and tubular phosphate reabsorption) had an insignificant predictive value.[16,30]

Treatment

There have been no randomized trials of treatment for AAN or BEN. However, a pilot study in 35 AAN patients with CKD demonstrated a significant reduction in the number of patients reaching ESRD after 1 year of corticosteroid therapy.[28] Corticosteroid therapy was later confirmed, in a larger cohort with historical controls, to slow down the progression of renal failure.[29] It is suggested that corticosteroids, 1 mg/kg of predniso(ol)ne for 4 weeks followed by a maintenance dose of 0.1 mg/kg taper ever 2 weeks, be initiated in those with biopsy-proven AAN and an estimated GFR (eGFR) greater than 20 ml/min per 1.73 m^2. It is recommended to discontinue steroid therapy after 6 months if the eGFR continues to decrease. Based on nonrandomized studies of corticosteroids in AAN, a trial of corticosteroids is reasonable in those with BEN as well, in addition to blood pressure control and management of electrolyte abnormalities. Although renin-angiotensin system

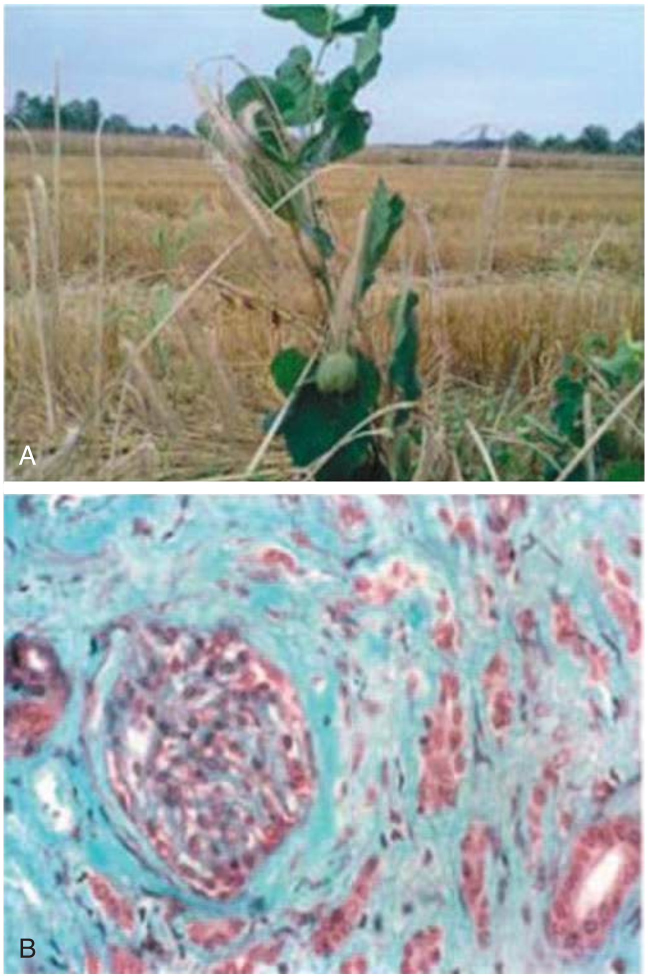

Fig. 76.4 **Chinese herb or aristolochic acid nephropathy.** (A) Guang Mu Tong, a Chinese herb that contains AAs. (B) Extensive paucicellular interstitial fibrosis and tubular atrophy typically found in Chinese herb or aristolochic acid nephropathy. The same pathologic appearances are seen in Balkan Endmeic Nephropathy. (From reference 9. Courtesy, Dr. Bojan Jelaković.)

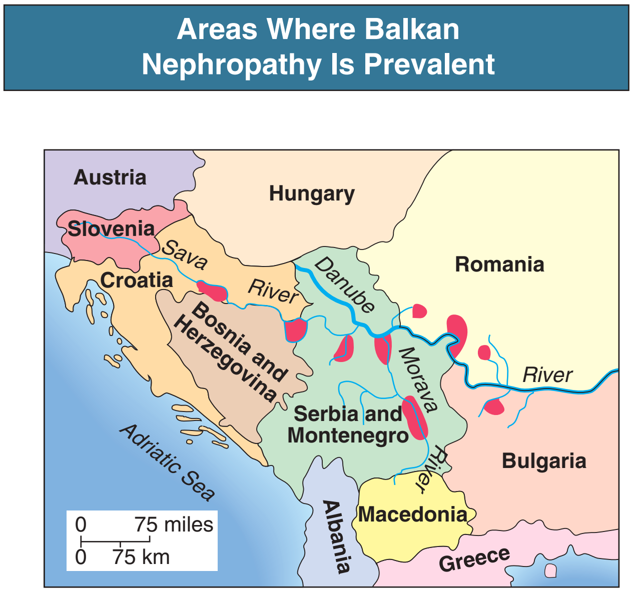

Fig. 76.5 **Areas where Balkan nephropathy is prevalent.** The endemic areas are in *red.* (From reference 16.)

BOX 76.1 Diagnostic Criteria for Aristolochic Acid Nephropathy, Including Balkan Endemic Nephropathy

- Epidemiologic pattern
- Known exposure to aristolochic acid–containing medicines or living in endemic Balkan settlements
  - Clinical features
  - GFR decrease
  - Proteinuria usually less than 1 g/24 h
  - Bland urinary sediment
  - Markers of renal tubular damage (renal glycosuria, increased urinary excretion of β_2-microglobulin or α_1-microglobulin, and *N*-acetyl-β-D-glucosaminidase)
  - Typical renal histology showing hypocellular cortical interstitial fibrosis decreasing from the outer to the inner cortex (if renal biopsy feasible)
- Exclusion of other known kidney disease (e.g., chronic pyelonephritis [obstructive and atrophic], adult dominant polycystic kidney disease, glomerulonephritis)

Modified from reference 16, 30.

blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is important in managing CKD, there is no evidence that this strategy improves renal function or delays progression in AAN.[12,30]

Because patients with AAN are at increased risk for uroepithelial malignancies, all patients with AAN should undergo biannual cytologic evaluation of urine. In those patients with AAN who do not yet require renal replacement therapy (RRT), yearly surveillance is suggested with computed tomography imaging and ureteroscopy. In addition, prophylactic bilateral nephroureterectomy is strongly recommended for all patients with ESRD caused by AAN who are going to be the recipient of a kidney transplant and subsequent immunosuppression.[31]

KIDNEY INJURY CAUSED BY OTHER MEDICINALS

Aside from AAs, the use of other herbal therapy may lead to renal injury or various toxic insults, especially in renal patients. Various renal syndromes have been reported after the use of medicinal plants, including acute tubular necrosis, acute interstitial nephritis, Fanconi syndrome, hypertension, papillary necrosis, chronic interstitial nephritis, and nephrolithiasis.[6,32] Herbal plants reported as the cause for renal injury include *Securidaca longepedunculata* (or violet tree), *Euphorbia matabelensis, Crotalaria laburnifolia, Uncaria tomentosa* (cat's claw), *Lepidium meyenii* (common name: maca), *Tripterygium wilfordii* (Lei Gong Teng), licorice root *(Glycyrrhiza glabra);* irumban puli *(Averrhoa bilimbi),* cape aloe, *Callilepis laureola* (Impila), mushrooms, and djenkol beans (*Pithecellobium*). In addition, the medicinal grass carp *(Ctenopharyngodon idellus)* gallbladder has been noted to cause hepatitis and acute renal failure.[1,32-36]

ACUTE KIDNEY INJURY

T. wilfordii Hook F (TWHF) is a Chinese herbal medicine used for over 2000 years. When made into a cream it is used externally for treatment of arthritis and inflammatory swelling. Extracts of TWHF have been found to have immunosuppressive effects, which could successfully treat rheumatoid arthritis, lupus, minimal change disease, and other autoimmune disorders. The adverse effects of TWHF include gastrointestinal upset, infertility, and leukopenia. In addition, it has been reported that AKI, profound hypotension, and shock after ingestion of an extract of TWHF been reported. In rats, daily intragastric ingestion of an effective compound extracted from TWHF for 16 days led to proximal tubular dysfunction.[32,33]

Cat's claw, or *Uno degatta,* is a Peruvian herbal preparation made from *Uncaria,* a woody vine found in the Amazon basin. It has been used for treatment of cirrhosis, gastritis, gonorrhea, cancers of the female genital tract, and rheumatism. The oxindole alkaloids from the root bark of cat's claw are thought to invoke its putative antiinflammatory effects, but other unknown substances contribute to the overall effect of cat's claw extracts. A case of reversible acute interstitial nephritis after the use of this preparation has been reported, likely an idiosyncratic allergic reaction to the remedy.[34]

Mushrooms

The majority of renal problems associated with mushrooms are a consequence of renal failure resulting from mushroom-induced hepatic failure. However, throughout Europe and North America there are a variety of nephrotoxic mushrooms that can be confused with edible mushrooms and can cause AKI. The *Cortinarius* spp. (*Cortinarius callisteus, Cortinarius cinnamomeus* group, *Cortinarius gentilis, Cortinarius orellanus, Cortinarius rainierensis, Cortinarius speciosissimus, Cortinarius splendens,* and *Cortinarius semisanguineus* group) are the most notorious. The most common nephrotoxic mushroom is probably *C. gentilis.* In 2014 there were 6474 mushroom exposures reported in the United States and its territories, with three fatalities. The type of mushroom is unknown in over 80% of the cases.[35] The history of mushroom ingestion may be remote, particularly with *Cortinarius* spp. Although gastrointestinal symptoms are usually noted at the time of ingestion, they may not be severe enough for patients to seek medical attention, and symptoms of renal failure may not manifest until 1 to 3 weeks after exposure. Presentation with a shorter latent period suggests a more severe toxicity and greater risk for severe renal failure. Improvement in renal function may occur within several weeks to months, but patients may require chronic dialysis or renal transplantation.

A more recently described mushroom syndrome involves *Amanita smithiana* or *Amanita proxima.* It is thought that the toxin is 2-amino-4,5-hexadienoic acid.[36] Although it causes acute tubular necrosis within hours of ingestion, the clinical outcome is usually good.

Diagnosis of Acute Kidney Injury Induced by Folk Remedies

An accurate assessment of the contribution of herbs to AKI is made difficult by failure to elicit a history by the physician unfamiliar with these risks or denial by the patients because of fear of stigmatization or social pressure. It is often difficult to discount the contribution to AKI of the original illness for which the herbal medicine was prescribed. AKI may be either the sole manifestation or part of a multisystem and metabolic involvement.

Treatment

Management of AKI is usually supportive and includes volume replacement and correction of metabolic abnormalities. RRT support is offered for the usual indications. About 60% all folk-remedy related AKI cases need RRT, with 25% to 75% mortality. Charcoal hemoperfusion is effective in clearing alfa-amanitin from circulation in those with poisoning from *Amanita* mushrooms.[37]

OTHER RENAL COMPLICATIONS OF HERBAL REMEDIES

Hypertension

Ma huang is an ephedra-containing herbal preparation used in the treatment of bronchial asthma, cold and flu symptoms, fever and chills, headaches and other aches, edema, and lack of perspiration. In Western countries, ephedrine and herbal ephedra preparations are used to promote weight loss and enhance athletic performance. Dietary supplements that contain ephedra alkaloids have been reported to induce hypertension, palpitations, tachycardia, and stroke. Prescribed ephedrine was not associated with a substantially increased risk for adverse cardiovascular outcomes in a registry-based case-crossover study.[38,39] However, ephedra may pose a serious health risk to some users, such as renal patients who are prone to hypertension.

The dried roots of the licorice plant *(G. glabra)* have been consumed for over 6000 years and are used as flavoring and sweating agents, as demulcents and expectorants in the Western world, and as antiallergic and antiinflammatory agents in Asian countries, including China, Japan, and Korea. Licorice contains glycyrrhizin. After oral administration of licorice preparations, glycyrrhizinic acid is hydrolyzed by intestinal bacteria into glycyrrhetic acid. Glycyrrhetic acid can inhibit distal tubule 11-β-hydroxysteroid dehydrogenase-2 (11-BOHD-2), which converts the corticosteroid hormone cortisol to cortisone. Decreased activity of 11-BOHD-2 leads to an excess of cortisol and an overstimulation of the mineralocorticoid receptor, leading to sodium and water retention and increased excretion of potassium. Large doses of glycyrrhizinic acid over a prolonged period can cause pseudoaldosteronism, with hypokalemia, hypernatremia, edema, and hypertension, as well as arrhythmia and other cardiac disorders.[1] To minimize the adverse effects, it is recommended that licorice not be ingested for longer than 4 to 6 weeks.[40]

Crystalluria and Nephrocalcinosis

Many health drinks that are well tolerated by individuals with normal renal function can cause serious problems in patients with limited renal function. One example is star fruit (carambola) juice, which can contain as much as 800 mg of oxalate in 100 ml and can provoke oxalate crystalluria. Sour carambola juice is a popular beverage in Taiwan. Although preparation of commercial carambola juice, by pickling and dilution, markedly reduces oxalate content, fresh juice or only mildly diluted postpickled juice may contain high quantities of oxalate. Cranberry concentrate tablets also can lead to an increase in oxaluria. Ingestion of ma huang have been reported to lead to kidney stones, and the use of ephedrine and guaifenesin individually or in combination has been shown to cause greater than 35% of urinary stones that are related to pharmaceutical metabolites and 0.1% of all urinary stones.[41]

Hyperkalemia

Dietary potassium restriction is a common recommendation for people with renal impairment, especially because hyperkalemia is a side effect of many medications used to slow the progression of renal disease. Common foods high in potassium include oranges, bananas, tomatoes, avocadoes, and potatoes. However, some health drinks are also very high in potassium. Noni juice, often taken to increase energy, contains more potassium than any other fruit juice. The legume alfalfa *(Medicago sativa)* and the plants dandelion *(Taraxacum officinale)*, stinging nettle *(Urtica dioica)*, and horsetail *(Equisetum arvense)* all contain significant amounts of potassium[42] and may induce hyperkalemia in persons with CKD.

Urinary Obstruction

Djenkol beans or Jering *(Pithecellobium jiringa)* are broad, round, reddish beans that grow during monsoon season in Myanmar, Indonesia, and Malaysia and are considered a delicacy. The Jering seeds are extolled for their supposed ability to prevent diabetes and high blood pressure. In addition, the seeds have bladder spasmodic properties and are used as a remedy to eliminate stones from the bladder. Jering poisoning or djenkolism is characterized by spasmodic suprapubic and/or flank pain, urinary obstruction, and AKI.[42] Chronic djenkol bean consumption is associated with a fourfold higher risk for nonglomerular hematuria. The djenkol bean contains a large amount of djenkolic acid in the range of 0.3 to 1.3 g/100 g wet weight; 93% of the acid exists in a free state. Djenkolic acid crystals may lacerate renal tissue and cause bleeding or obstruction. Obstruction of the renal tubules by crystals of djenkol acid is a possible mechanism of acute tubular necrosis. Mild djenkolism requires pain control and hydration. Severe djenkolism, manifested by anuria and AKI, is usually managed with analgesia, aggressive hydration, and alkalinization of the urine with sodium bicarbonate to increase the solubility of djenkolic acid. Some cases of severe djenkolism with anuria do not respond to conservative therapy and require surgical intervention.[43]

Renal Toxicity From Contaminants Within Herbal Medicines

Herbal medicines may be contaminated with excessive or banned pesticides, microbial products, heavy metals, or chemical toxins or adulterated with orthodox drugs. These contaminants are related to the source of these herbal materials, whether grown in a contaminated environment or contaminated during collection or intentionally or intentionally during storage. The presence of orthodox drugs is often a result of the intentional adulteration of the herbal remedy by the manufacturers.[44] A report found undeclared pharmaceuticals or heavy metals in 32% of Asian medicines sold in the state of California. These included ephedrine, chlorpheniramine, methyltestosterone, phenacetin, sildenafil, corticosteroids, and fenfluramine; 10% to 15% contained lead, mercury, or arsenic. Of more than 500 Chinese drugs, approximately 10% contained undeclared drugs or heavy metals.[4]

Several case reports link these adulterations with renal injury. The first report was a 73-year-old Malaysian woman who presented with renal failure and bilateral papillary necrosis after having consumed 2 tablets daily of a traditional herbal preparation, freely available from Chinese medical halls, for 10 years for osteoarthritis. She denied the consumption of any other analgesics, but the analysis of the herbal preparation showed 120 mg of phenylbutazone in each tablet. The second report concerned a 34-year-old housewife taking a mixture of Chinese herbs who presented with Fanconi syndrome and nephrogenic diabetes insipidus. She had a urinary excretion of cadmium 50 times greater than normal. In another report, a patient presented with AKI with marked albuminuria, pyuria, and hematuria after a 4-week treatment with Tung Shueh pills for arthralgias. The cause was acute interstitial nephritis, and the Tung Shueh pills were found to contain both diazepam and mefenamic acid. In Morocco, the traditional *el badia,* a powder made of the seeds of *Tamarix orientalis,* is used as hair dye; however, in times when the *T. orientalis* seeds are scarce, they are replaced with *Takaout roumia,* which contains paraphenylenediamine. Inadvertent ingestion of paraphenylenediamine is an issue in a number of African countries; for example, in Morocco it is responsible for about 10% of all cases of AKI, 50% of all cases of rhabdomyolysis, 25% of intensive care unit admissions for poisonings, and two thirds of poisoning-related deaths.[4,6]

In Thailand and other parts of Southeast Asia and India, there are reports of contamination of herbal remedies with cadmium and/or mercury. In South Africa, about 15% of herbal remedies are contaminated with uranium. In the United States ginseng dietary supplements have been shown to contain the pesticides quintozene and hexachlorobenzene or to exceed the standard for lead content.

Herb-Drug Interactions Resulting in Adverse Renal Effects

Herbs with potential for pharmacokinetic and/or pharmacodynamic herb-drug interactions are often taken concomitantly with therapeutic drugs, without the prescribing physician's knowledge. Pharmacokinetic herb-drug interactions are caused by altered absorption, metabolism, distribution, and excretion of drugs. A frequent underlying mechanism of altered drug concentrations by concomitant herbal medicines is the induction or inhibition of hepatic and intestinal cytochrome P-450 enzymes (CYPs). There are reports of 32 drugs interacting with herbal medicines in humans. These drugs include anticoagulants (warfarin, aspirin, and phenprocoumon), sedatives and antidepressants (midazolam, alprazolam, and amitriptyline), oral contraceptives, antiretroviral agents (indinavir, ritonavir, and saquinavir), immunosuppressants (cyclosporine and tacrolimus), and anticancer drugs (imatinib and irinotecan), and digoxin. Most of them are substrates for CYPs and/or P-glycoprotein, and many have narrow therapeutic indices. Toxicity arising from drug-herb interactions may be minor, moderate, or even fatal, depending on a number of factors associated with the patients, herbs, and drugs.[1]

St. John's wort, derived from the plant *Hypericum perforatum,* has been used since ancient times for depression and anxiety. It is the most common antidepressant used in Germany. St. John's wort induces a hepatic enzyme through activation of the CYP system, leading to decreased serum levels of a wide range of prescribed drugs, with possible clinically serious consequences. For example, St. John's wort ingested for 10 days by a group of healthy volunteers reduced the bioavailability of digoxin by an average of 25%. St. John's wort ingested for 2 weeks reduced the total absorption of indinavir by 50%, which is large enough to cause treatment failure. Other reports indicated significant increases in the metabolism of warfarin, theophylline, oral contraceptives, and cyclosporine. Use of St. John's wort in transplant recipients is associated with both toxicity and underdosage of calcineurin inhibitors as a result of phytochemically triggered activity changes of isoenzyme CYP3A4 metabolism and drug transport proteins.[45,46]

Gingko biloba is one of the most popular plant extracts in Europe and is approved in Germany for the treatment of dementia. *G. biloba* is composed of several flavonoids, terpenoids (e.g., ginkgolides), and organic acids believed to act synergistically as free radical scavengers. *G. biloba* should not be administered with concomitant anticoagulation or in patients with bleeding disorders. Concomitant use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), as well as anticoagulants such as warfarin and heparin, should be avoided. Spontaneous hyphema and spontaneous bilateral subdural hematomas has been observed in patients taking *G. biloba* and is attributed to ginkgolide B, a potent inhibitor of platelet-activating factor needed to induce arachidonate-independent platelet aggregation. Hemorrhagic complications were observed often in patients administered concomitant antiaggregate or anticoagulant therapy. However, the exact mechanism of the interaction of *G. biloba* with aspirin, warfarin, and NSAIDs remains unclear. Experimental data from rats suggest that a *G. biloba* diet markedly increased the content of CYP and activity of glutathione-*S*-transferase and markedly induced the level of CYP2B1/2, CYP3A1, and CYP3A2 messenger RNA in the liver.[47]

Most information about the toxicity of herbal medicines is found only in case reports, and precise identities of the culprit substances, toxicologic characteristics, and pathogenic mechanisms of herbal medicines remain largely unknown. Whereas many herbs have been used for centuries without evidence of acute renal damage, insidious damage caused by long-term use is a concern because many herbs have not been rigorously tested for toxicity.

OVER-THE-COUNTER MEDICINES AND THE KIDNEY

In addition to the increasing popularity of OTC health foods, nutritional supplements, and medicinal products from plants or other natural sources, there is increasing consumption in many countries of pharmaceutical products bought OTC, particularly analgesics and agents for treatment of dyspepsia.

Analgesics

OTC analgesics used for fever and minor musculoskeletal symptoms are one of the most widely used classes of drugs in the developed world. NSAIDs are also used to treat inflammatory conditions; and aspirin is used prophylactically as an anticoagulant in thrombosis-related disorders. Acetaminophen (paracetamol), aspirin, ibuprofen, and naproxen are available OTC in many countries, sometimes in combinations. Easy access to OTC analgesics runs the risk for unwarranted and unsupervised chronic intake. Although studies on the association between the long-term use of aspirin, NSAIDs, and other analgesics and ESRD have given conflicting results, many studies have suggested an association between chronic ingestion of analgesics and kidney disease.

Because analgesic use is widespread, even a small percentage of increased risk for kidney disease may have major public health implications. NSAIDs inhibit cyclooxygenase and may inhibit lipoxygenase, decreasing the production of prostaglandins and leukotrienes, which account for many NSAID-induced renal effects. In patients with volume depletion, renal perfusion depends on circulating prostaglandins to vasodilate the afferent arterioles, allowing more blood flow through the glomerulus. So the contribution of prostaglandins to renal homeostasis is most critical in elderly patients and those with circulatory disturbances, such as renal or liver dysfunction, congestive heart failure, or volume depletion.[48]

Patients who warrant chronic therapy with analgesics and NSAIDs should be monitored by regular screening with dipstick urinalysis and serum creatinine for early evidence of kidney injury. Specifically, low-risk patients should be monitored within 3 months and have studies repeated every 6 to 12 months and high-risk patients should be monitored within 1 to 3 weeks and have studies repeated every 3 to 6 months. Early detection and removal of the offending agent could halt or even reverse analgesic-induced kidney injury. There is a pressing need for multicenter prospective studies to assess the true incidence of this problem and study the effects of various analgesic agents (alone and in combination) in at-risk populations.

Analgesic Nephropathy

Analgesic nephropathy, resulting from the habitual consumption over several years of compound analgesics, is characterized by renal papillary necrosis and chronic interstitial nephritis. It is an increasingly rare condition because phenacetin (the analgesic most implicated as a causative agent) is banned in many countries. Phenacetin alone was not the cause of analgesic nephropathy (in fact phenacetin was never marketed as a single agent); it was the use of phenacetin in combination analgesics that caused the problem. A retrospective cohort study using data from the Australia and New Zealand Dialysis and Transplant Registry showed that among 31,654 patients receiving RRT over the previous 35 years, 10.2% had analgesic nephropathy, but there was a marked decrease in the incidence more recently to less than 3.5% in 2005.[49] Analgesic nephropathy is discussed further in Chapter 62.

Proton Pump Inhibitors

Proton pump inhibitors, such as omeprazole, are now available OTC in many countries and can be associated with granulomatous allergic interstitial nephritis (see Chapter 60). Use of PPIs has been linked epidemiologically to an increased risk for CKD in the general population.

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SELF-ASSESSMENT QUESTIONS

1. A very slender 25-year-old international fashion model presented with renal failure, minimal hypertension, and mild proteinuria. Renal function deteriorated, and the patient received a renal transplant. Six months later, she developed bilateral urogenital tract tumors. What was the most likely cause of her kidney disease?
   A. Analgesic nephropathy
   B. Aristolochic acid nephropathy
   C. Anorexia nervosa
   D. Heavy metal intoxication
2. A 30-year-old recent emigrant from Romania presents with a 3-month history of fatigue, dyspnea on exertion, anorexia, and nausea. On physical examination, she is thin and appears chronically unwell. Blood pressure is 160/100 mm Hg, with otherwise normal physical examination findings. Laboratory workup is significant for hematocrit 22, serum potassium 5.7 mmol/l, serum bicarbonate 19 mmol/l, serum glucose 90 mg/dl, blood urea nitrogen 80 mg/dl, and serum creatinine 4 mg/dl. Urinalysis shows 1+ glucose, 2+ protein, 20 to 30 leukocytes per high-power field. Urine culture is negative for bacteria and acid-fast bacilli. Urine protein was 500 mg/24 h; renal ultrasound, right kidney, 9.8 cm; left kidney, 9.6 cm; and no hydronephrosis. What is the most likely cause of her renal impairment?
   A. Acute renal failure from tubular necrosis
   B. Chronic glomerulonephritis
   C. Chronic tubulointerstitial nephritis (Balkan endemic nephropathy)
   D. Occult diabetic nephropathy
3. A previously noncompliant patient with stage 4 chronic kidney disease secondary to hypertension comes into your office saying he has changed his ways. He has lost weight, is taking all of his medications, and is drinking homemade star fruit (carambola) juice for its antioxidant properties. His serum creatinine is 5.1 mg/dl (previously 2.4 mg/dl). In the figure, which picture are you most likely to see on urinalysis?
   A. Cystine crystal
   B. Urate crystal
   C. Triple phosphate
   D. Oxalate crystal
4. A 52-year-old woman 5 years after kidney renal transplantation is on mycophenolate mofetil and cyclosporine with stable transplant function. She reports that she just came back from a health spa and that she feels wonderful. She said she was diagnosed with depression and was started on St. John's wort by the herbalist. Which of the following transplant-related problems are you are most concerned about?
   A. Acute rejection
   B. Crystal formation in the graft
   C. Cyclosporine toxicity
   D. Hypertension

77

Epidemiology of Chronic Kidney Disease and Dialysis

Morgan E. Grams, Stephen P. McDonald

The 2015 Global Burden of Disease Study reported an enormous increase in global life expectancy between 1980 and 2015, from 61.7 years to 71.8 years.[1] Much of this improvement is attributable to declining mortality from communicable, maternal, neonatal, and nutritional disease. However, with the aging of the population, chronic kidney disease (CKD) has become one of most common noncommunicable diseases in the world as well as a leading cause of mortality. Half of the people in the United States are expected to develop CKD during their lifetime.[2] Associated with huge health system costs, particularly in the advanced stages, which includes kidney failure treated with dialysis as well as kidney transplantation, CKD has come into focus as a common, morbid, and often preventable disease.[3]

DEFINING CHRONIC KIDNEY DISEASE

Chronic Kidney Disease Staging

Over the past decade, the definition of CKD has evolved to incorporate advances in knowledge of prognosis.[4] The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines published in 2002 classified CKD into five stages on the basis of glomerular filtration rate (GFR) and signs of kidney damage (proteinuria, abnormal urinary sediment, structural abnormalities, presence of a kidney allograft).[5] This staging system was modified in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines to reflect the independent contributions of GFR, albuminuria, and cause of CKD.[6] Although the incorporation of cause of CKD in the classification system has been used relatively infrequently in subsequent CKD research, in part because of a paucity of data, the two-dimensional "heatmap" that classifies CKD in GFR categories (G-stages) and albuminuria categories (A-stages) has been widely accepted and robustly validated (Fig. 77.1).[7]

Classification Based on Estimated Glomerular Filtration Rate

Serum creatinine is the most commonly used filtration marker for the estimation of GFR, and GFR estimating equations incorporating serum creatinine as well as age, race, and sex generate precise and accurate assessments of kidney function in the vast majority of both CKD and non-CKD populations.[8] In North America, the best available GFR estimating equation is that developed by the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) collaboration, and most commercial laboratories automatically report estimated GFR (eGFR) using this equation.[9] The accuracy of GFR estimation also has benefited from universal standardization of the creatinine laboratory assay (see Chapter 3).[10]

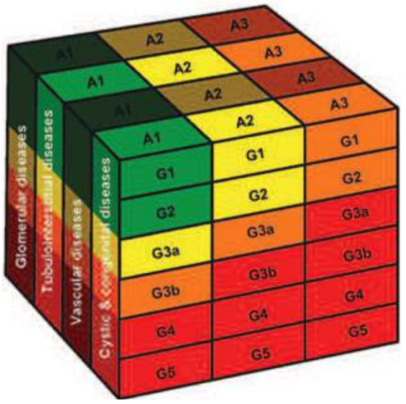
Classification Based on Albuminuria

Compared with the estimation of GFR, efforts to accurately quantify albuminuria are in their infancy. Multiple techniques exist to estimate urine albumin excretion. The semiquantitative dipstick method is most common, followed by spot and 24-hour urine protein or albumin excretion assessments. All are subject to limitations. Dipstick testing is inexpensive, but the diagnostic accuracy, particularly for moderately increased levels of albuminuria, can be low.[11] Although a full day's collection of urine albumin is generally considered the gold standard in albuminuria estimation, the process is tedious and imposes substantial burden on the patient. Thus the KDIGO guidelines recommend a spot collection of urine, with early morning timing preferred, as the initial screening test.[6] Urine albumin is recommended over urine protein assessment given the superiority of the laboratory assay and standardization as well as the relative importance in prognosis. Spot samples are standardized to urine creatinine to normalize to 24-hour excretion and account for any differences in concentration (e.g., albumin-to-creatinine ratio [ACR]). Of note, any abnormalities in GFR or albuminuria must persist over 3 months to meet the definition of CKD (see Chapter 3).

Classification Based on Chronic Kidney Disease Cause

The cause of kidney disease ("C" in the KDIGO-proposed CGA staging) is the least-studied aspect of the CKD definition. The proposed KDIGO classification categorizes disease by the presence of underlying systemic disease and the location of the abnormality (see Fig. 77.1). Thus diabetic nephropathy (DN) might be classified as a systemic disease affecting the glomerulus, and obstructive nephropathy as a primary kidney disease affecting the tubulointerstitium. Limitations of this approach include the infrequent use of kidney biopsy, the gold standard for assessment of pathologic location of kidney abnormalities. On the other hand, decisions not to perform kidney biopsies are often driven by the uncertain benefit of precise localization of pathologic abnormalities in terms of prognostic implications—a vicious circle begetting sparse evidence.

Chronic Kidney Disease Classification According to Glomerular Filtration Rate and Albuminuria



GFR categories (ml/min/1.73 m^2) description and range		
G1	Normal or high	≥90
G2	Mildly decreased	60-89
G3a	Mildly to moderately decreased	45-59
G3b	Moderately to severely decreased	30-44
G4	Severely decreased	15-29
G5	Kidney failure	<15

Persistent albuminuria categories description and range		
A1	A2	A3
Normal to mildly increased	Moderately increased	Severely increased
<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol

Classification of CKD based on presence or absence of systemic disease and location within the kidney	
Presence of systemic disease affecting the kidney	Primary kidney diseases
Glomerular diseases	
Tubulointerstitial diseases	
Vascular diseases	
Cystic and congenital diseases	

Fig. 77.1 Depiction of chronic kidney disease classification, G-stages and A-stages. The cube denotes how the three components of the chronic kidney disease classification scheme (glomerular filtration rate [G], albuminuria [A] and underlying kidney disease) interact to influence the risk of progression to kidney failure. This risk is represented in qualitative terms (lowest to highest) by green, yellow, orange and red colors.

Odds of Laboratory Abnormalities by Estimated Glomerular Filtration Rate

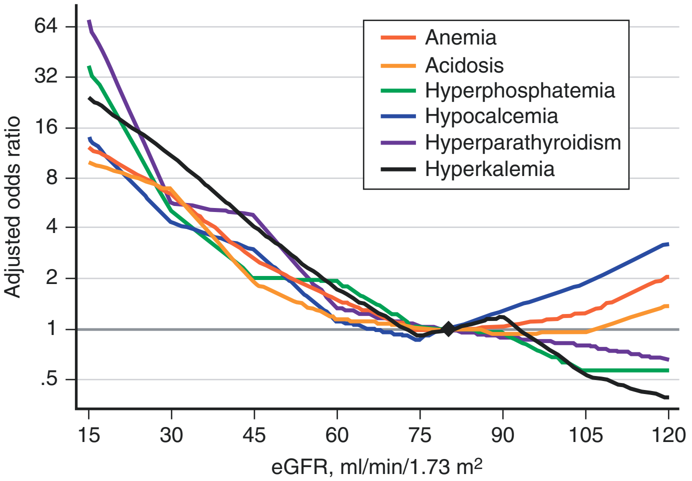


Fig. 77.2 Odds of laboratory abnormalities according to estimated glomerular filtration rate (eGFR) among people from the general United States Population. (Data are from the Continuous National Health and Nutrition Examination Survey [NHANES] during 1999–2010.)

Rationale for the Chronic Kidney Disease Definition

Associations With Adverse Outcomes

The cut-points of GFR and albuminuria used to define disease (<60 ml/min/1.73 m^2 and ≥30 mg/g, respectively) have been rigorously examined. Each represents a higher risk state compared with normal levels for a variety of outcomes. For example, the relationship between GFR and the prevalence of anemia, acidosis, hyperphosphatemia, hypoalbuminemia, and hyperparathyroidism demonstrates a continuous increase in risk with GFR less than 60 ml/min/1.73 m^2 (Fig. 77.2).[12] Furthermore, the risk for future kidney outcomes, including acute kidney injury, CKD progression, and end-stage renal disease (ESRD), all exhibit graded associations with lower GFR.[13] Although relationships with progression to ESRD are strongest, both lower eGFR and higher albuminuria are independently associated with cardiovascular mortality and all-cause mortality as well (Fig. 77.3).[7] For example, for a given value of GFR, higher albuminuria is associated with higher risk for adverse events compared with albuminuria levels below 30 mg/g.[3]

Persistent Relationships Within Subgroups

Although there remains some controversy about the use of different thresholds for different groups of people, some have argued that the pathologic threshold for GFR should be lower in older adults or that there should be sex-specific definitions of pathologic albuminuria.[14] The risk relationships between eGFR and ACR with adverse outcomes are remarkably robust in different subgroups, including older and younger adults and men and women. Although reduced GFR is more common among older individuals, it remains a strong risk factor for ESRD compared with higher levels of GFR (Fig. 77.4).[15] Similarly, the risk relationships between ACR and adverse outcomes actually appear to increase earlier in women than men, counter to the proposed sex-specific definitions that assign a higher ACR threshold in women (Fig. 77.5).[16] On the other hand, the argument that the ACR threshold of 30 mg/g may miss clinically relevant disease is supported by a continuous increase in risk beginning at levels greater than 10 mg/g.

GLOBAL BURDEN OF CHRONIC KIDNEY DISEASE

Accurate estimations of CKD prevalence are difficult because tests for creatinine and albuminuria are not uniformly performed; however, many believe the global burden of CKD to be large and increasing.[17] The best estimates are derived from nationally representative samples such as the National Health and Nutrition Examination Survey (NHANES) in the United States; estimates based on populations receiving health care may overestimate (or, in some cases, underestimate) disease prevalence.[18] In

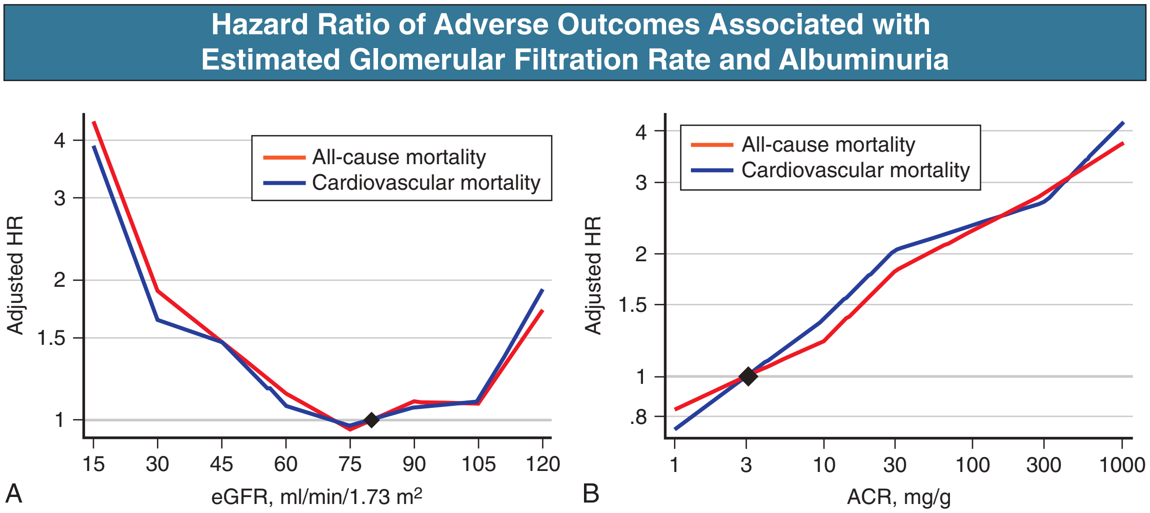


Fig. 77.3 Hazard ratios *(HR)* of adverse outcomes associated with estimated glomerular filtration rate *(eGFR)* (A) and albuminuria (B) among people from the general United States population. *ACR,* Albumin-to-creatinine ratio. (Data are from the National Health and Nutrition Examination Survey III [1988-1994] and the continuous National Health and Nutrition Examination Survey [1999-2010].)

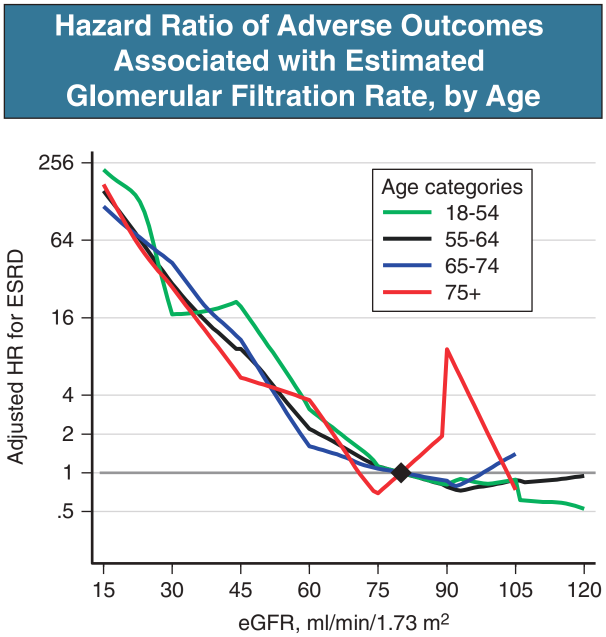


Fig. 77.4 Hazard ratios *(HR)* of adverse outcomes associated with estimated glomerular filtration rate *(eGFR),* by age. *ESRD,* End-stage renal disease. (From reference 15.)

the United States, estimates of CKD prevalence based on a one-time measurement of serum creatinine recently placed the proportion of the population with stage G3 or G4 CKD at 6.9%; using a definition of ACR greater than 30 mg/g or eGFR less than 60 ml/min/1.73 m^2, the prevalence of any CKD was 14.2%.[19] This definition likely overestimates prevalence because the persistence of albuminuria was not taken into account. Publications from countries in Europe show wide variation in CKD prevalence, from 3.3% in Norway to 17.3% in northwest Germany, but this may reflect differences in sampling strategy rather than true population-level differences.[20] Estimates in developing countries are less available, but most place the global population burden between 8% and 16%, affecting nearly 500 million adults worldwide in 2010.[21]

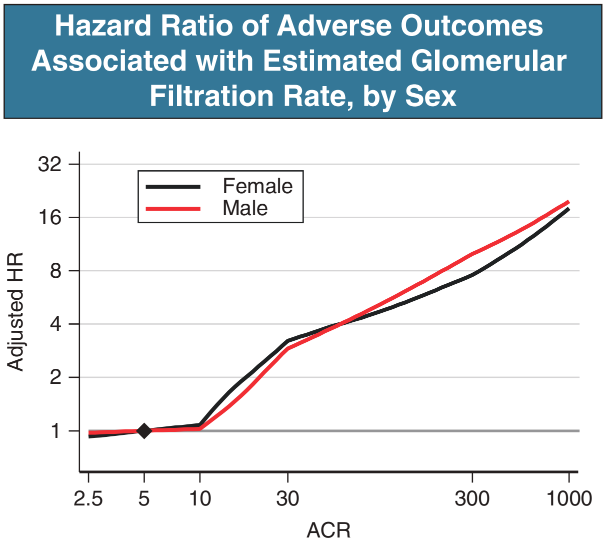


Fig. 77.5 Hazard ratios *(HR)* of adverse outcomes associated with albuminuria, by sex. *ACR,* Albumin-to-creatinine ratio. (From reference 16.)

RISK FACTORS FOR CHRONIC KIDNEY DISEASE

Age

Many risk factors have been implicated in the development of CKD. Age is a strong risk factor for GFR below 60 ml/min/1.73 m^2, and so population aging is almost inevitably associated with an increase in CKD burden. Interestingly, although incidence rates of ESRD tend to be highest among persons over 65 years, older age is often associated with a lower risk for developing ESRD in multivariable-adjusted analyses.[3,22] In other words, for the same level of kidney function, a younger person is at higher risk for progression to ESRD than an older person, likely in part because the competing risk for pre-ESRD mortality is lower in younger persons and younger persons may be more willing to accept or likely to be prescribed a notoriously grueling therapy (dialysis or transplantation) compared with older persons.

Sex and Race

Risk for CKD differs by other demographic factors as well. Women are generally at higher risk for incident CKD but lower risk for incident ESRD than men.[2] In the United States, race demonstrates a similar, paradoxical finding: Black individuals have a lower prevalence of mild CKD and a higher prevalence of ESRD than White individuals. Two recent genetic discoveries can partially explain this disparity; two genetic risk variants common in persons of African descent confer higher risk for CKD and ESRD.[23,24] The genetic variants, sickle cell trait and the *APOL1* high-risk genotype, protect against two different parasites and are prevalent in 7% and 13% of the U.S. African American population, respectively. The presence of sickle cell trait is thought to confer risk via subclinical sickling in the oxygen-poor medulla, leading to impairments in concentrating ability and hematuria over time. The mechanism of the *APOL1* risk alleles is as yet uncertain, but it appears to be mediated through the development of albuminuria.

Social Determinants

Socioeconomic factors also play a role in CKD risk. People with lower socioeconomic status face greater burden of CKD and rapid GFR decline in the United States, and this finding has been replicated in many other developed countries.[3,6] Many postulate that racial differences would greatly attenuate with equal access to health care. Indeed, several studies have demonstrated attenuation or elimination of racial disparities in kidney outcomes with accounting for differences in income and the presence of health insurance, including risk for AKI, eGFR decline, and delay in transplantation in children.[25]

Comorbid Conditions

Diabetes mellitus and hypertension are often cited as the major attributable causes of CKD in the developed world, and recent studies suggest similarities in the developing world.[3] Nearly half of the population with CKD and ESRD has diabetes. Persons with diabetes and CKD merit concern not only for the risk for albuminuria and CKD progression but also for heightened risk for many other adverse outcomes, particularly cardiovascular disease. On the other hand, the risk for CKD among those with diabetes mellitus is eminently manageable through tight control of blood glucose, blood pressure, and the use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Hypertension also has shown a graded association with the risk for ESRD in observational studies, although the relationship with kidney disease is more complex than that of diabetes and CKD because hypertension is both a cause and a consequence of CKD. Obesity may confer increased risk for CKD over the long term, possibly mediated through the development of obesity and hypertension, and smoking has been linked to higher ESRD risk.[26] Other clinical characteristics such as elevated uric acid and elevated serum osmolality have been associated with the development of CKD; however, whether there is a causal role of these risk factors has not yet been determined.

ISSUES WITH IDENTIFYING CHRONIC KIDNEY DISEASE

Lack of Awareness

Often a silent disease until the most advanced stages, CKD is largely underrecognized by providers and patients. Fewer than 10% of people with laboratory-confirmed CKD in the NHANES survey reported being aware that they had kidney disease, a finding corroborated in other regions.[3] Provider awareness may not be much higher; only 12% of patients with CKD had an associated diagnostic code in Stockholm health care.[27] Low awareness of disease may lead to low testing and referrals, because only 27% of patients with eGFR below 60 ml/min/1.73 m^2 had albuminuria screening, and 23% were appropriately referred to a nephrologist. In the Stockholm cohort, 38% of patients with diabetes were evaluated for albuminuria, very similar to the proportion among U.S. Medicare patients with diabetes.[3]

Imperfect Biomarkers

Another issue in CKD identification is the occasional fallibility of existing biomarkers. Serum creatinine, the most widely used filtration marker to estimate GFR, has non-GFR determinants, including diet and muscle mass. For example, amputees and persons with reduced muscle mass may have a falsely elevated eGFR when creatinine is used. Thus the KDIGO guidelines recommend a confirmatory measurement performed for persons in whom measuring creatinine may be less accurate.[6] To confirm diagnosis (or eGFR level for drug dosing or kidney donation), KDIGO recommends obtaining a cystatin C–based eGFR or clearance measurement. Of course, cystatin C has its own non-GFR determinants, body mass index and inflammation. For this reason, for the general population the most accurate estimating equation uses both creatinine and cystatin (see Chapter 3).[28]

Errors in Urine Albumin Assessment

Variability in albumin excretion and measurement also can confound CKD identification. In clinical practice, spot samples are usually assessed and standardized to urine creatinine to correct for error induced by differences in hydration status. However, urine albumin and creatinine excretion are thought to follow a circadian rhythm with variation induced by differences in posture, exercise, and diet.[29] Moreover, many providers quantify urine protein rather than urine albumin, a less sensitive and specific marker of glomerular permeability. Urine protein measurement is additionally hampered by interlaboratory variation in methods and calibration and the lack of a reference measurement protocol.[6] For these reasons, urine albumin assessment is generally preferred over urine protein assessment, and repeated 24-hour collections offer the most accurate estimation of true albuminuria.

OUTCOMES OF CHRONIC KIDNEY DISEASE

Associations With Adverse Outcomes

The public health implications of CKD are enormous because of the strong associations with adverse outcomes—in particular, cardiovascular disease, ESRD, and mortality. Many have argued that CKD should be considered a coronary heart disease risk equivalent, much like diabetes, and some guidelines recommend preventive statin use for all patients with CKD older than 50 years.[30] The independent associations of GFR and albuminuria with adverse outcomes has been demonstrated in general, high-risk, and CKD populations, as well as in separate geographical regions.[7,31] Albuminuria and GFR have been shown to be independent risk factors for AKI, gastrointestinal bleeding, thrombosis, and infection.

Variation in Absolute Risk for Adverse Outcomes

Increasingly, risk scores are used to inform patient counseling and treatment decisions. Guidelines encourage the incorporation of ESRD risk prediction in RRT planning, and several risk scores now exist.[6] The kidney failure risk equation developed in two Canadian cohorts is probably the most widely used, and has been validated in 31 cohorts worldwide.[22] It was noted that the absolute risk for progression to ESRD was slightly lower in non–North American countries and that this difference was not explained by differences in demographic or clinical characteristics. Variation in absolute risk for ESRD thus might suggest differences in treatment availability, patient or provider acceptance, or differences in the competing risk for death.

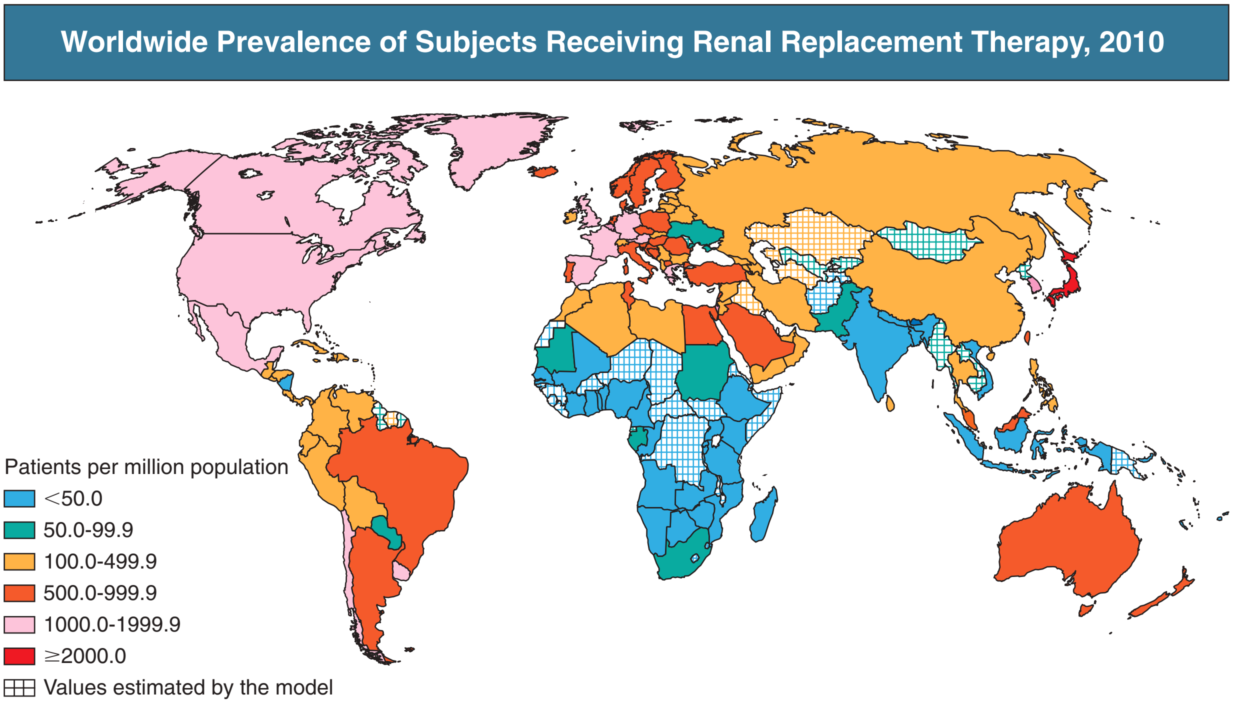

Worldwide Prevalence of Subjects Receiving Renal Replacement Therapy, 2010
Patients per million population
<50.0
50.0-99.9
100.0-499.9
500.0-999.9
1000.0-1999.9
≥2000.0
Values estimated by the model

Fig. 77.6 Patients receiving renal replacement therapy in 2010. (From reference 32.)

DIALYSIS EPIDEMIOLOGY

The number of people receiving chronic RRT (dialysis or kidney transplantation) for kidney failure worldwide has progressively increased over the 50 years since these treatments became available, and this increase continues. Initially available only to selected patients in restricted centers in some countries, both long-term dialysis and kidney transplantation have become progressively more available not just in high-income countries, but also in many low-income countries. Approximately 2.5 million people were estimated to be receiving chronic RRT in 2010[32]; absolute rates are high in North America, but the highest prevalent rates (people currently receiving RRT) per million population are in Taiwan and Japan (Fig. 77.6), where the vast majority of people receive long-term dialysis. Good data are available throughout the developed world and in many parts of the developing world because of the existence of regional and national dialysis registries. These registries typically report rates, outcomes, and practice patterns of dialysis at a national level; many also have a major role in provision of hospital-specific information and other safety and quality reporting, as well as providing a substantial resource for clinical research.

Incidence and Prevalence of Chronic Dialysis

Incidence rates (the number of new RRT patients) comprise patients starting chronic or long-term dialysis and a small number of people receiving preemptive kidney transplants. Incidence rates are highest in Taiwan, Mexico, and the United States, followed by various Asian countries. There is substantial variation among countries in every region around the world (Fig. 77.7). DN has been the main factor in the increase in incidence rates in almost all countries. In most countries, DN is attributed as the cause for ESRD in 40% to 60% of cases.

The trends in incidence rates vary across different regions. In many Asian countries (e.g., Korea, Singapore, Malaysia, Thailand) rates continue to increase. However, in the United States, Canada, Western Europe, Australia, and New Zealand, incidence rates have generally stabilized over the last 5 to 10 years. Nevertheless, in these countries the *prevalent* numbers and rates of dialysis continue to increase because the number of people leaving dialysis programs (deaths and transplant recipients) is smaller than the incident number.

Not every person with kidney failure receives dialysis or transplantation. In some situations (particularly those with substantial comorbidities or limited life expectancy), dialysis may not be clinically appropriate, or a decision is made for a conservative (nondialysis) approach to treatment (see Chapters 89 and 112). Registries typically report rates of RRT, which is synonymous with ESRD, a U.S administrative term meaning treatment with dialysis or kidney transplantation for chronic kidney failure. Estimating the total burden of kidney failure requires incorporation of both the number of people commencing RRT and the number of people dying of kidney failure without treatment. This has been examined using data linkage (of registry data with death certificates) in Australia[33] and in cohort studies, most notably in Alberta, Canada.[33] These studies suggest that among the older groups (older than 75 years) dialysis therapy is used in less than 50% of people with kidney failure. Consistent with this is evidence suggesting that among older patients with comorbidities, there is little or no survival advantage of dialysis therapy.[34]

Dialysis is a resource-intensive therapy, and there is a relationship between the provision of (and access to) dialysis and the overall economic development of a country (Fig. 77.8). As with other chronic diseases, there is also a gradation seen within many societies in rates of dialysis, with higher rates seen among those at the lower end of the socioeconomic spectrum.[35,36] Gradients with income and education are also seen among predialysis patients.[37]

Incidence rates vary with sex, with rates lower among women than men.[38] Incidence rates increase with older age, up to 75 to 80 years old. There have been progressive changes differing across age-specific incidence rates over many years, with increasing incidence rates of progressively older age groups over a long period followed by stabilization in more recent years. An example of this (from Australia, but typical of that seen in developed countries) is shown in Fig. 77.9.

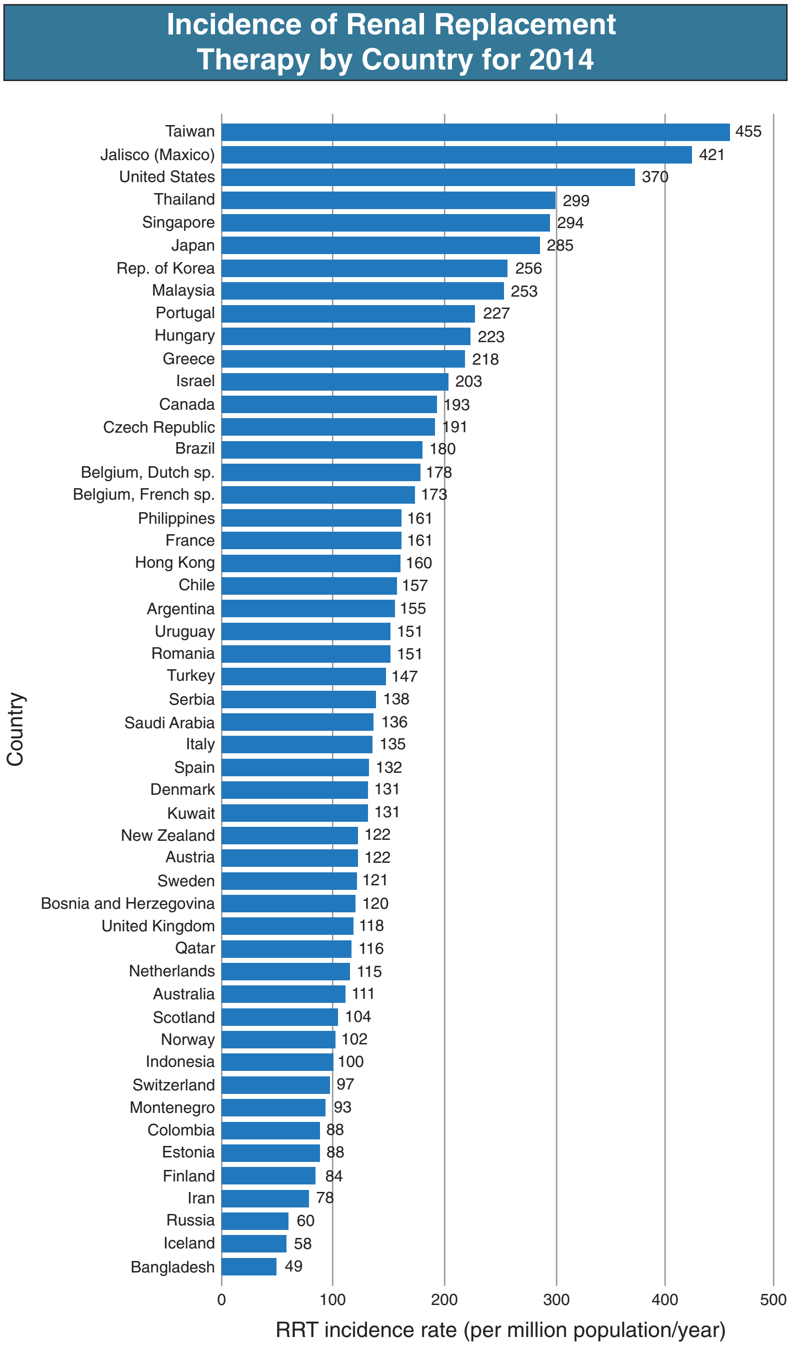


Fig. 77.7 Incidence rate of renal replacement therapy (RRT) (per million population per year), by country for 2014. (From reference 40.)

Some ethnic groups experience particularly high rates of kidney failure and dialysis. Indigenous peoples in Australia, New Zealand, Canada, and the United States have very high rates of kidney disease, poorer outcomes, and less access to transplantation.[39] The causes underlying this are complex, but common elements appear to include very high rates of diabetes, metabolic syndrome, and hypertension driving high rates of CKD.

Dialysis Practice Patterns

Dialysis practice patterns vary widely across countries, with different usage of PD, HD, and home HD. For prevalent patients the regions with the highest proportion of PD are Hong Kong (72% of prevalent patients) and the Jalisco region of Mexico (47% of prevalent patients).[40]

Home HD is most commonly used in New Zealand and Australia, where 18% and 9%, respectively, of prevalent RRT patients are treated with this modality. Practice patterns also vary in the application of various techniques of HD; for example, dialysis sessions are generally longer in Japan, with slower blood flow rates.

Outcomes

The rationale for dialysis is to prevent death from uremia, and hence the outcome for dialysis treatment is usually reported as mortality rate. Other important outcomes commonly reported include cause-specific mortality rates, hospitalizations, and technique failure. Patient-reported outcomes (including measures of quality of life and functional ability) are also extremely important but recorded much less frequently.

Prevalence of Patients Receiving Renal Replacement Therapy (RRT) as a Function of Per Capita Gross Domestic Product

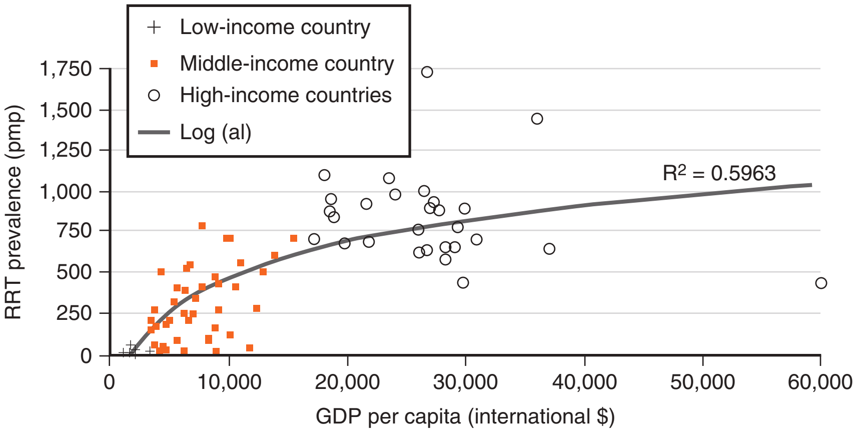


Fig. 77.8 Prevalence of patients receiving renal replacement therapy *(RRT),* as at December 31, 2002 and gross domestic product *(GDP)* per capita. *PMP,* per million population. (From reference 50.)

Age-Specific Renal Replacement Therapy Rates in Australia

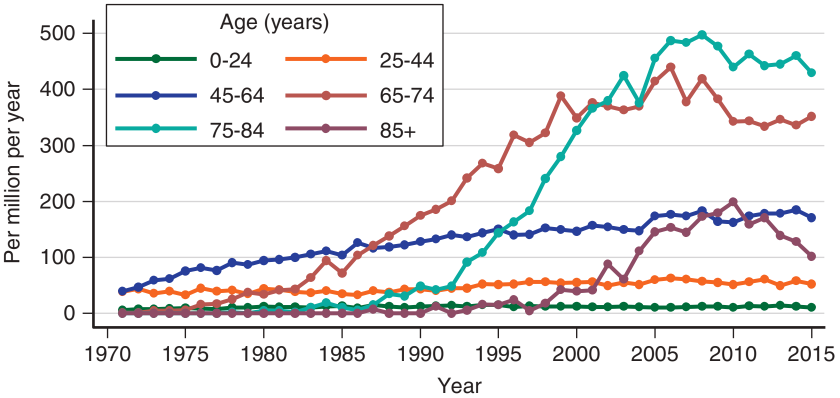


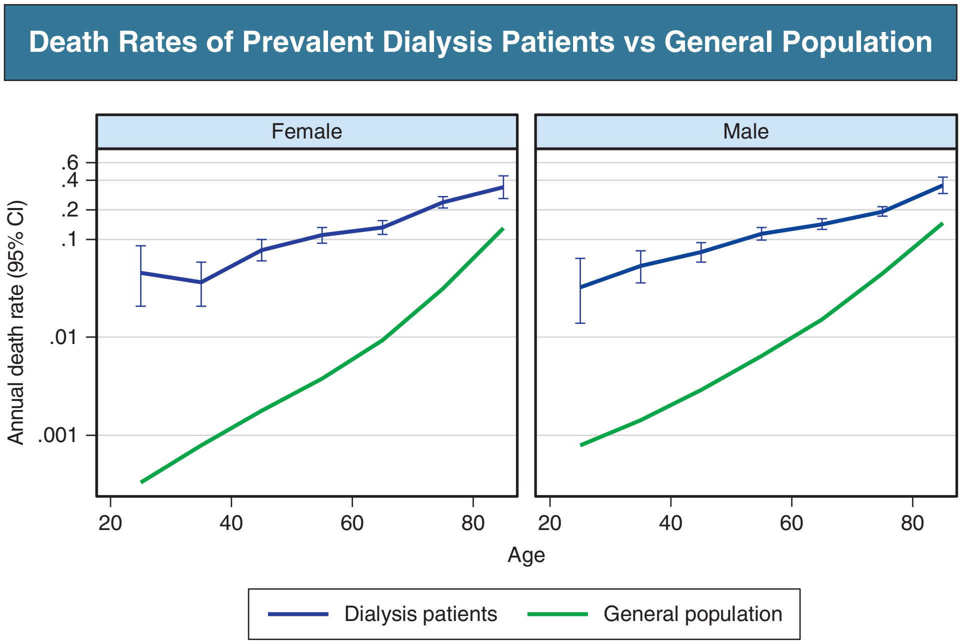
Fig. 77.9 Age-specific renal replacement therapy incidence rates in Australia. (Data from reference 51.)

Crude mortality rates vary widely; a multinational observational study (Dialysis Outcomes and Practice Patterns Study [DOPPS]) reported rates from 6.6% per year in Japan to 21.7% in the United States.[41] Mortality rates among dialysis patients are substantially higher than in the general population, a differential particularly marked among younger age groups (Fig. 77.10). The excess mortality is primarily driven by cardiovascular and infectious causes. There is also a modest (approximately threefold) excess risk for cancer among dialysis patients, even after exclusion of cancers directly related to the cause of kidney disease.[42] An issue unique to categorization of deaths among the dialysis cohort is assignment of deaths as a result of withdrawal from therapy. There is a wide range in reported frequency of withdrawal, from less than 5% to more than 20% of all deaths.[43] These differences may in part reflect different coding mechanisms but are also likely to reflect differences in practice patterns in the commencement of therapy among older patients with higher levels of comorbidity.

There is variation in mortality rates over time, with the highest rates seen in the first 3 months after commencing dialysis, particularly among older age groups (Fig. 77.11). After this period, mortality rates approximate the longer term rates. There are a number of possible contributors to this, including the risk associated with commencement of dialysis (such as the placement of central venous catheters) and increased severity of comorbidities associated (or causing) the deterioration of renal function.

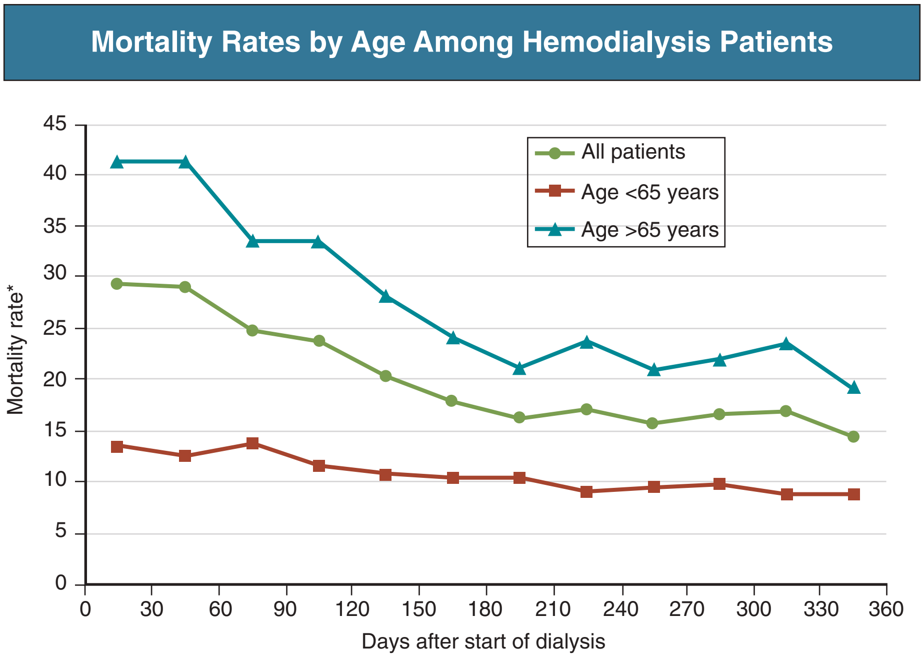
Multiple observational studies have compared mortality between PD and HD, but there has been no randomized controlled trial (RCT) successfully conducted despite a number of attempts. Results from observational studies have varied across countries; common elements are the presence of multiple interactions such that the comparison depends on comorbidities and patient age, the length of follow-up, and selection biases and local/regional outcomes of each technique.

For PD (and to a lesser extent home HD), "technique survival" is a common metric. This refers to the proportion of people continuing on PD at various time points. It is a combined end-point, with patient death and transfer to HD considered failures. Typically 30 days of HD is considered to be a permanent transfer to HD. It is important to



Death Rates of Prevalent Dialysis Patients vs General Population

Fig. 77.10 Death rates of prevalent dialysis patients versus general population. *CI,* Confidence interval. (From reference 51.)



Mortality Rates by Age Among Hemodialysis Patients

Mortality rate during the first 360 days of HD treatment

	0-30	31-60	61-90	91-120	121-150	151-180	181-210	211-240	241-270	271-300	301-330	331-360
All patients	29.3	28.9	24.9	23.8	20.4	17.9	16.2	17.0	15.7	16.5	16.8	14.4
Age <65 years	13.3	12.6	13.5	11.6	10.7	10.4	10.2	9.1	9.3	9.7	8.9	8.7
Age >65 years	41.2	41.2	33.7	33.5	28.2	24.0	21.1	23.6	21.0	21.9	23.5	19.2

Fig. 77.11 Overall mortality rates among hemodialysis patients by age. *Mortality rate: Number of deaths per 100 patient-years. *HD,* hemodialysis. (From reference 43.)

ensure consistency of definitions in comparisons of technique survival; alternative duration definitions have substantial effects on the calculated technique survival.

EPIDEMIOLOGIC CONCEPTS

Epidemiologic factors influence the reported rates of RRT; understanding the potential biases is a necessary part of interpretation of these data.

The *prevalent* number of RRT patients at any point in time receiving a form of RRT reflects both the rate of people starting treatment (for overall RRT numbers, the *incidence* rate) and the rate of people ceasing treatment (the *mortality* rate). These rates can be considered *transition probabilities* among various states. This concept can be applied to the overall number of people receiving RRT, the number receiving dialysis or transplantation, and other subgroups. For example, the determinants of the prevalent number of people receiving dialysis at any point in time can be determined from the existing population plus the number of new patients (incidence rate plus the number of people who have lost graft function) less the number of deaths (mortality rates during dialysis) and kidney transplants.

This form of multistate model is often known as a Markov model. Use of these models to estimate future trends can be used by health services and others in predicting the future number of people receiving RRT. This can be done under existing conditions and under various hypothetical scenarios to model the effects of various interventions.

The *incidence* rates reported for ESRD typically exclude dialysis for AKI. Definitions of the start point of RRT vary across registries and data collections. In many cases, an "intent" definition is used (i.e., dialysis is commenced with the intention of long-term treatment, underpinned by a diagnosis of irreversible ESRD). The other approach (used by the U.S. and European registries) is to use day 90 after dialysis start as the point at which patients are deemed to require "chronic" dialysis. Although this approach eliminates uncertainty around people with prolonged acute (or acute on chronic) kidney injury who may or may not recover, it does prevent analysis of early mortality.

Selection bias affects incidence rates. There may be constrained provision of dialysis services that affects ability to access dialysis services. There have also been changes in clinical practice over time affecting the propensity to treat in certain situations (especially among older and more frail patients). These factors will influence observed rates; differences in these selection biases will be relevant to comparisons of disease incidence among groups and also to the same group between different times. This is likely to have contributed to the increasing dialysis rates among progressively older people observed in the 1970s to late 1990s.

Lead time bias occurs when the time point of observation differs between groups. One example of this is the comparison of PD and HD cohorts. Patients commencing RRT with PD typically do so at a higher eGFR than those commencing with HD; current U.K. data suggest this mean difference is around 0.5 ml/min/1.73 m^2.[44] Although small, this may amount to 2 to 3 months of difference in starting point of analyses.

Competing risks are seen in several areas. This phenomenon arises when an illness may lead to multiple possible outcomes, but the occurrence of one precludes another. For example, changes in cardiovascular mortality may affect the incidence rate of RRT because patients who survive despite significant heart disease may avoid premature death that would preclude dialysis treatment. Another example is the influence of kidney transplantation in evaluation of survival of a dialysis cohort: increased occurrence of transplantation may lead to higher mortality in dialysis cohort.

Immortal time bias arises when an inappropriate time point is chosen for comparators. An example of this might be comparison of mortality after coronary angiography performed as a pretransplant assessment between those transplanted and not transplanted; the transplanted group will accumulate "immortal" follow-up time between angiography and transplantation, in contrast to the nontransplanted group.

EVIDENCE QUALITY

There is a relative dearth of RCTs supporting practice in the area of dialysis, compared with other disciplines. Most large-scale trials examining dialysis-specific interventions have yielded negative or inconclusive results; for example, the use of non–calcium-containing phosphate binders,[45] increased dialysis dose,[46] use of statins in dialysis patients,[47] and hemodiafiltration.[48] In response to this, clinical trials networks with a focus on nephrology have been established in several countries to catalyze the conduct of trials (particularly where there is limited commercial interest).

The outcomes examined in trials also have been critically examined. Given the time delay and multiple contributing factors to mortality, many trials have used surrogate outcomes. Given the association of many biochemical abnormalities with increased mortality, their use appears logical. However, as in other areas of medicine, use of surrogate outcomes in trials and evidence generation in nephrology has been problematic, with changes in surrogates not reflected by reduction in mortality or other hard end-points. An example of this is the use of phosphate (and parathyroid hormone) as a surrogate to assess the effectiveness of cinacalcet. Partly as a response to this, initiatives have been instituted to develop and codify the outcomes for trials.[49] An important element of this is also the inclusion of input from patients and consumers of services in setting research priorities.

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SELF-ASSESSMENT QUESTIONS

1. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 chronic kidney disease (CKD) classification includes all of the following in the staging of CKD *except:*
   A. The severity of hypertension
   B. The severity of albuminuria
   C. The level of glomerular filtration rate (GFR)
   D. Cause of disease
2. Which statement is true?
   A. Low GFR is unimportant in older adults.
   B. Higher albuminuria is worse for men than women.
   C. Higher albuminuria is associated with acute kidney injury.
   D. Assays for proteinuria are more accurate than assays for albuminuria.
3. Racial disparities in ESRD incidence is in part attributable to:
   A. The higher prevalence of APOL1 genetic risk variants in those of European descent
   B. Lower socioeconomic status and poorer access to health care in Black individuals
   C. Greater rates of smoking among Black individuals
   D. Lipoxins
4. Which statement is most true about rates of new dialysis patients?
   A. They are highest in Eastern European countries.
   B. An increase in rates of glomerulonephritis is the major driver.
   C. Rates are higher among older than younger people.
   D. Rates are higher among women.
   E. Rates are generally lower among groups with lower socioeconomic status.
5. Regarding competing risks in comparison of rates of new dialysis patients between groups:
   A. Competing risks refers to higher rates seen among health systems in which funding is allocated on a competitive grants basis.
   B. Men more than women are affected because testosterone leads to greater competitive drive.
   C. Competing risks from transplantation will not be a factor if measured covariates are included and adjustment is made for them.
   D. Incident dialysis rates might be higher if vascular mortality associated with CKD were lower.
   E. Propensity score matching can largely address the problems raised by competing risks.

78

Pathophysiology of Disease Progression in Proteinuric and Nonproteinuric Kidney Disease

Ariela Benigni, Norberto Perico, Giuseppe Remuzzi

Chronic kidney disease (CKD) is a worldwide threat to public health and has a risk-multiplier effect on major noncommunicable diseases, including cardiovascular diseases.[1] More than 322 million individuals are currently affected by CKD worldwide,[2] and the number of patients with end-stage renal disease (ESRD) treated with renal replacement therapy (RRT) with dialysis or transplantation globally exceeds 2.6 million people.[3] Independent of the initial insult, progression to ESRD is relatively common in chronic nephropathies. Many forms of progressive noncystic renal disease are glomerular in origin, and yet it is the intensity of the accompanying or evolving injury of the tubulointerstitial compartment, rather than the extent of glomerular changes, that predicts the overall decline in renal function.[4] Although genetic factors contribute to susceptibility and progression of renal disease, increased glomerular capillary flow and pressure consistently leading to increased urinary protein traffic have been claimed as independent factors of progression and poor renal outcomes in nondiabetic and diabetic kidney disease.[5,6] The Ramipril Efficacy in Nephrology (REIN) study was the first trial to formally test the role of proteinuria in the progression of kidney disease.[7-9] The trial showed that in 352 patients with proteinuric nephropathies from different etiologies, higher proteinuria at inclusion was associated with faster glomerular filtration rate (GFR) decline and progression of ESRD on follow-up.[5,10] Notably, in the REIN trial, larger proteinuria reduction and less residual proteinuria at follow-up were both associated with slower GFR decline and more effective protection against progression to ESRD, independent of treatment allocation.[11] Greater proteinuria reduction predicted slower progression, as in the patients with type 2 diabetes with overt nephropathy included in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)[6] study and Irbesartan Diabetic Nephropathy Trial (IDNT).[12] The predictive pathogenic role of proteinuria was confirmed by a pooled analysis of 2387 CKD patients included in 11 trials, which showed that, irrespective of treatment, short-term changes in proteinuria were strongly consistent with long-term outcomes, whereas no effect on proteinuria predicted no long-term benefit.[13] Thus efforts to dissect the mechanisms and mediators underlying disease progression in proteinuric nephropathies are of utmost importance to help design novel medications to further improve the efficacy of current renoprotective interventions.

FROM GLOMERULAR HYPERTENSION TO LOSS OF SIZE-SELECTIVE PROPERTIES

Studies from animal models in the early 1980s have shown that most renal diseases progress to renal failure as a consequence of functional adaptations that occur in the kidney, after the original disease process causes an initial loss of nephron units.[14] Thus a variety of insults result in a common pathway of glomerular capillary hyperperfusion and hypertension, followed by increased permeability with excess passage of proteins across the glomerular capillary wall and progressive glomerular injury.[14] Enhanced intraglomerular capillary pressure stretches the glomerular wall, which, in addition to directly injuring glomerular cells,[15] impairs the selective function of the glomerular capillary, an effect explained by the appearance of very large pores that exceed the sizes observed in normal conditions and allow increased filtration of plasma proteins[16] (Fig. 78.1). Mechanical strain also increases angiotensin II (Ang II) production and expression of Ang II type 1 (AT_1) receptors in podocytes.[17] Independent of its hemodynamic effects, Ang II may directly impair the glomerular barrier sieving function, possibly through inhibition of podocyte expression of nephrin, the essential protein component of the glomerular slit-diaphragm[18] (Fig. 78.2). This observation has been confirmed in studies in diabetic animals showing that blockade of Ang II synthesis/activity preserved the expression of nephrin in the glomeruli and prevented overt proteinuria.[19] Thus in the setting of diabetes, after the initial insult of hyperglycemia and intraglomerular hypertension, Ang II plays a relevant role in sustaining glomerular injury via persistent activation of Notch1 and Snail signaling in the podocyte, eventually resulting in persistent downregulation of nephrin expression.[20] The consistency of the findings in Zucker diabetic fatty rats with overt nephropathy and in patients with type 2 diabetes and established nephropathy provides a robust reason to infer an important role for the Ang II Notch 1/Snail axis in perpetuating loss of glomerular size–selective properties.

Podocyte Response to Protein Trafficking

After loss of size selectivity, the intercellular junction and cytoskeletal structure of the podocyte foot processes are altered and the cells show a simplified, effaced phenotype.[21] These alterations result in the disappearance of the typical slit-diaphragm structures, leading to enhanced protein trafficking. Thus podocytes are damaged by excessive protein load after size selectivity is lost.[22] Protein uptake by podocytes may occur through binding to megalin, a receptor for albumin and immunoglobulin light chains that is endocytosed after ligand binding, as shown in cultured murine podocytes.[23] Excessive protein uptake by podocytes also induces transforming growth factor-β (TGF-β) production, which contributes to cell apoptosis, an additional cause of podocyte loss in proteinuric glomerulopathies.[24]

Finally, podocytes possess a fully functional endothelin (ET) system, and evidence has highlighted the role of ET-1 in promoting structural and functional alteration of these cells in renal disease.[25] This possibility is supported by the beneficial effects of ET receptor antagonists on the development of proteinuria and glomerular injury in type 1 diabetic animals, partially attributed to attenuation of podocyte loss.[19] Although the mechanism of podocyte preservation by ET receptor antagonism

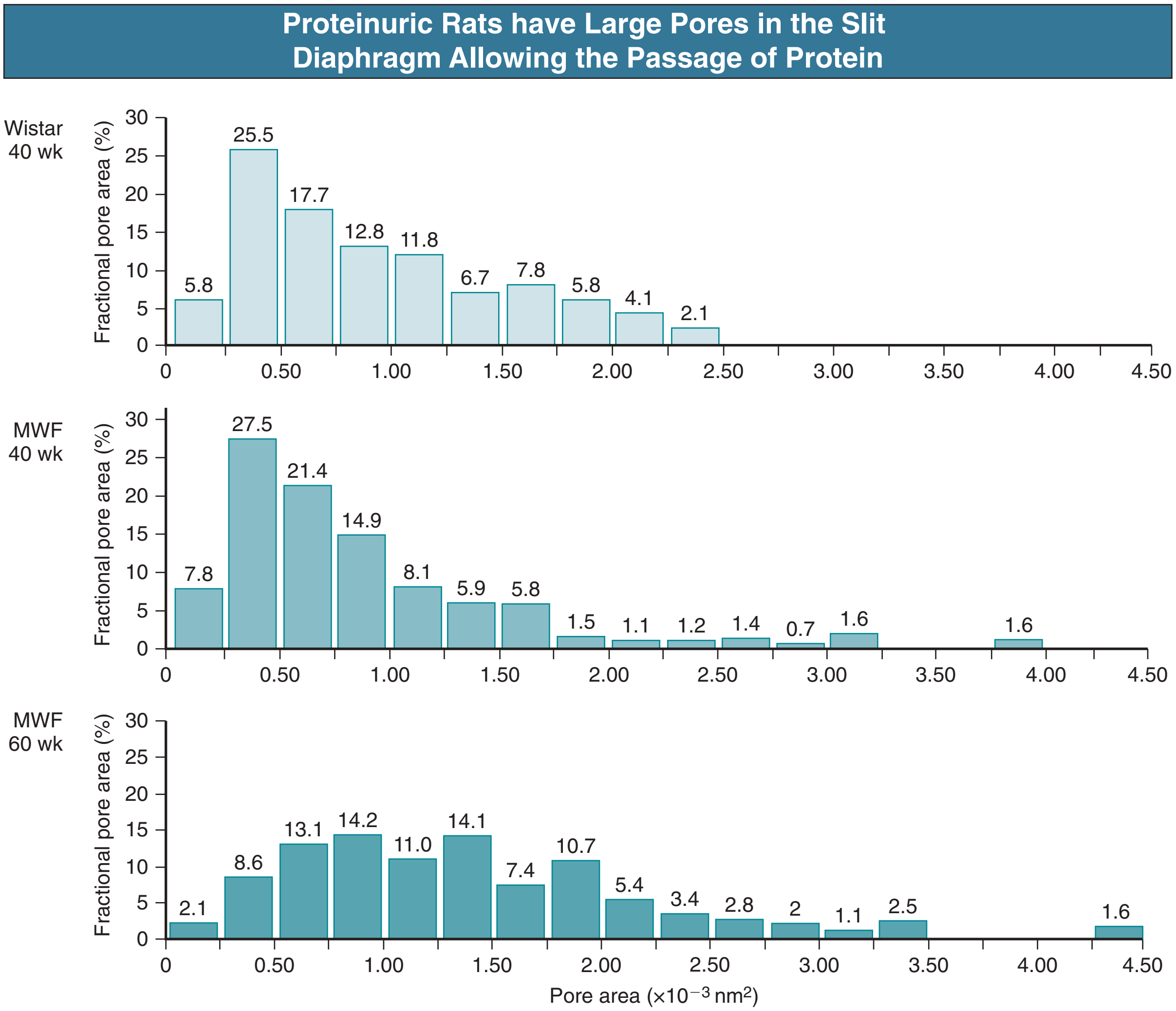

Fig. 78.1 Proteinuric Munich Wistar Fromter (MWF) rats have large pores in the glomerular capillary slit-diaphragm that exceed the size observed in normal animals. Distribution of fractional pore area (the fraction of the total pore area for given pore area interval) calculated for slit pores in 40-week-old normal Wistar rats and in 40- or 60-week-old proteinuric MWF rats. (From reference 16).

remains ill defined, recent observations indicate that ET-1 induces an epithelial-to-mesenchymal transition-like event associated with increased podocyte motility.[26] This is dependent on the activation of ET$_A$ receptor, which recruits β-arrestin 1, leading to epithelial growth factor receptor translocation and β-catenin phosphorylation, in turn promoting the expression of migratory genes.[26]

Furthermore, the preservation of podocyte structure under ET receptor antagonism could be secondary to a reduction in the protein load reaching the cells, as suggested by recent findings in diabetic apoE knockout mice.[27] In this model, the ET$_A$ receptor antagonist atrasentan restored the structural integrity of glomerular endothelial glycocalyx—a gel-like polyanionic carbohydrate layer that covers endothelial cells—normalizing the barrier against the excessive traffic of albumin through the capillary wall up to podocytes.[27]

Crosstalk of Podocytes With Mesangial and Endothelial Cells

The mesangial cells are a critical part of the glomerular functional unit, interacting closely with podocytes.[28] Alterations in one cell type can produce changes in the others. Whether cytokines generated by podocytes influence mesangial cells has yet to be clearly defined, but the observation that podocyte injury frequently results in mesangial cell proliferation supports the existence of such cytokine crosstalk.[28] Moreover, podocyte abnormalities are accompanied by upregulation of TGF-β messenger RNA and enhanced production of the related protein,[22] which ultimately induces differentiation of mesangial cells into myofibroblasts, abnormal extracellular matrix (ECM) deposition, and glomerulosclerosis.[29,30]

Loss of podocytes secondary to protein-induced cell injury may lead to reduced production of vascular endothelial growth factor (VEGF), a molecule constitutively expressed and secreted by podocytes,[31] influencing the formation of glomerular endothelial fenestrae and eventually promoting endothelial cell apoptosis.[32] How VEGF reaches endothelial cells against the urine flow is not yet known, however. Conversely, in vitro evidence has shown that blockade of VEGF in glomerular endothelial cells enhanced the release of ET-1, which induced nephrin shedding from podocytes,[33] leading to further dysfunction of glomerular protein permeability (Fig. 78.3).

Activation of Parietal Epithelial Cells

Changes in glomerular perm-selective function, as it occurs in proteinuric glomerulopathies, elevate the filtered load of plasma albumin and

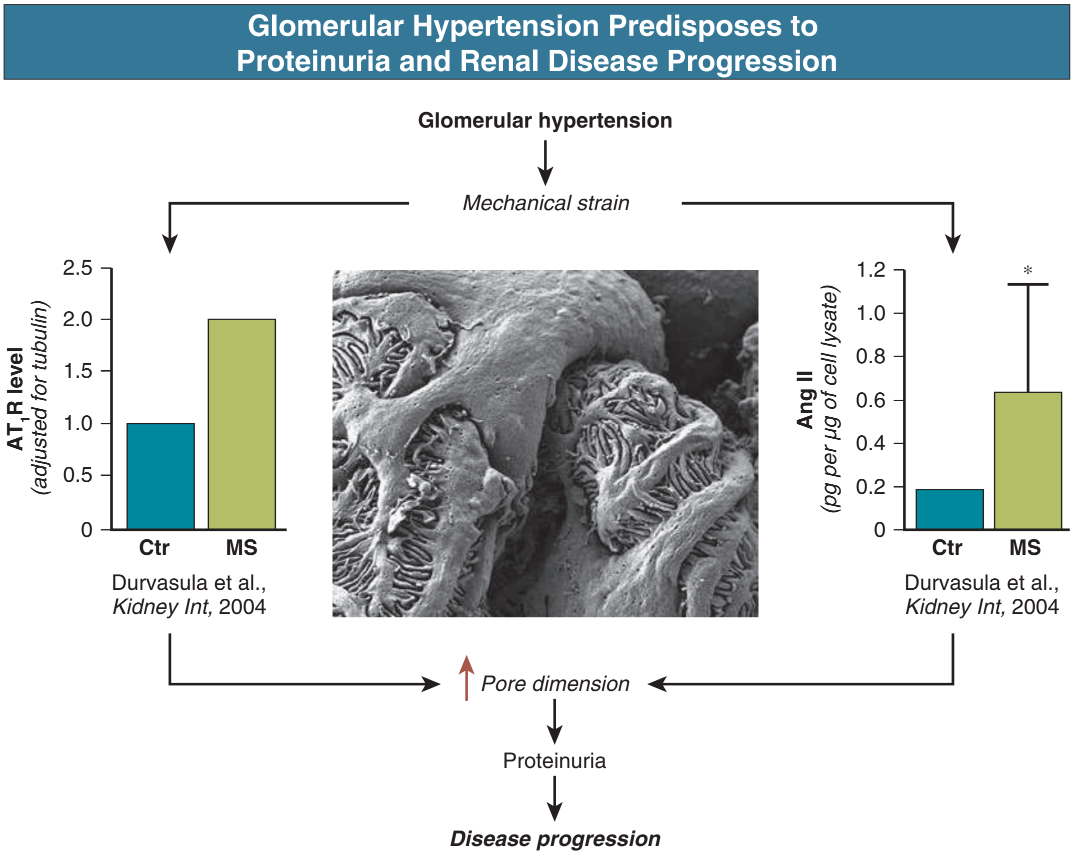
Glomerular Hypertension Predisposes to Proteinuria and Renal Disease Progression
Glomerular hypertension
Mechanical strain
AT_1R level (adjusted for tubulin)
2.5
2.0
1.5
1.0
0.5
0
Ctr
MS
Durvasula et al., Kidney Int, 2004
Ang II (pg per μg of cell lysate)
1.2
1.0
0.8
0.6
0.4
0.2
0
*
Ctr
MS
Durvasula et al., Kidney Int, 2004
Pore dimension
Proteinuria
Disease progression

Fig. 78.2 Schematic process linking glomerular capillary hypertension to proteinuria and renal disease progression. After the original disease process causes an initial loss of nephron units, enhanced intraglomerular capillary pressure stretches the glomerular wall, impairing its size-selective function. Mechanical strain also increases angiotensin II (Ang II) production and expression of Ang II type 1 receptors (AT_1R) in podocytes, eventually directly contributing to loss of the glomerular barrier sieving function through inhibition of podocyte slit-diaphragm nephrin expression (see reference 17). Ctr, Control; MS, mechanical strain.

consequently its concentration in the Bowman space[34] (Fig. 78.4). Evidence has been provided that the abnormally filtered albumin impairs the mechanism underlying regeneration of damaged podocytes.[35] Indeed, although podocytes have limited capacity to divide, they can potentially get replaced by differentiation of a population of renal progenitor cells localized within the Bowman capsule.[36] In vitro, albumin overload blocked the differentiation of human renal progenitor cells into podocytes expressing podocin and other functional molecules. The albumin-dependent block of relevant gene transcription and of progenitor differentiation was explained by specific binding and sequestration of retinoic acid, which is endogenously synthesized by the cells from retinol (see Fig. 78.4).[35]

The abnormal concentration of proteins in the ultrafiltrate also can lead to activation and accumulation of parietal epithelial cells (PECs) within the Bowman space as a common response to glomerular injury,[37] as shown in several human proliferative glomerulonephritides. This possibility is supported by findings in Munich Wistar Fromter (MWF) rats, which are genetically programmed to undergo renal damage characterized by excessive migration and proliferation of parietal progenitor cells, leading to their accumulation into cellular lesions and glomerulosclerosis.[38] Along the Bowman capsule in the adult MWF rats, a population of PECs expressing the neural cell adhesion molecule (NCAM), a marker of metanephric mesenchyme,[39] together with CD24, a mouse and human kidney stemness marker, has been identified.[38] Double-staining of NCAM with the podocyte marker WT1 identified three cell populations lining the Bowman capsule: immature progenitor cells expressing NCAM, transitional cells expressing markers from progenitor cells and podocytes ($\text{NCAM}^+\text{WT1}^+$), and more differentiated epithelial cells, the parietal podocytes ($\text{NCAM}^-\text{WT1}^+$). NCAM^+ PECs in vitro differentiate into podocytes, confirming their progenitor nature.[38] We investigated the behavior and role of NCAM^+ PECs in the evolution of glomerular lesions in MWF rats that showed early lesions consisting of bridges between the parietal and visceral epithelium, followed by hyperplastic lesions that eventually evolve to sclerosis.[38] The majority of cells in glomerular lesions were claudin^+ PECs of the Bowman capsule, whereas there were few podocytes. In old MWF animals, the claudin^+ PECs increased in number, proliferated, and accumulated in the Bowman space, whereas parietal podocytes decreased. These findings suggested dysregulation of PECs' ability to differentiate into podocytes and to repair injury.[38]

PECs expressing the progenitor cell marker also have been reported to proliferate and accumulate into the multilayered cellular lesions in patients with glomerulonephritides characterized by extracellular capillary proliferation.[40] Upregulation of the CXCR4 chemokine receptor on these progenitor cells was found to be accompanied by high expression of its ligand, SDF-1, in podocytes.[40] Moreover, PEC proliferation was associated with increased expression of the AT_1 receptor. Renin-angiotensin system blockade normalized CXCR4 and AT_1 receptor expression on parietal progenitor cells concomitant with regression of crescentic lesions.[40] Together these findings suggest that the glomerular hyperplastic lesions derive from the proliferation and migration of renal progenitor cells in response to injured podocytes and that the

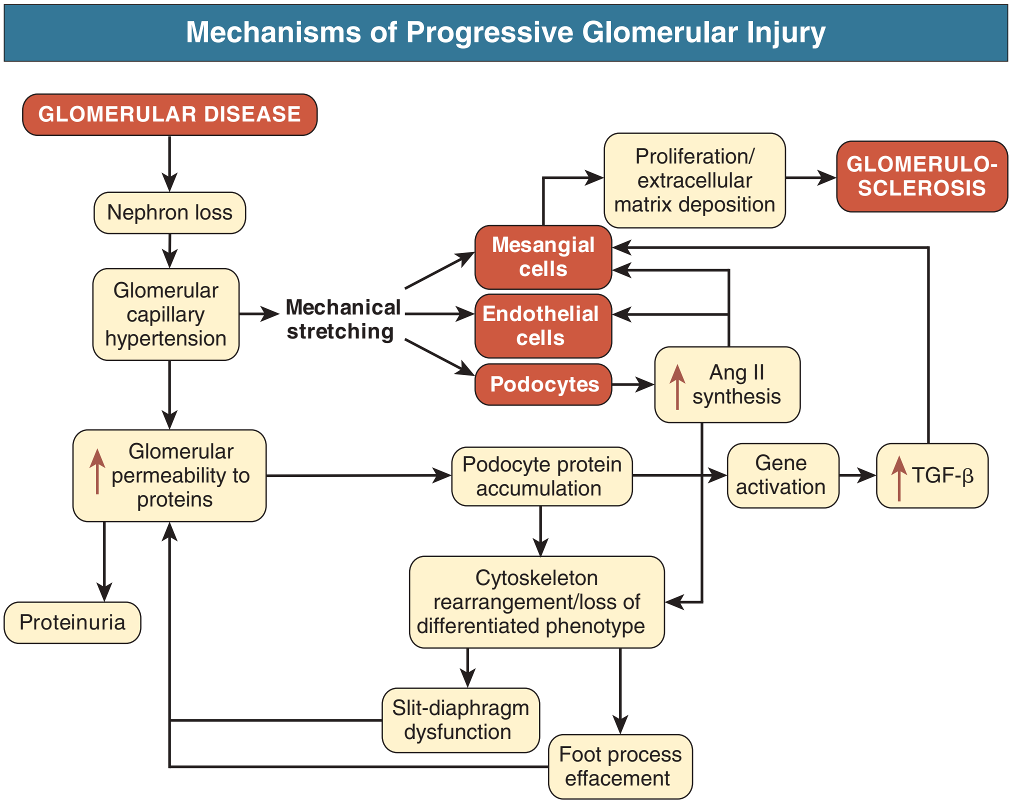
Mechanisms of Progressive Glomerular Injury
GLOMERULAR DISEASE
Nephron loss
Glomerular capillary hypertension
Mechanical stretching
Mesangial cells
Endothelial cells
Podocytes
Proliferation/ extracellular matrix deposition
GLOMERULO-SCLEROSIS
↑ Ang II synthesis
↑ Glomerular permeability to proteins
Podocyte protein accumulation
Gene activation
↑ TGF-β
Proteinuria
Cytoskeleton rearrangement/loss of differentiated phenotype
Slit-diaphragm dysfunction
Foot process effacement

Fig. 78.3 **Mechanisms of progressive glomerular injury.** A reduction in the number of nephrons as a consequence of various glomerular diseases results in compensatory glomerular hemodynamic changes that are ultimately detrimental. By mechanical stretching, the increased glomerular capillary pressure directly injures glomerular cells. Glomerular hypertension also impairs the glomerular capillary size-selective function, which causes excessive protein ultrafiltration and, eventually, podocyte injury and proteinuria. Ang II, Angiotensin II; TGF-β, transforming growth factor-β.

Ang II/AT$_1$ receptor pathway may contribute, together with SDF-1/CXCR4 axis, to the dysregulated response of PEC precursors. A very recent study highlighted the key role of complement components C3 and C3a in determining podocyte dysfunction and loss leading to PEC activation.[41] Proliferation and migration of PECs in response to activated complement contribute to the development of glomerular sclerotic lesions.[41] Consistently, studies on renal biopsy samples from patients with proteinuric nephropathies and PEC activation showed concomitant glomerular C3 and C3a deposition, indicating the key role in the development of glomerular lesions.[41]

PROXIMAL TUBULAR CELL INJURY

Glomerular ultrafiltration of excessive amounts of plasma protein–associated factors incites tubulointerstitial damage and further promotes the effects of glomerular disease on the tubulointerstitial compartment.

The noxious substances in the proteinuric ultrafiltrate may set off tubular epithelial injury with tubular apoptosis, secondary generation of inflammatory mediators, and peritubular inflammation.[29] The mechanisms by which increased urinary protein concentration leads to toxic injury are multifactorial and involve complex interactions among numerous pathways of cellular damage.

Tubular Cell Apoptosis

Renal proximal tubular cells have a remarkable ability to reabsorb large quantities of albumin through clathrin- and megalin receptor–mediated endocytosis.[42] Kidneys in rats with albumin overload proteinuria[43] or passive Heymann nephritis (PHN)[44] showed increased numbers of terminal deoxynucleotidyl transferase nick-end labeling-positive apoptotic cells in the tubulointerstitial compartment. In tubules, most of the positive cells expressed Ang II type 2 (AT$_2$) receptors.[43] Findings of reduced phosphorylation of extracellular signal-regulated kinase and Bcl-2 suggested an AT$_2$ receptor–mediated mechanism underlying tubular cell apoptosis.[43] Similarly apoptotic cells expressing both proximal and distal tubular phenotypes were detected in biopsy specimens from patients with primary focal segmental glomerulosclerosis (FSGS), and a positive correlation was documented between proteinuria and incidence of tubular cell apoptosis.[45]

Proximal tubular cell apoptosis has been shown to contribute to tubuloglomerular disconnection and atrophy in response to proteinuria in animal models of proteinuric nephropathies.[44] When passive PHN rats were given the angiotensin-converting enzyme (ACE) inhibitor lisinopril, which limits proteinuria, tubular atrophy and disconnection were remarkably prevented.[44] PHN animals that did not respond to ACE inhibition in terms of reduction of proteinuria had a glomerular population consisting mainly of atubular glomeruli and glomeruli connected with atrophic tubules, which again is consistent with the possibility that excessive protein tubular handling favors disconnection.[44]

Tubular Cell Phenotypic Changes

Excessive protein uptake at the apical pole of the proximal tubular cells is associated with phenotypic changes characteristic of an activated state.

Insights into specific mechanisms linking protein uptake to cell activation have come from in vitro studies using polarized tubular cells

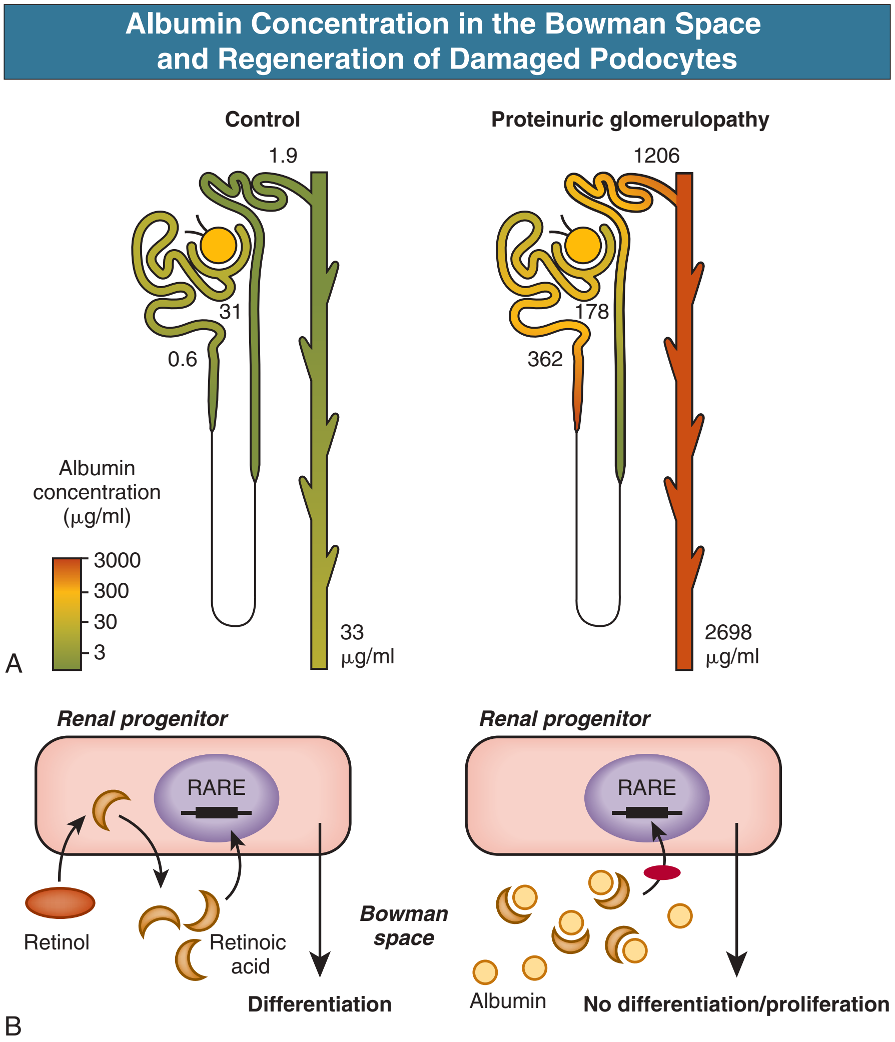
Albumin Concentration in the Bowman Space and Regeneration of Damaged Podocytes

Fig. 78.4 Albumin concentration in the Bowman space and regeneration of damaged podocytes. (A) In the proteinuric glomerulopathies, changes in glomerular perm-selective function results in high concentration of albumin in the Bowman space. Color-coded graphical representation of estimated albumin concentration along the entire nephrons in two animal groups (control and renal mass ablation model). Numbers represent local group average albumin concentration in micrograms per milliliter (modified from reference 34). (B) In vitro albumin overload, prevented the differentiation to podocytes from human renal progenitor cells by sequestering retinoic acid, thus impairing retinoic acid response element *(RARE)*-mediated transcription of podocyte-specific genes. After early podocyte injury, retinol is lost through the injured glomerular filtration barrier and transformed into retinoic acid. Albumin overload also promotes proliferation and migration of renal progenitor cells into the Bowman space. (Modified from reference 35).

to assess the effect of apical exposure to proteins. Collectively, they show that protein overload induces a proinflammatory phenotype[46] (Fig. 78.5). Indeed upregulation of inflammatory and fibrogenic genes and production of related proteins have been reported after a challenge of proximal tubular cells with plasma proteins. They include cytokines, chemokines, and vasoactive substances, such as monocyte chemoattractant protein-1 (MCP-1); regulated upon activation, normal T cell expressed and secreted (RANTES); interleukin-8, fractalkine; and ET-1.[46] Moreover, levels of the profibrogenic cytokine TGF-β and its type I receptor, tissue inhibitors of metalloproteinase (TIMP-1 and TIMP-2), as well as membrane surface expression of the αvβ5 integrin were also highly increased in vitro on stimulation by plasma proteins.[46] Investigation of the molecular mechanisms underlying chemokine and growth factor upregulation in proximal tubular cells on protein challenge has focused on the activation of the transcription factor nuclear factor kappa-B (NF-kB).[46] In this context, a very recent study showed that albumin is capable of inducing chromatin modification, making the promoter region of the gene encoding miR-184, which plays a key role in tubulointerstitial nephritis of diabetic rats, more accessible to NF-kB inducing the miR-184 transcription.[47] Other studies confirmed the role of the NF-kB pathway and revealed reactive oxygen as a second messenger.[48] The link of excessive protein reabsorption to tubular cell activation has been confirmed by in vivo studies in animal models. Evidence of early activation of proximal tubule cells during nonselective proteinuria was derived from experiments in megalin knockout/NEP25 mice treated with the immunotoxin LMB2, a model of nephrotic syndrome, FSGS, and tubulointerstitial injury.[49] Megalin-deficient proximal tubule cells reabsorbed fewer proteins in vivo and expressed fewer tubular injury markers, such as MCP-1 and heme-oxygenase.[49] Moreover, a recent report using podocin knockout mice as a model of FSGS demonstrated that increased reabsorption of abnormally filtered albumin and other proteins in proximal tubule cells was associated with massive increase

Tubular Cell Phenotype Induced by Proteins

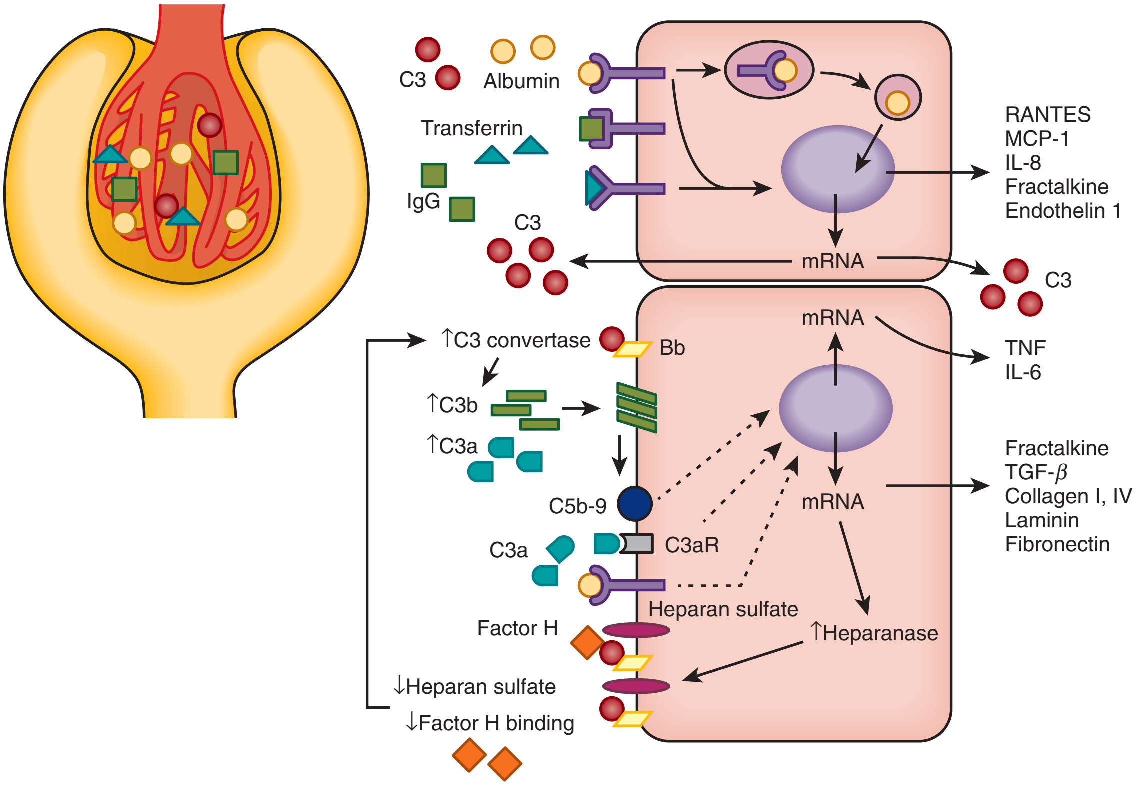

Fig. 78.5 Tubular cell phenotypic changes induced by proteins. Protein overload of proximal tubular cells as a consequence of increased glomerular permeability to proteins activates intracellular signals that promote cell apoptosis or cause increased production of inflammatory and vasoactive mediators and growth factors. IgG, Immunoglobulin G; IL-6, interleukin-6; IL-8, interleukin-8; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated upon activation, normal T cell expressed and secreted; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor.

of lysosomal proteolysis.[50] However, high expression of proinflammatory and profibrotic mediators (MCP-1 and TGF-β) in the kidney also occurred almost simultaneously with the increase in tubular content of megalin ligands.[50] This suggests that, despite the effective degradation of endocytosed proteins by lysosomes in this model, the excessive protein uptake by tubule cells was still capable of activating phenotypic changes by upregulation of proinflammatory and growth factor encoding genes.

With proteinuria, a putative key factor in tubular cell activation and damage is the excess glomerular filtration of plasma-derived complement C3, the central molecule in the complement system that exerts proinflammatory potential. Renal tubule epithelial cells appear more susceptible to luminal attack by the C5b-9 membrane attack complex because of the relative lack of membrane-bound complement regulatory proteins, such as membrane cofactor protein (CD46), decay-accelerating factor, or CD55 and CD59 on the apical surface.[51] In rats with reduced renal mass, C3 colocalized with proximal tubular cells engaged in high protein uptake. By limiting the transglomerular passage of proteins, treatment with ACE inhibitors was an effective manner to reduce the C3 load of tubular cells in remnant kidneys.[52] C3 and other complement proteins are also found in proximal tubules in renal biopsy material from patients with nephrosis.[53] Furthermore, proximal tubular cells are able to synthesize C3 and other complement factors and to upregulate C3 in response to serum proteins in vitro.[54] Studies in C3-deficient kidneys transplanted into wild-type mice have helped clarify that ultrafiltered C3 contributes more to tubular damage induced by protein overload than locally synthesized C3.[55]

INTERSTITIAL INFLAMMATION AND FIBROSIS

In proteinuric kidney disease, progressive inflammation and injury to the renal interstitium are secondary events after glomerular or vascular damage. Cytokines and chemokines synthesized by proximal tubular epithelial cells are released into the interstitium, where they contribute to recruit inflammatory cells and lymphocytes causing progressive fibrosis.[46]

Resident Monocyte and Lymphocyte Activation

The interstitium of normal kidneys contains numerous resident monocytic myelocytes, which express dendritic cell markers and can present antigens.[56] Dendritic cells have been described to form an immune sentinel network through the entire kidney, where they probe the environment in search of antigens.[57] An inflammatory environment converts the tolerogenic status of resident dendritic cells into an immunogenic one, favoring recruitment of T cells. The importance of kidney dendritic cell activation to renal injury has been demonstrated by the fact that in transgenic NOH mice (which selectively express the model antigens ovoalbumin and hen egg lysozyme in podocytes), dendritic cell depletion resolved established periglomerular mononuclear infiltrates.[58] In vitro experiments also have shown that exposure of rat proximal tubular cells

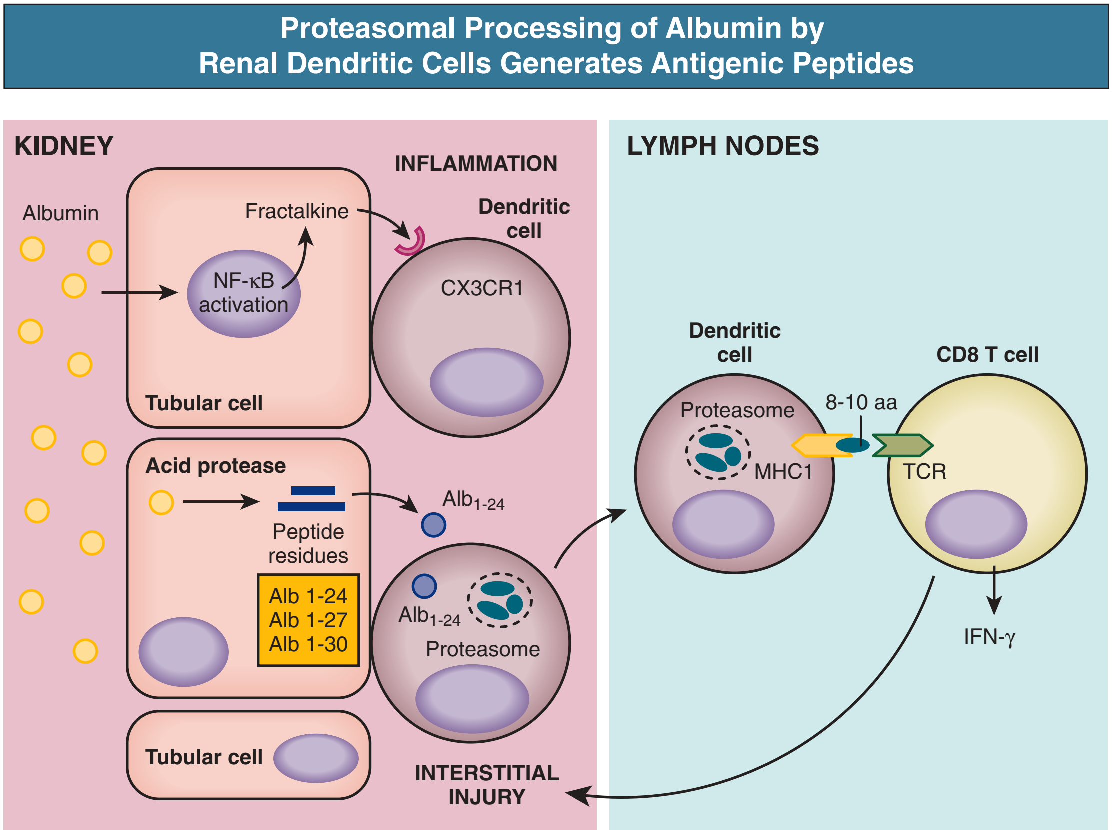

Fig. 78.6 Proteasomal processing of albumin by renal dendritic cells generates antigenic peptides. Exposure of proximal tubular cells to excess autologous albumin, as in the case of proteinuric nephropathies, results in the formation of the N-terminal 24-residue fragment of albumin. This peptide is acquired by dendritic cells, where it is further processed by proteasome into antigenic peptides. Then dendritic cells move to regional lymph nodes, where they activate effector CD8$^+$ T cells. These cells are then recruited in the renal interstitium. Alb$_{1\text{-}24}$, N-terminal 24-residue fragment of albumin; aa, aminoacids; IFN-γ, interferon-γ; MHC, major histocompatibility complex.

to excess autologous albumin, as in the case of proteinuric nephropathies, results in the formation of the N-terminal 24-residue fragment of albumin (ALB$_{1\text{-}24}$).[59] This peptide is taken up by dendritic cells, where it is further processed by proteasomes into antigen peptides. These peptides were shown to have the binding motif for major histocompatibility complex (MHC) class I and to be capable of activating CD8$^+$ T cells. Moreover, in vivo, in the rat model of renal mass ablation, accumulation of dendritic cells in the renal parenchyma peaked 1 week after surgery and decreased thereafter, concomitant with their appearance in the renal draining lymph nodes. Dendritic cells from renal lymph nodes loaded with the albumin peptide ALB$_{1\text{-}24}$ activated syngeneic CD8$^+$ T cells in primary culture.[59] Thus inflammatory stimuli released from damaged tubules after protein overload may represent danger signals that, in the presence of albumin peptides, alert dendritic cells to promote local immune response via CD8$^+$ T cells, which are activated in regional lymph nodes and recruited in the renal interstitium (Fig. 78.6).

The interstitium infiltrate in most human chronic renal diseases consists of a number of different effector cells, including macrophages and CD4$^+$ T cells, in addition to CD8$^+$ T cells.[60] However, there is substantial functional diversity among CD4$^+$ T cells, so that certain subpopulations, such as CD4$^+$CD25$^+$ T cells, hinder rather than help the immune response.[61] Findings of a study using the green fluorescence protein - *Foxp3* mouse suggest that *Foxp3* expression identifies the regulatory T cell population.[62] In the murine model of adriamycin nephropathy, the adoptive transfer of *Foxp3*-transduced T cells protected against renal injury. Urinary protein excretion and serum creatinine were reduced, and there were significant decreases in glomerulosclerosis, tubular damage, and interstitial infiltrates.[63] These findings highlighted a complex interplay between effector/inflammatory cells and regulatory T cells in the setting of proteinuric chronic renal diseases.

Fibroblast Activation and Extracellular Matrix Deposition

The process of interstitial fibrosis involves the accumulation of myofibroblasts and ECM proteins[64] (Fig. 78.7). Resident interstitial fibroblasts and myofibroblasts proliferate in response to macrophage-derived profibrogenic cytokines, and their number correlates with the subsequent formation of a scar.[64] These cells may derive from trans-differentiated tubular epithelial cells or pericytes of peritubular capillaries, a process promoted by profibrogenic cytokines, including TGF-β, expressed by macrophages.[65] Activated renal fibroblasts may secrete chemokines that in turn may further attract macrophages and perpetuate interstitial injury.[66] Moreover, miRNAs are emerging as both downstream effectors of TGF-β–dependent regulation of the fibrogenic process.[67] TGF-β upregulates the expression of the profibrotic miR-21 in cultured proximal tubular epithelial cells via Smad3 signaling, both at the transcriptional and post-transcriptional level.[68] A functional link between miR-192 and TGF-β–driven renal fibrosis also has been documented, although the effect of TGF-β on miR-192 expression is not consistent across various studies.[67]

Eventually activated fibroblasts produce interstitial matrix components that contribute to interstitial collagen deposition and fibrosis.

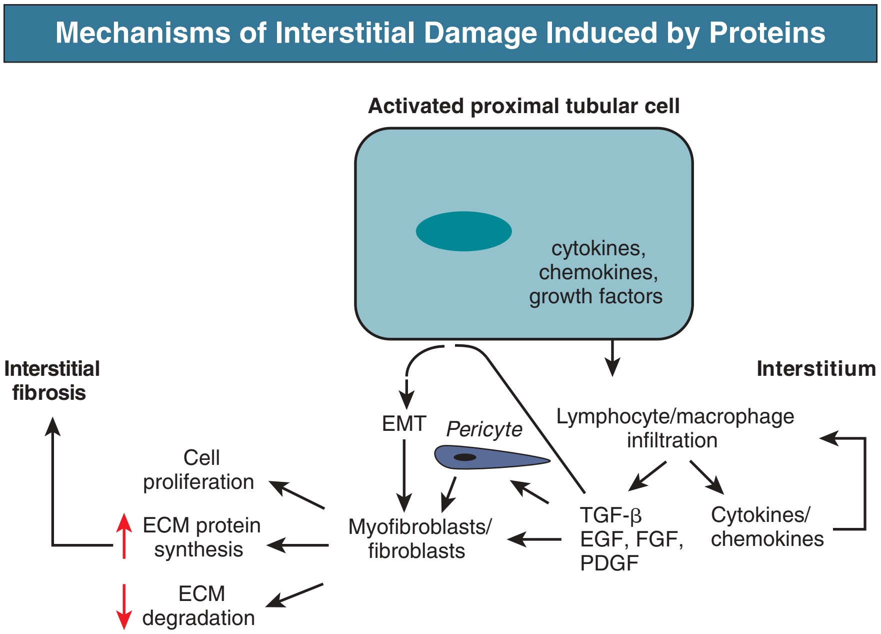
Mechanisms of Interstitial Damage Induced by Proteins
Activated proximal tubular cell
cytokines, chemokines, growth factors
Interstitial fibrosis
Interstitium
EMT
Pericyte
Lymphocyte/macrophage infiltration
Cell proliferation
ECM protein synthesis
ECM degradation
Myofibroblasts/ fibroblasts
TGF-β EGF, FGF, PDGF
Cytokines/ chemokines

Fig. 78.7 **Mechanisms of interstitial damage induced by proteins.** Cytokines, chemokines, and growth factors are released from the activated tubule into the interstitium, where they contribute to recruit inflammatory cells and lymphocytes, causing progressive fibrosis. ECM, Extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-to-mesenchymal transdifferentiation; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β.

Increased tubulointerstitial fibrosis is a common feature of kidney injury and results from accumulation of ECM structural proteins. However, it is maintained by continuous remodeling through the proteolytic action of matrix metalloproteinases (MMPs) and the synthesis of new proteins. MMPs are inhibited by tissue inhibitors of TIMPs. Of note, TIMP-3 levels are upregulated in patients with diabetic nephropathy, which anticipates more interstitial fibrosis.[69]

Chronic Hypoxia

One of the most important contributors to the development of tubulointerstitial fibrosis is chronic ischemia.[70] The production of Ang II and the inhibition of the production of nitric oxide underlie chronic vasoconstriction, which may contribute to tissue ischemia and hypoxia.[71] In that regard, histologic studies of the human kidney have documented that there is often a loss of peritubular capillaries in areas of tubulointerstitial fibrosis.[71] Downregulation of VEGF may be functionally implicated in the progressive attrition of peritubular capillaries and tissue hypoxia. Moreover, given that the size of the interstitial compartment determines the diffusion distance between peritubular capillaries and tubular cells, interstitial fibrosis further impairs tubular oxygen supply. Focal reduction of capillary blood flow leading to the starvation of tubuli may underlie tubular atrophy and loss. Under these conditions the remaining tubules are subject to functional hypermetabolism, with increased oxygen consumption, which in turn creates an even more severely hypoxic environment in the renal interstitium. Such hypoxia stimulates fibroblast proliferation and ECM production by tubular epithelial cells.[72]

PRIMARY CHRONIC TUBULOINTERSTITIAL INJURY

Tubulointerstitial disease is common to all chronic progressive renal diseases, irrespective of the initial trigger or site of injury. Once viewed as an inconsequential corollary to pathologic events that overwhelm glomeruli, tubulointerstitial disease is now recognized as a key and prominent factor in the progression of renal disease. In addition to the setting of proteinuric nephropathies, inflammation and injury of the renal interstitium also can occur in nonproteinuric kidney disease, as exemplified by primary chronic tubulointerstitial diseases. In this case, the key event is the expression of local nephritogenic antigens. They are derived from renal cells and tubular basement membranes (TBMs) or exogenous antigens processed by tubular cells. The case of molecules, including drugs, which may become nephritogenic antigens by acting as haptens or through molecular mimicry, is particularly unusual. A humoral response underlies rare cases of interstitial nephritis in which a portion of a drug (e.g., methicillin) may act as a hapten, bind to the TBM, and elicit anti-TBM antibodies.[73] Among the numerous causes of primary chronic tubulointerstitial injury, drugs and toxins (see Table 62.1), in addition to genetic cystic diseases, are major players.

Analgesics and Nonsteroidal Antiinflammatory Drugs

Analgesic nephropathy is a specific form of renal disease characterized by renal papillary necrosis and chronic interstitial nephritis, caused by prolonged and excessive consumption of analgesic mixtures. It is invariably caused by compound analgesic mixtures containing aspirin or antipyrine in combination with phenacetin, paracetamol, or salicylamide and caffeine or codeine, in popular over-the-counter proprietary mixtures.[74] The mechanisms responsible for the renal injury are incompletely understood. Phenacetin is metabolized to acetaminophen and to reactive intermediates that can injure cells, in part by lipid peroxidation.[75] These metabolites tend to accumulate in the medulla along the medullary osmotic gradient (created by the countercurrent system). As a result, the highest concentrations are seen at the papillary tip, the site of the initial vascular lesions.[76] The potentiating effect of aspirin, with both phenacetin and acetaminophen, may be related to two factors. (1) Acetaminophen undergoes oxidative metabolism by prostaglandin H synthase to reactive quinoneimine, which is conjugated to glutathione. If acetaminophen is present alone, there is sufficient glutathione generated in the papillae to detoxify the reactive intermediate. However, if acetaminophen is ingested with aspirin, the aspirin is converted to salicylate, which becomes highly concentrated and depletes glutathione in both the cortex and papillae of the kidney. With the cellular glutathione depleted, the reactive metabolite of acetaminophen then produces lipid peroxides and arylation of tissue proteins, ultimately resulting in necrosis of the papillae.[76,77] (2) Aspirin and other nonsteroidal antiinflammatory drugs suppress prostaglandin production by inhibiting cyclooxygenase enzymes. Renal blood flow, particularly within the renal medulla living at the edge of hypoxia, is highly dependent on systemic and local production of vasodilatory prostaglandins. The final injury is therefore due to both the hemodynamic and the cytotoxic effects of these drugs, resulting in papillary necrosis and interstitial fibrosis.

Aristolochic Acid

In 1992 nephrologists in Belgium noted an increasing number of women presenting with renal failure, often near end-stage, after their exposure to a slimming regimen containing Chinese herbs.[78,79] As of early 2000, a total of more than 120 cases had been identified. The main histologic lesion in human biopsy samples, which is located principally in the cortex, is extensive interstitial fibrosis with atrophy and loss of the tubules. Cellular infiltration of the interstitium is scarce. Important tryptase-positive mast cells were observed in the fibrotic areas in renal biopsy samples.[80] Thickening of the walls of the interlobular and afferent arterioles resulted from endothelial cell swelling. The glomeruli are spared, relatively speaking, and immune deposits are not observed. These findings suggest that the primary lesions may be centered in the vessel walls, thereby leading to ischemia and interstitial fibrosis.[81]

A plant nephrotoxin, aristolochic acid, has been proposed as the possible etiologic agent. Support for this hypothesis is provided by findings in animal models. In a first study, rabbits were given intraperitoneal injections of aristolochic acid (0.1 mg aristolochic acid/kg 5 days per week for 17 to 21 months[82]). Histologic examinations of the kidneys and genitourinary tract revealed renal tubular atrophy, interstitial infiltration/fibrosis, and atypical and malignant uroepithelial cells. Moreover, the daily subcutaneous administration of 10 mg/kg of aristolochic acid to salt-depleted rats induced, after 35 days, moderate renal failure associated with tubular atrophy and interstitial fibrosis.[83] In vitro (opossum kidney cell line) and in vivo (rats) proximal tubular injury occurs early after aristolochic acid intoxication in rats. There is a link between specific aristolochic acid–DNA adduct formation and decreased megalin expression and inhibition of receptor-mediated endocytosis of low molecular weight proteins.[84] Cytotoxicity data obtained in LLC-PK cells suggest that the nitro and methoxy groups are critical determinants of nephrotoxicology potency of aristolochic acid.[85] It remains unclear why only some patients exposed to the same herbal preparations develop renal disease. Women appear to be at greater risk than men. Other potentially important factors include toxin dose, batch-to-batch variability in toxin content, individual differences in toxin metabolism, and a genetically determined predisposition toward nephrotoxicity and/or carcinogenesis.[86]

Notably, Balkan endemic nephropathy, a chronic, familial, noninflammatory tubulointerstitial disease, most commonly seen in Southeastern Europe, also has been potentially attributed to chronic exposure to dietary aristolochic acid.[87] In the Balkan region, aristolochic acid exposure may come from the consumption of the seeds of *Aristolochia clematitis* (European birthwort), a plant native to the endemic region, which is thought to commingle with wheat used for bread.[88]

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic renal disorder, accounting for 8% to 10% of patients receiving RRT for ESRD worldwide.[89] Its clinical phenotype is progressive and substantial enlargement of the kidneys, caused by the sustained expansion of many fluid-filled cysts that originate from the tubule wall, leading to adjacent nephrons being crowded, injury to normal parenchyma, intestinal inflammation and fibrosis, and eventually kidney failure.[90,91] The progressive enlargement of cysts derived from renal tubules is largely attributable to the proliferation of mural epithelial cells and transport of fluid into cavities generated by accelerated epithelial cell growth.[92] In vitro evidence suggests that these cells' growth and transepithelial secretion of fluid is controlled by cyclic adenosine monophosphate.[92] Moreover, the Ser/Thr kinase mammalian target of rapamycin (mTOR) activation also mediates cyst expansion.[93] Insights into the pathophysiology of ADPKD have helped develop novel disease-modifying treatments.[94,95]

CONCLUSIONS

There is now clear evidence that, rather than simply a marker of damage, abnormal ultrafiltration of proteins can be toxic to the kidney and incites complex pathways and mediators that target glomerular, tubular, and interstitial cells, eventually promoting renal disease progression to ESRD. Moreover, tubulointerstitial injury is also common in nonproteinuric kidney diseases and is critical for their progression to ESRD. More insights in the pathophysiologic mechanisms of progressive proteinuric and nonproteinuric renal diseases will be instrumental to search for novel biomarkers that allow intervention in the earlier stages of CKD and may open the way to new potential treatments.

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SELF-ASSESSMENT QUESTIONS

1. What is the pathologic podocyte response to protein trafficking throughout glomerulus?
   - **A.** Podocytes start to proliferate.
   - **B.** Podocytes are damaged by excessive protein load and uptake of albumin.
   - **C.** Podocytes adhere to the Bowman capsule.
2. What is the main consequence of podocyte loss on endothelial cells during chronic renal injury?
   - **A.** Endothelial cell apoptosis
   - **B.** Endothelial cell proliferation
   - **C.** Increase of vascularization of the kidney
3. What is the role of resident dendritic cells in the kidney during proteinuric diseases?
   - **A.** Dendritic cells proliferate.
   - **B.** Dendritic cells generate albumin peptides that activate CD8$^+$ T cells.
   - **C.** Dendritic cells undergo apoptosis.
4. How does the progressive enlargement of renal cysts in autosomal dominant polycystic kidney disease develop?
   - **A.** It develops from mesangial cell proliferation.
   - **B.** It develops from endothelial cell proliferation.
   - **C.** It develops from tubular cell proliferation and fluid transport into the cyst cavity.

79

Retarding Progression of Kidney Disease

Samir V. Parikh, Nabil J. Haddad, Lee A. Hebert

Progression to end-stage renal disease (ESRD) usually occurs because of activity of the primary kidney disease and the mechanisms of natural progression (see Chapter 78). In those older than 40 years of age, the nephropathy of aging can contribute to progression. Its pathogenesis is unclear; however, the nephropathy of aging appears to be categorically different from that of natural progression because, unlike natural progression, the nephropathy of aging proceeds without important increases in proteinuria. Whether therapy can slow the nephropathy of aging is unclear. However, natural progression is treatable.

Natural progression creates a vicious cycle that is approached when nephron loss leads to hyperperfusion of the surviving glomeruli and to the metabolic dysfunctions of decreased glomerular filtration rate (GFR). The cycle is entered when the hyperperfusion and metabolic dysfunctions are sufficient to inflict kidney injury. This chapter discusses the evidence-based therapies to prevent entry into the cycle or slow the cycle once it has been entered.

LEVEL OF GLOMERULAR FILTRATION RATE AND THE RISK FOR NATURAL PROGRESSION

Typically, natural progression does not proceed until nephron loss exceeds 50%.[1] For example, it is very unusual for kidney donors to progress to ESRD. Nevertheless the 15-year risk for ESRD in kidney donors is 3.5 to 5.3 times higher than that of nondonors matched to donor risk factors.[2] In addition, a normal solitary kidney is vulnerable to natural progression whether congenital or acquired early in life or if it is associated with obesity, hypertension, hyperlipidemia, or hyperglycemia. Also, natural progression to ESRD can result from low birth weight, particularly in males, presumably because of paucity of nephrons or defective nephron development.[1]

PROTEINURIA MAGNITUDE AND THE RISK FOR NATURAL PROGRESSION

Proteinuria-induced glomerular and renal tubular injury is a key mechanism of natural progression (see Chapter 78). The threshold for natural progression attributable to proteinuria appears to be crossed when proteinuria exceeds 500 mg/day.[1] Proteinuria magnitude is the strongest single risk factor in chronic kidney disease (CKD) progression (Fig. 79.1).[1] An exception is highly selective proteinuria (the urine protein is almost entirely albumin), which can persist in the nephrotic range for more than 10 years without causing renal structural damage.[1] Also to be taken into account is the cause of the proteinuria. For example, at a proteinuria level of 3 to 5 g/day, primary membranous nephropathy shows relatively slow progression (<3.0 ml/min/year), whereas primary focal and segmental glomerulosclerosis (FSGS) progresses at 3 to 6 ml/min/year, and immunoglobulin A (IgA) nephropathy progresses at 6 to 9 ml/min/year.[3]

DIAGNOSIS OF NATURAL PROGRESSION

Natural progression is a diagnosis of exclusion. Therefore, in the CKD patient showing signs of progression, it must first be determined whether the primary renal disease is active. If that can be reasonably excluded, it must then be determined whether another kidney disorder has been superimposed (see Chapter 71). The nephropathy of aging also must be excluded. This is relatively easy because it starts after 40 years of age, the decline in GFR is slow (about 1 ml/year), and it generally does not involve important increases in proteinuria.[1] Findings that help confirm the diagnosis of natural progression are as follows:

- The serum creatinine generally is above the expected level for the patient's age, sex, and race (Box 79.1). Natural progression is unusual if the serum creatinine is in the normal range.
- Natural progression is usually indolent. For example, the increased serum creatinine has been stable for at least several years before signs of progression occur.[4] An exception can occur when there are extraordinarily strong forces promoting natural progression, such as a very high salt intake, poorly controlled hypertension, or both.
- Increase in proteinuria is usually the first sign of natural progression. Only after a year or more of rising proteinuria does the serum creatinine begin to increase.[4]
- The urine sediment is unremarkable, although broad hyaline and granular casts may be present.

In summary, natural progression is seen mainly in those with increased serum creatinine. Generally there is a prolonged period of increasing proteinuria before the serum creatinine begins to increase. However, keep in mind that this pattern is also commonly seen in CKD patients whose condition is progressing because of activity of the underlying glomerular disease. Also relevant are the forms of CKD that progress even though proteinuria is minimal (Box 79.2).

MONITORING KIDNEY DISEASE PROGRESSION

Progression can be monitored by structural changes, such as with renal biopsy or renal ultrasound, or by functional changes, for example, changes in GFR or proteinuria. Here we discuss the latter, which are the most practical and commonly used methods to monitor CKD progression.

Monitoring Proteinuria Trends

Proteinuria is the strongest single predictor of GFR decline.[1] In addition, the lower the eGFR, the stronger is the relationship between

BOX 79.1 Suggested Thresholds for Serum Creatinine According to Body Size, Sex, and Race

Large (e.g., >90 kg) nonobese men: S_{Cr} ≥1.30 mg/dl (1.40 mg/dl if African ancestry)

Small (e.g., <60 kg) men without muscle wasting/cachexia: S_{Cr} ≥1.10 mg/dl (1.20 mg/dl if African ancestry)

Large (e.g., >70 kg) nonobese women: S_{Cr} ≥1.00 mg/dl (1.10 mg/dl if African ancestry)

Small (e.g., <50 kg) nonobese women: S_{Cr} ≥0.80 mg/dl (0.90 mg/dl if African ancestry)

The estimates are based on experience with a clinical laboratory that reports a normal serum creatinine (S_{Cr}) range for men of 0.8 to 1.30 mg/dl, and for women of 0.60 to 1.10 mg/dl. The modification of diet in renal disease (MDRD) study estimated glomerular filtration rate (eGFR) that corresponds to each of the listed categories of S_{Cr} according to sex and race were calculated for persons aged 40 years. Each S_{Cr} value yielded an abnormal eGFR value (<90 ml/min/1.73 m^2). For men the eGFR values ranged from 65 to 86 ml/min/1.73 m^2; for women the eGFR values ranged from 65 to 79 ml/min/1.73 m^2. For persons older than 40 years, the corresponding eGFR values would be even lower.

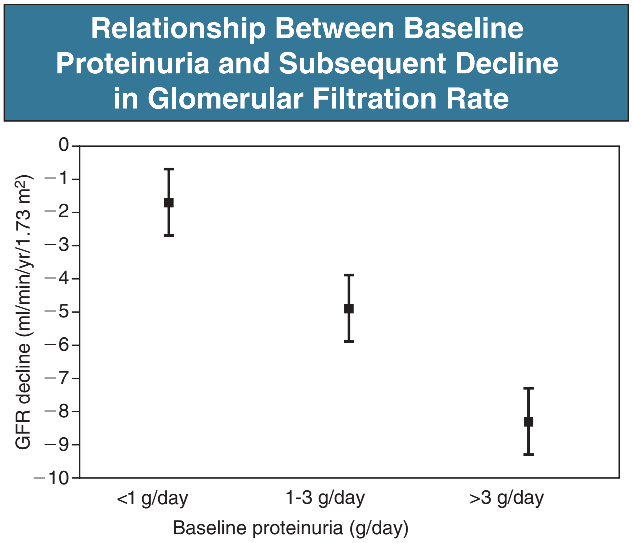


Fig. 79.1 Relationship between baseline proteinuria and subsequent decline in glomerular filtration rate (GFR). (Data from reference 52.)

proteinuria magnitude and risk for CKD progression.[5] Therapies that decrease proteinuria generally slow GFR decline (see Chapter 78).[1,6] The most widely used methods to assess proteinuria are measurement of urine albumin and urine total protein (see Chapter 4). The latter is the sum of urine albumin plus nonalbumin proteins. In the typical CKD patient the nonalbumin urine proteins consist mainly of low molecular weight proteins such as cystatin C and β_2-microglobulin. They escape reabsorption because of tubular damage (see Chapter 15). In this chapter, total proteinuria is referred to simply as *proteinuria*.

Recently, albuminuria measurement has gained favor over proteinuria measurement in CKD management. However, of the two studies that compared the urine albumin-to-creatinine ratio (uACR) and urine protein-to-creatinine ratio (uPCR) as predictors of GFR decline, one found uACR better than uPCR, and the other found uPCR not inferior to uACR.[1] The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend uACR. However, albumin assays cost more than protein assays. Furthermore, when proteinuria exceeds 500 mg/day, uACR and uPCR generally change in parallel.[1] If 24-hour proteinuria is less than 500 mg/day, this relationship is lost and uACR is more sensitive.[7] On this basis, we recommend uACR for detection of early CKD progression. Thereafter, uPCR is recommended. The recommended methods for monitoring proteinuria trends in individual patients are shown in Table 79.1. The key points are as follows:

BOX 79.2 Common Forms of Chronic Kidney Disease in Which Important Progression Can Occur With Only Minimal Proteinuria

Early phase of diabetic nephropathy, type 1 or type 2 diabetes mellitus
Hypertensive nephrosclerosis (especially in persons of African ancestry)
Polycystic kidney disease (autosomal dominant or recessive)
Chronic nonsteroidal antiinflammatory drug nephropathy
Obstructive uropathy
Nephropathy of aging
Bilateral renal artery stenosis caused by atherosclerosis, fibromuscular disease, or renal artery dissection
Renal atheroembolism or thromboembolism
Crystal induced tubulopathy:
  A. Calcium (e.g., chronic high-dose oral Ca CO_3 ingestion, Dent disease)
  B. Oxalate (e.g., bariatric surgery that results in fat malabsorption, primary hyperoxaluria, chronic vitamin D overdose)
  C. Urate (e.g., leukemia causing increased uric acid production from increased cell turnover)
Mitochondrial disease
Radiation nephritis
CKD of unknown etiology (such as Mesoamerican nephropathy)

Kidney diseases in which substantial progression can occur with only minimal proteinuria. For example, serum creatinine (Scr) increases to above 2.0 mg/dl, but 24-hour protein urine is low; for example, urine albumin-to-creatinine ratio (uACR) below 0.2, urine protein-to-creatinine ratio (uPCR) below 0.3. For conditions 1 through 11 see Chapters 29, 33, 44, 56, 62, and 65, respectively.

- The gold standard for monitoring proteinuria is the protein content of an accurately collected 24-hour urine specimen. Unfortunately, in practice, nominal 24-hour urine collections often are substantial undercollections or overcollections.[8]
- Creatinine should be measured in all intended 24-hour urine collections. The uPCR of the intended collection is a reliable estimate of the uPCR of the complete 24-hour collection, if the collection is at least 50% complete based on its total creatinine content.[1]
- In individual patients, the uPCR of spot (single void) urine collections is an unreliable estimate of proteinuria magnitude because of the large and inherent variability of spot uPCR[8] (Fig. 79.2).
- Urine collections of intermediate duration (e.g., overnight collections) have merit. However, such collections may not be representative of the uACR or uPCR of the entire 24-hour collection. For example, variations in diet, timing of antihypertensive medications, exercise on the day of the overnight collection, or contamination with semen may substantially alter the uACR or uPCR, rendering the overnight collection nonrepresentative.[8]
- Cost of uACR and uPCR from spot collections is essentially the same as that of uACR and uPCR from 24-hour urine collections. Given the high degree of unreliability of spot uACR and uPCR, spot collections can be regarded as having an unfavorable cost-to-benefit ratio.
- The inconvenience of 24-hour urine collections can be mitigated by the following:

TABLE 79.1 Methods for Monitoring Proteinuria or Albuminuria

Methods	Comments
Recommended	
uPCR or uACR* of intended 24-h urine collections that are at least 50% complete based on creatinine content†	Most accurate method (see text). Also can be used to assess nutrient intake relevant to CKD management (e.g., Na, K, urea nitrogen, water). Inconvenient, but this can be mitigated (see text).
uPCR or uACR ratio from overnight collections (first morning void)	More convenient than 24-h collections but provides a lower estimate of proteinuria than 24-h collections and is more vulnerable to artifacts (see text).
Not Recommended	
Intended 24-h urine collection in which protein or albumin is measured but creatinine is not measured	Large overcollections and undercollections are common in intended 24-h urine collections. If creatinine content is not measured, the degree of overcollection or undercollection cannot be reliably assessed.
Spot uPCR or uACR	Convenient but highly inaccurate estimate. Cost-to-benefit ratio is low because cost is about the same as 24-h urine testing, but often the results of spot testing are misleading.
Dipstick test for proteinuria (albuminuria)	Convenient and low-cost point-of-care measure but not reliable for monitoring CKD patients.

Methods for monitoring proteinuria or albuminuria. E = (140 − Age) × Weight (Nonobese) in kg × 0.2 × 0.85 if female.
An M/E ratio exceeding 0.5 is evidence that the collection is more than 50% complete.
*uACR is recommended if 24-hour proteinuria is <500 mg (uPCR if <0.3 for average-sized person). uPCR is recommended if 24-hour proteinuria is above 500 mg.
†Degree of completeness of an intended 24-hour urine collection = measured creatinine content *(M)/*expected creatinine content *(E).*
CKD, Chronic kidney disease; *uACR,* urine albumin-to-creatinine ratio; *uPCR,* urine protein-to-creatinine ratio.

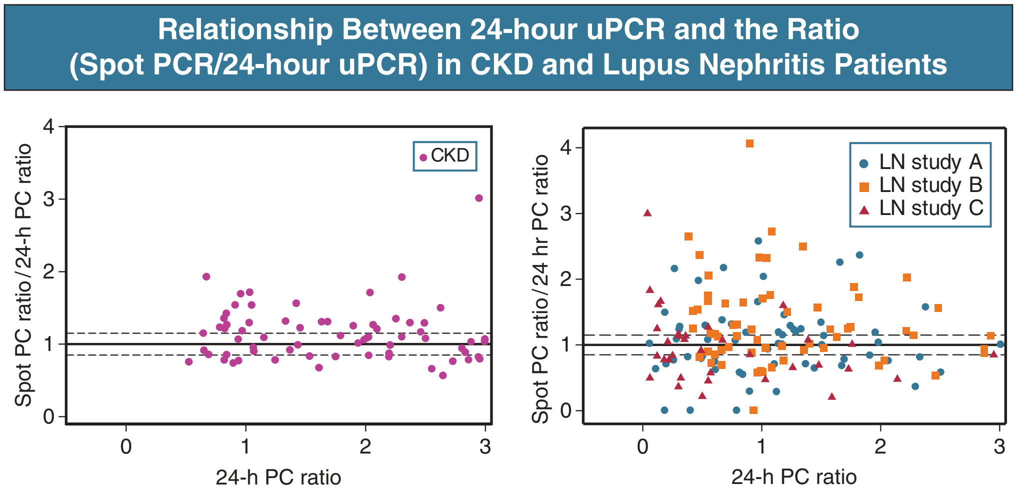

Relationship Between 24-hour uPCR and the Ratio (Spot PCR/24-hour uPCR) in CKD and Lupus Nephritis Patients

Fig. 79.2 **Relationship between 24-hour urine protein-to-creatinine ratio *(uPCR)* and the ratio of spot uPCR to 24-hour uPCR in chronic kidney disease *(CKD)* and lupus nephritis *(LN)* patients.** The *dashed line* indicates the expected limits of agreement if morning spot uPCR provides the same results as testing an aliquot of the intended 24-hour collection. This figure shows that spot uPCR is an unreliable estimate of 24-hour uPCR, especially in lupus nephritis. The spot collections were obtained under ideal circumstance, the morning when the 24-hour urine collection was presented. (From reference 7.)

- It is acceptable if an occasional void is missed, but the gap should not be large (e.g., the entire work day).
- A wide-mouth "sports bottle" that is carried in a duffle bag can be used to collect urine when not at home. It is not necessary to refrigerate the collected urine unless it will be several days before the urine specimen is submitted to the clinical laboratory.

Dipstick testing for proteinuria is convenient but unreliable in individual patients [9] (see Chapter 4).

Proteinuria testing in CKD is recommended every 6 to 12 months if proteinuria level is low (e.g., <500 mg/day) and every 2 to 4 months if heavier proteinuria.

If 24-hour uPCR increases from below 0.5 to 1.0 or higher, or from below 1.0 to 2.0 or higher, likely these are real changes[9] and should prompt reassessment.

Monitoring Glomerular Filtration Rate Trends

In individual patients, it is usually sufficient to monitor GFR trends by serial serum creatinine measurements. In interpreting serum creatinine change, one must keep in mind the circumstances that can change serum creatinine by mechanisms that do not involve a change in GFR, as follows: increased creatinine production (eating cooked meat, creatine ingestion, increased exercise, increasing muscle mass, fenofibrate use) or decreased creatinine production (vegetarian diet, muscle wasting, decreased exercise). Also, serum creatinine can be spuriously increased by drugs that interfere with the creatinine assay, and by increased serum ketones (from fasting or poor diabetes control) or actually increased by drugs that decrease tubular secretion of creatinine (cimetidine, trimethoprim). If a chronic progressive change in creatinine production is occurring (e.g., muscle wasting), GFR trends can be monitored by measuring cystatin C or serial 24-hour urine creatinine clearance.[1]

GFR also can be monitored by the creatinine-based estimated glomerular filtration rate (eGFR) equations—in particular, the Modification of Diet in Renal Disease (MDRD4) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (see Chapter 3). These approaches to standardizing GFR assessment have greatly advanced the study of CKD epidemiology. However, the eGFR equations have important limitations when applied to individual patient management. First, the MDRD4 and CKD-EPI equations assume that all patients of the same age, sex, and race have the same rate of creatinine production and the same body surface area (BSA). As a result, these equations substantially underestimate actual GFR in those with high BSA and/or creatinine production and substantially overestimate actual GFR in those with low BSA and/or creatinine production.[10] Second, because of inaccuracy in quantifying normal GFR, some laboratories do not report eGFR by MDRD4 or CKD-EPI equation if the eGFR is greater than 60 ml/min/1.73 m^2. In this circumstance the clinician must determine whether the serum creatinine is likely to be normal or abnormal. The following can be helpful (see Box 79.1):

- Large persons tend to have higher serum creatinine values than small persons.
- Men tend to have higher serum creatinine values than women.
- In North America, those of African ancestry tend to have higher serum creatinine values than those of non-African ancestry.

Role of Cystatin C in Estimating Glomerular Filtration Rate for Clinical Management

Cystatin C is a small molecular weight protein produced at a constant rate by all cells. It is freely filtered in the glomerulus and not reabsorbed or secreted by the renal tubules. So, serum cystatin C blood levels reflect GFR. Compared with measurement of serum creatinine, serum cystatin C is less affected by age, sex, muscle mass, and a diet that is high in cooked meat (a major source of serum creatinine). On the other hand, serum cystatin C levels are more affected by body fat mass, inflammation, thyroid disorders, and diabetes. Cystatin C is usually not provided by the local laboratory. This incurs delays in reporting the results. There are also concerns about analytic accuracy.[11] In head-to-head clinical comparisons the variability of cystatin C is at least as great as that of serum creatinine measurement.[12] For these reasons cystatin C is not recommended for routine assessment of eGFR.

Glomerular Filtration Rate Trajectories in Chronic Kidney Disease

GFR trajectory in CKD generally is well described as a linear decline; thus GFR loss per unit of time is approximately constant.[1] However, those of African ancestry deemed to have hypertensive nephrosclerosis can experience large unexplained changes in eGFR trends, especially decreases followed by stability.[13] Noteworthy is that increased variability of GFR decline over time is associated with increased mortality.[1]

THERAPY FOR NATURAL PROGRESSION

CKD usually progresses slowly. Therefore even relatively small reductions in GFR loss can delay the onset of ESRD by years. For this reason an aggressive, multiple–risk factor intervention to slow GFR decline is warranted, except in patients with low ESRD risk. For example, those with (1) corticosteroid-responsive minimal change disease; (2) those with a solitary kidney that is normal, is acquired in adulthood, and is not accompanied by other CKD risk factors; (3) normotensive adults with hereditary nephritis or thin glomerular basement membrane in whom the only renal manifestation is microscopic hematuria; and (4) the elderly with idiopathic and moderately elevated serum creatinine (1.30 to 2.00 mg/dl), a 24-hour uPCR below 1.0, and whose renal parameters have been stable for at least 1 year. These patients are much more likely to die of cardiovascular disease (CVD) than to progress to ESRD.[1]

BOX 79.3 Recommended Kidney Protective Therapies According to Level of Recommendation

Level 1 Recommendations

Control blood pressure (BP).
Administer angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or renin inhibitor.
Avoid dihydropyridine calcium channel blockers (DH-CCBs) unless needed for BP control.
Control protein intake.

Level 2 Recommendations

Restrict NaCl intake/diuretic therapy.
Administer NDH-CCB therapy.
Control each component of the metabolic syndrome.
Administer aldosterone antagonist therapy.
Administer β-blocker therapy.
Control serum phosphorous.
Instigate smoking cessation.
Control hyperuricemia.
Administer alkali therapy.
Avoid anticoagulant-related nephropathy.
Monitor serum creatinine in patients receiving proton pump inhibitors.
Correct vitamin D deficiency.
Avoid/minimize nonsteroidal antiinflammatory drug use.

The goal for the chronic kidney disease (CKD) patient is to implement all level 1 recommendations and as many level 2 recommendations as is feasible.

Therapies recommended in this chapter are listed in Box 79.3. The goals of progression therapy are to reduce proteinuria as much as possible, ideally to less than 500 mg/day, which is a safe level of proteinuria for most forms of CKD (see earlier discussion), and slow GFR decline as much as possible, ideally to about 1 ml/min/year, which is the rate of GFR decline attributable to the nephropathy of aging (see Chapter 67).

Level 1 Recommendations to Slow Natural Progression

Control Blood Pressure

The low blood pressure (BP) goal (sitting systolic BP [SBP] in the 120s or less, if tolerated) is recommended. However, the evidence supporting the low goal is not robust.[1] It is based largely on the subset of patients in the MDRD study whose baseline proteinuria was greater than 1.0 g/day; the African American Study of Kidney Disease and Hypertension (AASK), but only in the long-term cohort study; and the Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial in children.

Another reason to favor the low BP goal is that in both the MDRD study and AASK, those assigned to the low BP goal had a significantly lower risk for ESRD during long-term (post-trial) follow-up than those assigned to the usual (higher) BP goal. This is remarkable because during the post-trial follow-up the low BP goal was recommended to all patients. In addition, in a meta-analysis of placebo-controlled randomized trials of antihypertensive drug therapy in which there was post-trial follow-up of at least 7 years, it was found that the mortality rate during post-trial follow-up was significantly lower in the group that had been randomized to the study drug than in the group that had been randomized to placebo, even though during the post-trial follow-up both groups were advised to receive the study drug. This benefit of having received the antihypertensive study drug during the randomized trial was independent of the class of the antihypertensive study drug.[1]

The Systolic blood Pressure Intervention Trial (SPRINT) is the most recent major BP and intervention trial to study the effect of BP control on CKD progression.[14] The unique feature of SPRINT was the aggressiveness of the "intensive" BP intervention, which targeted an SBP of less than 120 mm Hg. The "standard" target was 135 to 139 mm Hg. In SPRINT the achieved mean SBP was 121 mm Hg in the Intensive cohort and 136 mm Hg in the Standard cohort. In CKD patients, the Intensive intervention did not slow CKD progression. However, SPRINT involved mainly elderly patients (mean age 68 years, 28% older than 75 years) and the CKD patients had low level proteinuria. On this basis, the results of SPRINT should not be generalized to the younger CKD population who typically have substantial proteinuria and therefore may be more susceptible to the benefits of intensive BP lowering.

When the findings cited earlier are taken together, it seems that the low BP goal is more beneficial than the usual BP goal, even though it may take several years for the benefit to be shown. These results also suggest that achieving the low goal BP sooner rather than later is important.

In CKD patients, in general, the greater the proteinuria, the greater is the benefit of the low BP goal in slowing CKD progression.[1] The low BP goal was also better than the usual BP goal at slowing the progression of proteinuria during the trials.[1] This may be evidence of kidney protection.

The BP should be taken in the sitting position after about 3 to 5 minutes of rest. Sitting BP is recommended because that was the method used in the pivotal BP intervention trials. A period of rest is recommended, to minimize the effects of white coat hypertension.

SBP is the recommended target because, in general, it correlates better with CKD progression than diastolic BP (DBP).[1] Also, specifying both SBP and DBP goals can be confusing if one goal is met but the other is not and could lead to overtreatment or undertreatment of BP.[1]

There is mounting evidence that whenever feasible, BP control should include home BP monitoring (HBPM) rather than only office or clinic BP. The latter is a poor predictor of risk compared with HBPM or ambulatory BP monitoring (ABPM).[15] Among hypertensive CKD patients, masked hypertension (BP is normal in the office or clinic but hypertensive by HBPM or ABPM) is common (e.g., 50% of CKD patients) and carries a risk for CV events comparable to that of sustained hypertension, defined as increased BP both in the office/clinic and at home.[16] The technique of HBPM is discussed in Chapter 33.

The optimum frequency of HBPM measurement has not been rigorously studied. We recommend that initially HBPM be measured twice daily—morning and evening—until the BP is at goal. The frequency of HBPM can then be decreased. The recommended minimum frequency of HBPM is every 1 or 2 weeks, including both morning and evening testing. The HBPM measures need to be recorded and averaged. The average BP should be used to determine the degree of BP control.[1]

A recent meta-analysis of the trials in which there was a head-to-head comparison of antihypertensive drugs on CV outcomes and death concluded that there was no important difference in outcome after taking into account the BP-lowering effect of the drugs. So, the most important role of antihypertensive medication is to control BP. However, in CKD management, the goals of BP control also include optimizing the use of antihypertensive drugs that protect kidney function, particularly by controlling glomerular hypertension and reducing proteinuria. These goals are reflected in algorithms in Figs. 79.3 and 79.4, which are evidence and experience based. Although the algorithms recommend beginning with a single drug, if the SBP is more than 20 mm Hg above goal, two or more antihypertensive agents will usually be needed.[1]

In the effort to achieve optimum BP control it is important to avoid overcontrol of BP. Overcontrol is usually manifested by orthostatic hypotension (decrease in SBP >10 mm Hg and symptoms of lightheadedness when changing from the sitting to standing positions). Overcontrol of BP can result in falls and acute kidney injury, as described in the ACCORD and SPRINT trials.

Renin-Angiotensin System Blockade

Renin-angiotensin system (RAS) blockade with ACE inhibitors or angiotensin receptor blockers (ARBs) is recommended first-line therapy to reduce proteinuria, CKD progression, and CV risk (see Fig. 79.3). An ACE inhibitor is the first choice because of evidence from placebo-controlled randomized trials that ACE inhibitor therapy decreased the risk for death but ARB did not.[17] However, those of African ancestry need to be cautioned that ACE inhibitors can cause angioedema of the upper airways. It is a rare but serious problem that can occur any time during ACE inhibitor therapy. RAS blockade is recommended in CKD even if hypertension is not present, because the kidney and CV protection of RAS blockade is, at least in part, independent of BP control.[1] In general, the greater the ACE inhibitor or ARB dose, the greater is the effect on control of hypertension and proteinuria.[1,18]

RAS blockers are antiproteinuric even in inflammatory glomerulonephritis and should be continued even if GFR declines to stage 4 CKD (15 to 29 ml/min/1.73 m^2).[1] For prevention of hyperkalemia, dietary potassium restriction and the concomitant use of furosemide and sodium bicarbonate may be needed.[1]

Adipose tissue expresses all RAS components. Thus angiotensin II may play a greater role in obese CKD patients. Indeed, in the Ramipril in Non-diabetic Renal Failure (REIN) trial, ACE inhibitor therapy was significantly more effective in slowing GFR decline in the obese than in the nonobese.[1]

Combination Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Therapy

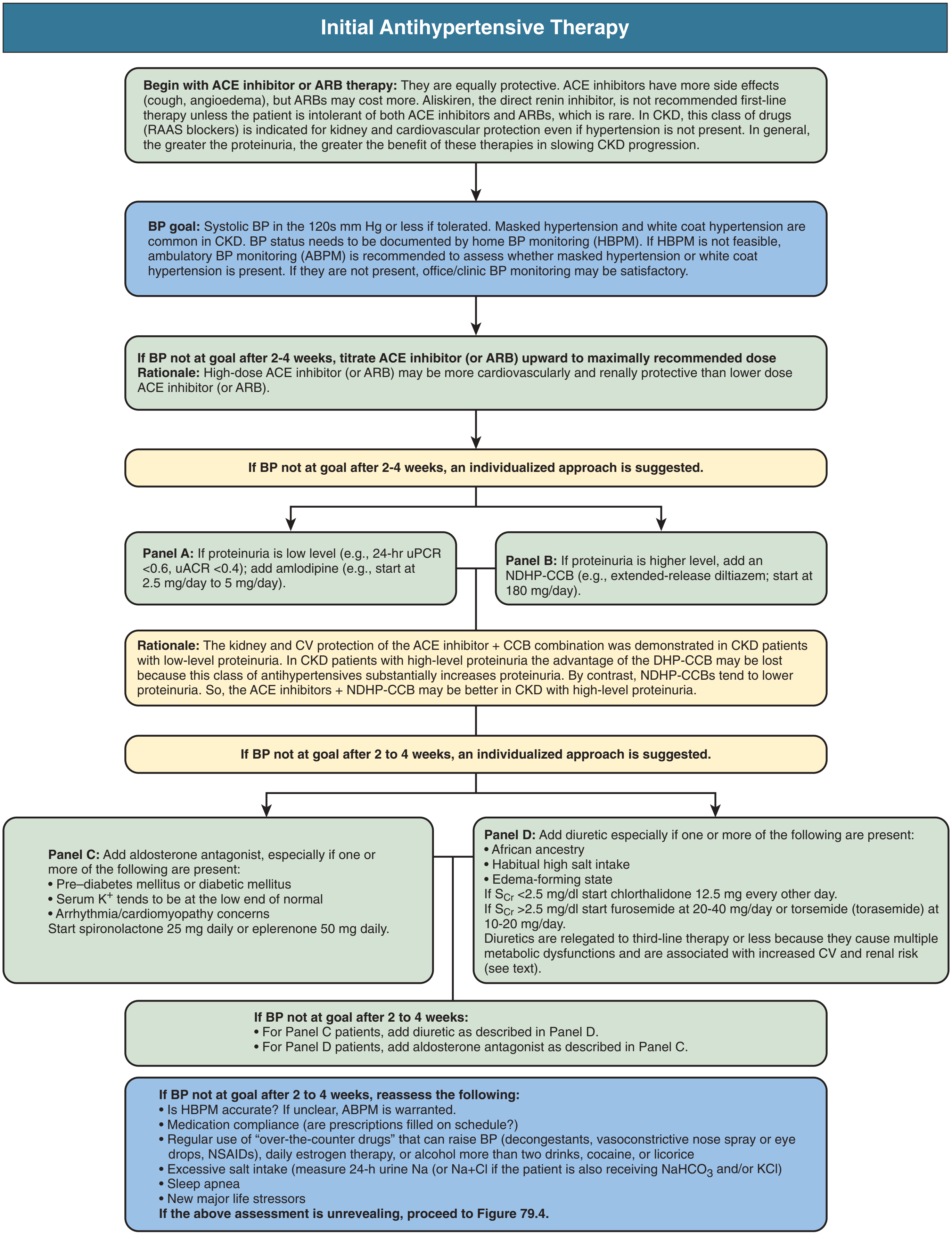
Combination ACE inhibitor and ARB (dual) therapy is more antihypertensive and more antiproteinuric than either drug alone.[19] However, in our experience dual therapy often has not been helpful in decreasing severe proteinuria, even when combined with aldosterone antagonist, salt restriction, protein restriction, diuretic therapy, and statin therapy.

Renin Inhibitor Therapy

Aliskiren, a direct renin inhibitor, is an effective antihypertensive agent and has been shown to reduce albuminuria in diabetic nephropathy and IgA nephropathy. However, when aliskiren was added to ACE inhibitor or ARB therapy in patients with type 2 diabetes and nephropathy, there was increased risk for renal impairment, hypotension, and hyperkalemia, without evident benefit.[1] Aliskiren may be a suitable alternative RAS blocker for those intolerant to both ACE inhibitors and ARBs.

Avoid Dihydropyridine Calcium Channel Blockers

Three randomized trials in CKD have shown that those assigned to dihydropyridine calcium channel blocker (DHP-CCB) therapy experienced less kidney protection than those not assigned to DHP-CCB,[1] perhaps because of DHP-CCB–induced arteriolar vasodilation resulting in glomerular hypertension. However, in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic



Initial Antihypertensive Therapy

Begin with ACE inhibitor or ARB therapy: They are equally protective. ACE inhibitors have more side effects (cough, angioedema), but ARBs may cost more. Aliskiren, the direct renin inhibitor, is not recommended first-line therapy unless the patient is intolerant of both ACE inhibitors and ARBs, which is rare. In CKD, this class of drugs (RAAS blockers) is indicated for kidney and cardiovascular protection even if hypertension is not present. In general, the greater the proteinuria, the greater the benefit of these therapies in slowing CKD progression.

BP goal: Systolic BP in the 120s mm Hg or less if tolerated. Masked hypertension and white coat hypertension are common in CKD. BP status needs to be documented by home BP monitoring (HBPM). If HBPM is not feasible, ambulatory BP monitoring (ABPM) is recommended to assess whether masked hypertension or white coat hypertension is present. If they are not present, office/clinic BP monitoring may be satisfactory.

If BP not at goal after 2-4 weeks, titrate ACE inhibitor (or ARB) upward to maximally recommended dose
Rationale: High-dose ACE inhibitor (or ARB) may be more cardiovascularly and renally protective than lower dose ACE inhibitor (or ARB).

If BP not at goal after 2-4 weeks, an individualized approach is suggested.

Panel A: If proteinuria is low level (e.g., 24-hr uPCR <0.6, uACR <0.4); add amlodipine (e.g., start at 2.5 mg/day to 5 mg/day).

Panel B: If proteinuria is higher level, add an NDHP-CCB (e.g., extended-release diltiazem; start at 180 mg/day).

Rationale: The kidney and CV protection of the ACE inhibitor + CCB combination was demonstrated in CKD patients with low-level proteinuria. In CKD patients with high-level proteinuria the advantage of the DHP-CCB may be lost because this class of antihypertensives substantially increases proteinuria. By contrast, NDHP-CCBs tend to lower proteinuria. So, the ACE inhibitors + NDHP-CCB may be better in CKD with high-level proteinuria.

If BP not at goal after 2 to 4 weeks, an individualized approach is suggested.

Panel C: Add aldosterone antagonist, especially if one or more of the following are present:
- Pre–diabetes mellitus or diabetic mellitus
- Serum K^+ tends to be at the low end of normal
- Arrhythmia/cardiomyopathy concerns

Start spironolactone 25 mg daily or eplerenone 50 mg daily.

Panel D: Add diuretic especially if one or more of the following are present:
- African ancestry
- Habitual high salt intake
- Edema-forming state

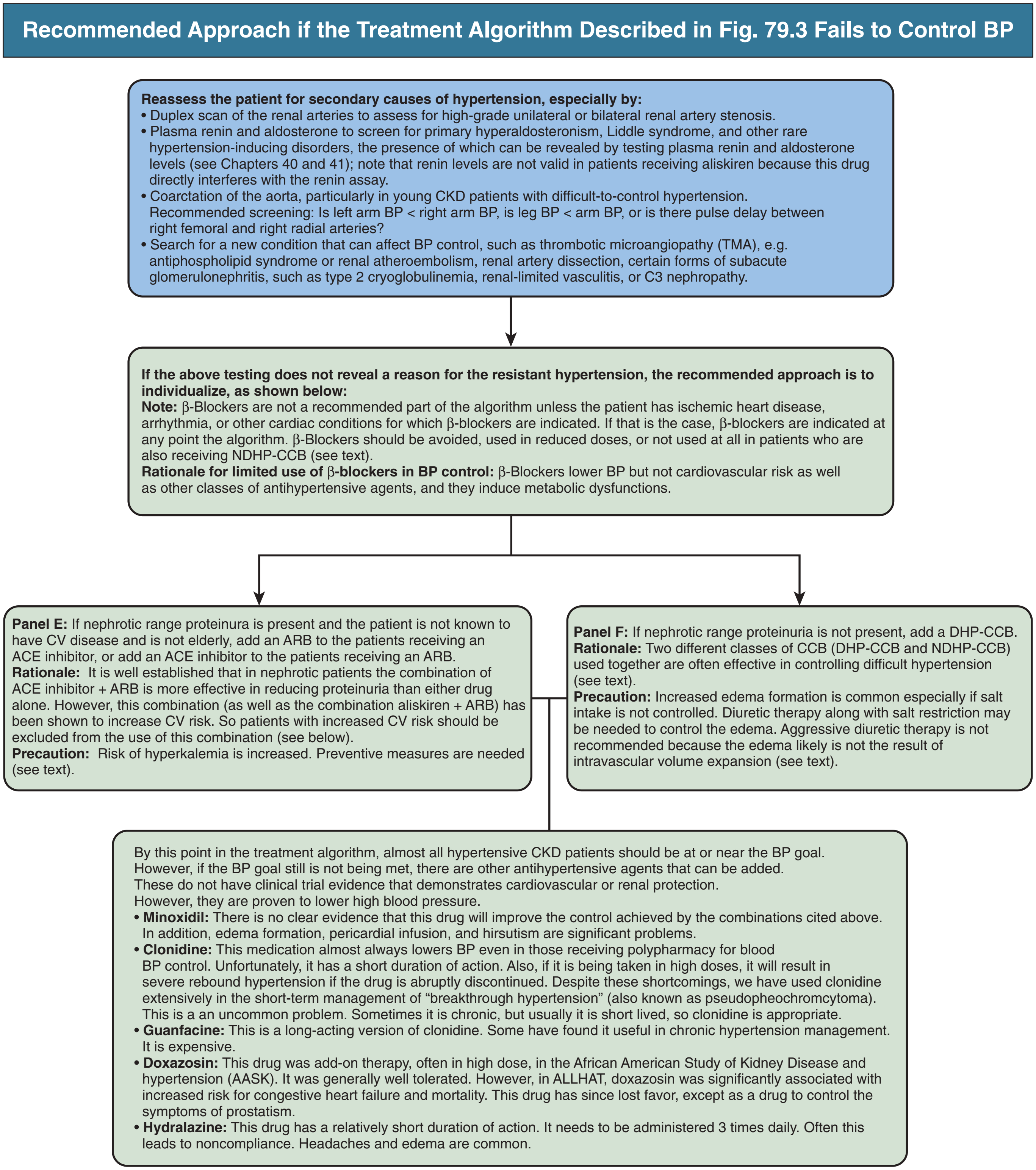
If S_{Cr} <2.5 mg/dl start chlorthalidone 12.5 mg every other day.
If S_{Cr} >2.5 mg/dl start furosemide at 20-40 mg/day or torsemide (torasemide) at 10-20 mg/day.
Diuretics are relegated to third-line therapy or less because they cause multiple metabolic dysfunctions and are associated with increased CV and renal risk (see text).

If BP not at goal after 2 to 4 weeks:
- For Panel C patients, add diuretic as described in Panel D.
- For Panel D patients, add aldosterone antagonist as described in Panel C.

If BP not at goal after 2 to 4 weeks, reassess the following:
- Is HBPM accurate? If unclear, ABPM is warranted.
- Medication compliance (are prescriptions filled on schedule?)
- Regular use of "over-the-counter drugs" that can raise BP (decongestants, vasoconstrictive nose spray or eye drops, NSAIDs), daily estrogen therapy, or alcohol more than two drinks, cocaine, or licorice
- Excessive salt intake (measure 24-h urine Na (or Na+Cl if the patient is also receiving $NaHCO_3$ and/or KCl)
- Sleep apnea
- New major life stressors

If the above assessment is unrevealing, proceed to Figure 79.4.

Fig. 79.3 **Initial antihypertensive therapy.** The algorithm shown here assumes that nonpharmacologic therapy to control blood pressure *(BP)* is in place (see text) and that the patient is not known to have renovascular hypertension, congestive heart failure, or ischemic or heart disease, and does not have hypertensive urgency. This approach focuses on BP control in proteinuric nephropathies, but is also appropriate for nephrosclerosis, polycystic kidney disease, and interstitial nephropathies. More details on each of the recommended drugs are provided in the text. *ACE,* Angiotensin-converting enzyme; *uACR,* urine albumin-to-creatinine ratio; *ARB,* angiotensin receptor blocker; *CKD,* chronic kidney disease; *CV,* cardiovascular; *NDHP-CCB,* nondihydropyridine calcium channel blocker; *NSAIDs*, nonsteroidal antiinflammatory drugs; *uPCR,* urine protein-to-creatinine ratio; *RAAS,* renin-angiotensin-aldosterone system; S_{Cr}, serum creatinine.



Recommended Approach if the Treatment Algorithm Described in Fig. 79.3 Fails to Control BP

Reassess the patient for secondary causes of hypertension, especially by:

- Duplex scan of the renal arteries to assess for high-grade unilateral or bilateral renal artery stenosis.
- Plasma renin and aldosterone to screen for primary hyperaldosteronism, Liddle syndrome, and other rare hypertension-inducing disorders, the presence of which can be revealed by testing plasma renin and aldosterone levels (see Chapters 40 and 41); note that renin levels are not valid in patients receiving aliskiren because this drug directly interferes with the renin assay.
- Coarctation of the aorta, particularly in young CKD patients with difficult-to-control hypertension. Recommended screening: Is left arm BP < right arm BP, is leg BP < arm BP, or is there pulse delay between right femoral and right radial arteries?
- Search for a new condition that can affect BP control, such as thrombotic microangiopathy (TMA), e.g. antiphospholipid syndrome or renal atheroembolism, renal artery dissection, certain forms of subacute glomerulonephritis, such as type 2 cryoglobulinemia, renal-limited vasculitis, or C3 nephropathy.

If the above testing does not reveal a reason for the resistant hypertension, the recommended approach is to individualize, as shown below:

Note: β-Blockers are not a recommended part of the algorithm unless the patient has ischemic heart disease, arrhythmia, or other cardiac conditions for which β-blockers are indicated. If that is the case, β-blockers are indicated at any point the algorithm. β-Blockers should be avoided, used in reduced doses, or not used at all in patients who are also receiving NDHP-CCB (see text).

Rationale for limited use of β-blockers in BP control: β-Blockers lower BP but not cardiovascular risk as well as other classes of antihypertensive agents, and they induce metabolic dysfunctions.

Panel E: If nephrotic range proteinura is present and the patient is not known to have CV disease and is not elderly, add an ARB to the patients receiving an ACE inhibitor, or add an ACE inhibitor to the patients receiving an ARB.

Rationale: It is well established that in nephrotic patients the combination of ACE inhibitor + ARB is more effective in reducing proteinuria than either drug alone. However, this combination (as well as the combination aliskiren + ARB) has been shown to increase CV risk. So patients with increased CV risk should be excluded from the use of this combination (see below).

Precaution: Risk of hyperkalemia is increased. Preventive measures are needed (see text).

Panel F: If nephrotic range proteinuria is not present, add a DHP-CCB.

Rationale: Two different classes of CCB (DHP-CCB and NDHP-CCB) used together are often effective in controlling difficult hypertension (see text).

Precaution: Increased edema formation is common especially if salt intake is not controlled. Diuretic therapy along with salt restriction may be needed to control the edema. Aggressive diuretic therapy is not recommended because the edema likely is not the result of intravascular volume expansion (see text).

By this point in the treatment algorithm, almost all hypertensive CKD patients should be at or near the BP goal. However, if the BP goal still is not being met, there are other antihypertensive agents that can be added. These do not have clinical trial evidence that demonstrates cardiovascular or renal protection. However, they are proven to lower high blood pressure.

- **Minoxidil:** There is no clear evidence that this drug will improve the control achieved by the combinations cited above. In addition, edema formation, pericardial infusion, and hirsutism are significant problems.
- **Clonidine:** This medication almost always lowers BP even in those receiving polypharmacy for blood BP control. Unfortunately, it has a short duration of action. Also, if it is being taken in high doses, it will result in severe rebound hypertension if the drug is abruptly discontinued. Despite these shortcomings, we have used clonidine extensively in the short-term management of “breakthrough hypertension” (also known as pseudopheochromcytoma). This is a an uncommon problem. Sometimes it is chronic, but usually it is short lived, so clonidine is appropriate.
- **Guanfacine:** This is a long-acting version of clonidine. Some have found it useful in chronic hypertension management. It is expensive.
- **Doxazosin:** This drug was add-on therapy, often in high dose, in the African American Study of Kidney Disease and hypertension (AASK). It was generally well tolerated. However, in ALLHAT, doxazosin was significantly associated with increased risk for congestive heart failure and mortality. This drug has since lost favor, except as a drug to control the symptoms of prostatism.
- **Hydralazine:** This drug has a relatively short duration of action. It needs to be administered 3 times daily. Often this leads to noncompliance. Headaches and edema are common.

Fig. 79.4 Recommended approach if the treatment algorithm described in Fig. 79.3 fails to control blood pressure *(BP).* If patients are intolerant or allergic to the drugs recommended in the algorithms, suggested alternatives include ethacrynic acid for thiazide diuretics, aliskiren for angiotensin-converting enzyme *(ACE)* inhibitors or angiotensin receptor blockers *(ARBs),* and minoxidil for calcium channel blockers *(CCBs).* Carvedilol or doxazosin may be appropriate at any point in patients in whom stress may play an important role in their hypertension, or in whom BP is particularly labile, in the absence of correctable factors to account for the lability. *ALLHAT,* Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial; *CKD,* chronic kidney disease; *CV,* cardiovascular; *DHP-CCB,* dihydropyridine calcium channel blocker; *NDHP-CCB,* nondihydropyridine calcium channel blocker.

Hypertension (ACCOMPLISH) trial, ACE inhibitor plus amlodipine therapy protected kidney function better than ACE inhibitor plus diuretic therapy, especially in non-Blacks. Possibly, the benefit of amlodipine in the ACCOMPLISH study was seen because the CKD patients had low-level proteinuria. In addition, there is evidence that chronic thiazide therapy is nephrotoxic.[1] Thus, if a CCB is needed for BP control, the first choice should be a nondihydropyridine CCB (NDHP-CCB) (discussed later).

Control Protein Intake

High-protein diets predict ESRD in CKD.[20] Also, reducing dietary protein intake from the usual level (in developed countries ~1 to 1.5 g/kg ideal body weight per day) to about 0.7 g/kg ideal body weight per day (low-protein diet) slows GFR decline in those with proteinuria of more than 1 g/day.[1] Another benefit of the lower protein intake in CKD is that it slows proteinuria progression, even in those who at baseline have only low-level proteinuria.[1]

Diets incorporating plant-based (e.g., soy) proteins may be more antiproteinuric than those composed of animal proteins only.[21]

Dietary protein intake should be monitored periodically, for example, every 4 to 6 months, by measuring urine urea nitrogen excretion in 24-hour urine collections. For a 70-kg person, a 50-g protein diet would achieve the dietary goal of 0.7 g/kg ideal body weight per day. In such a patient, the 24-hour urine collection would contain about 8 g urine urea nitrogen. Monitoring protein intake is particularly important in those who are not achieving their proteinuria goal. Men and those with glomerular disease may particularly benefit from the low-protein diet.[1] Red meat intake is particularly linked to CKD risk.[22]

Excessive protein restriction (<0.6 g/kg/day) should be avoided. In the MDRD study, long-term follow-up of those on the very low protein intake showed no benefit in reducing GFR decline and appeared to have an increased risk for death.[1]

A recent randomized trial compared a low-protein diet (0.6 g/kg/day) using usual dietary proteins to a very low vegetarian protein diet (0.3 g/kg/day) supplemented with ketoanalogues of essential amino acids. The latter diet was significantly better than the traditional diet in reducing renal end-points. Unfortunately, only 14% of the randomized patients were compliant with the vegetarian/supplemented diet.[21]

Level 2 Recommendations to Slow Natural Progression

Restrict Salt Intake and Avoid Diuretic Therapy

Salt restriction as a public health measure remains controversial.[23,24] However, in CKD, high salt intake appears to cause CKD progression[25] and increase the risk for CVD. Surprisingly, evidence that high salt intake increases the risk for CKD is lacking.[26]

Nevertheless, high salt intake (e.g., 200 mmol NaCl/day = 11.6 g NaCl or 4.6 g Na) can completely override the antiproteinuric effects of ACE inhibitor, ARB, or NDHP-CCB therapy. Also, high salt intake measured at baseline is a significant predictor of more rapid GFR decline.[27] In addition, it is well established that high salt intake worsens hypertension.

The recommended NaCl intake in CKD (assuming that renal salt wasting is not present) is about 2 to 3 g Na (5 to 7.5 g NaCl, 88 to 112 mEq Na). The NaCl intake of the average North American adult is about 10 g NaCl (4 g Na, 170 mEq Na Cl). Achievement of the CKD goal for salt intake would be documented by a 24-hour urine collection containing about 80 to 120 mmol (mEq) of sodium. Urine sodium should be measured each time 24-hour urine protein is measured (see the discussion of monitoring of proteinuria). In patients receiving $NaHCO_3$ therapy, urine chloride rather than sodium should be monitored, taking into account whether the patient is also receiving KCl.[1] The rationale is that urine Cl is almost entirely derived from ingestion of NaCl, unless the patient is also receiving KCl therapy. So, if the patient is not receiving KCl, 24-hour urine chloride in milliequivalents is equal to 24-hour urine NaCl in millimoles.

High fructose intake (in the form of table sugar or high-fructose corn syrup used in sugar-sweetened beverages) should be avoided in CKD because it increases renal sodium reabsorption and can worsen BP control (see the discussion of metabolic syndrome).

In patients receiving RAS blockers, diuretic therapy improves BP control and decreases proteinuria. Nevertheless, the ideal is to avoid diuretics because of the evidence of nephrotoxicity[1] and their multiple metabolic dysfunctions, which include hypokalemia, hyperglycemia, hyperlipidemia, hypomagnesemia, hyperuricemia, and stimulation of the RAS, which are known to increase CV risk.[1] Loop diuretics are more effective than thiazides if GFR is below 30 ml/min. If the GFR is higher, the preferred diuretic is chlorthalidone or indapamide because of greater efficacy in controlling BP and protection against CV events compared with hydrochlorothiazide.[28]

Nondihydropyridine Calcium Channel Blocker Therapy

NDHP-CCB (e.g., diltiazem and verapamil) are antiproteinuric and may be renoprotective. An NDHP-CCB together with a DHP-CCB can be a potent antihypertensive combination when used along with other antihypertensive therapies (see Fig. 79.4).[1]

Control Each Component of the Metabolic Syndrome

Metabolic syndrome and each of its components are risk factors for CKD progression,[1] and the prevalence of microalbuminuria and CKD increase in parallel with the number of components of the metabolic syndrome.[29]

Obesity increases the risk for CKD and is associated with glomerulopathy, FSGS, and proteinuria. Reducing even moderate obesity can reduce proteinuria in CKD.[1] Bariatric surgery in morbidly obese CKD patients is associated with stabilization or improved eGFR.[30] In type 2 diabetes, improvement in diabetic control is also seen.

The current KDIGO guideline (www.kdigo.org) recommends a statin or a statin plus ezetimibe for all non-ESRD CKD patients 50 years of age or older, regardless of the blood lipid levels. Disregard of the lipid levels is based on the Study of Heart and Renal Protection (SHARP), which showed that the benefits of lipid therapy are not related to baseline lipid level. For non-ESRD CKD patients younger than 50 years, KDIGO does not recommend statin therapy unless there is increased CV risk. The KDIGO-recommended statin doses are low (e.g., atorvastatin 20 mg/day).

These guidelines are based on a rigorous interpretation of the available data. We suggest, however, that for certain patients shared decision making regarding a less restrictive approach to statins might be appropriate. The argument is that CKD itself is a strong CV risk factor, the risk starts early in CKD (see Chapter 81), and CVD takes many years to develop. So starting lipid therapy early in CKD patients may be prudent, as has previously been suggested.[31] In addition, statins are well tolerated in CKD, even at high doses (e.g., atorvastatin 80 mg daily).[1] With regard to statin choice in CKD, atorvastatin may be better than simvastatin[32] and rosuvastatin may have nephrotoxicity.[33,34] Also to be considered in the shared decision making is the recent meta-analysis of randomized trials of fibrate therapy compared with placebo in mild to moderate CKD. Fibrate therapy reduced CV risk and albuminuria, although ESRD risk was unchanged. Noteworthy is that serum creatinine increased during the trial in those taking fenofibrate, probably because of increased creatinine production. However, when the fibrate was stopped after the trial, serum creatinine decreased to below baseline values, suggesting that kidney function was protected during fibrate therapy.[1] Fibrates decrease triglycerides significantly. These observations suggest a role for add-on fibrate therapy for CKD patients at high CV risk, especially those whose triglycerides are not controlled by statin therapy or a statin-ezetimibe combination.

Aldosterone Antagonist Therapy

Spironolactone and the more selective aldosterone antagonist eplerenone have substantial antihypertensive, cardioprotective, and antiproteinuric effects even at low doses (e.g., spironolactone 25 mg/day) and in the presence of combined ACE inhibitor and ARB therapy. The mechanism may involve blockade of aldosterone effects on endothelium and on fibrosis. Although there are no rigorous clinical trial data with hard end-points such as ESRD, the available evidence supports the use of aldosterone antagonists in high-risk CKD patients who have not reached their BP and proteinuria goals despite the use of an ACE inhibitor or ARB plus a CCB plus diuretic (see Fig. 79.3). However, the use of aldosterone antagonists should be restricted to those with eGFR greater than 30 ml/min. If spironolactone or eplerenone is used in patients receiving renin-angiotensin-aldosterone system (RAAS) blockers, it is especially important to prevent hyperkalemia. These measures include sodium bicarbonate therapy (see the discussion of alkali therapy), the avoidance of potassium-rich foods, and awareness of the symptoms of severe hyperkalemia. These include the relatively sudden onset of symmetric proximal muscle weakness (difficulty climbing stairs or rising from a chair) or muscle stiffness.

Aldosterone antagonists are particularly helpful in those with resistant hypertension and high salt intake[35] or those who experience aldosterone escape (failure to suppress serum aldosterone during ACE inhibitor or ARB therapy.[36]

β-Blocker Therapy

The AASK study showed that β-blocker therapy slows GFR decline better than DHP-CCB. However, β-blockers increase the likelihood of diabetes and, as monotherapy or when combined with diuretics, increase mortality compared with ACE inhibitors plus diuretics.[1] β-Blockers should be used in CKD to manage coronary heart disease or arrhythmia but may be less appropriate for the management of hypertension.[1] Carvedilol may be less likely to increase insulin resistance than metoprolol when it is used in combination with an ACE inhibitor.[1] However, carvedilol (a vasodilating β-blocker) does not lower central aortic pressure any better than the nonvasodilating β-blockers. This suggests that vasodilating β-blockers may not reduce mortality any better than nonvasodilating β-blockers, although this remains speculative.

Control Serum Phosphorous

Serum phosphorus generally does not become elevated until stage 4 CKD. In CKD, there is a significant association between increased serum phosphorous and either CKD progression or incident CKD and ESRD.[37] Phosphorus control should begin when serum phosphorus is consistently greater than 4.0 mg/dl (1.3 mmol/l). The first approach is to reduce phosphorous intake, with the precaution that severely reducing meat and dairy products could lead to protein malnutrition. Proteins in grain (e.g., a vegetarian-type diet) have a lower phosphorus content than the proteins in meat or milk. If plant-based proteins are substituted for meat and dairy products, better control of serum phosphorous can be achieved.

If dietary measures are ineffective, use of phosphate binders is generally recommended. However, which type of phosphate binder is best is controversial[38] (see Chapter 84).

Smoking Cessation

Cigarette smoking promotes progression of all forms of kidney disease in a dose-dependent manner, perhaps more in those of African American ancestry.[1]

Control Hyperuricemia

Three randomized trials[1] and one case-control study found that allopurinol therapy slows CKD progression.[39] One randomized double-blind study of febuxostat in CKD showed similar benefit.[40] In addition, abundant experimental evidence exists that uric acid is proinflammatory, vasculotoxic, and associated with increased CV and renal risk.[41]

A major concern in recommending allopurinol or, rarely, febuxostat to slow CKD is the risk, albeit very small, of severe and even fatal hypersensitivity reactions (e.g., Stevens-Johnson syndrome). A recent study also reported that febuxostat may be associated with increased cardiovascular mortality compared to allopurinol. Importantly, it is not known if febuxostat increases cardiovascular risk in subjects not receiving uric acid lowering therapy, and a few studies do suggest allopuriol may reduce cardiovascular events in subjects with CKD. A cogent argument can be made that these xanthine oxidase inhibitors have a favorable risk-to-benefit ratio in CKD, particularly in relationship to the traditional uses of these drugs, which are to treat nonlethal diseases, gout, and kidney stones.

Reducing the risk for severe hypersensitivity reaction to allopurinol in CKD patients may be accomplished by reducing the initial dose (see summary, later) and by advising patients who are about to start allopurinol or febuxostat to stop the drug immediately and call their physician should they develop rash, fever, or other signs of illness. Also, allopurinol should be avoided in patients with high-risk alleles (HLA-B58) for severe allopurinol hypersensitivity. This is particularly seen in those of Asian or African ancestry.[42] Testing for these risk alleles in these populations has been recommended.

In summary, there is evidence that xanthine oxidase inhibitors therapy, properly approached, may be helpful in hyperuricemic CKD patients to reduce cardiovascular risk and risk for CKD progression. For prevention of severe allergic reactions, the starting dose for allopurinol should be 1.5 mg × eGFR in ml/min/1.73 m^2. If after 8 weeks that dose is well tolerated, it can then be increased until the uric acid level is at goal (7 mg/dl). Also, the patient should be strongly cautioned to stop the allopurinol and seek medical advice if rash, fever, or other signs of illness develop. If febuxostat is used in CKD, the maintenance dose is unchanged.[43]

Avoid Anticoagulant-Related Nephropathy

Anticoagulant-related nephropathy (ARN) is a newly recognized clinical syndrome caused by coagulopathy because the warfarin international normalization ratio (INR) is greater than 3, typically in the mid-4s, or by coagulopathy caused by direct oral anticoagulants (DOACs) (e.g., dabigatran, rivaroxaban).[44] ARN is caused by severe glomerular hemorrhage, even though the glomeruli are normal or nearly normal. The extent to which DOACs cause ARN is unclear, but it is likely that ARN related to DOACs is not a rare occurrence.

Alkali Therapy

The evidence that alkali therapy slows CKD progression is based on three randomized trials and one nonrandomized study. In addition, metabolic acidosis may predict CVD.[1] Recommended forms of alkali are sodium bicarbonate ($NaHCO_3$), sodium citrate, and diets high in fruits and vegetables (i.e., potassium citrate). If $NaHCO_3$ therapy is used, the recommended dose is one to four 650-mg tablets twice daily. The goal is to raise plasma bicarbonate levels to greater than 22 mM/l. Alkali therapy improves protein nutrition by suppressing protein catabolism and protects against hyperkalemia. Whether metabolic acidosis needs to be present for benefit from alkali supplementation is not clear. However, benefit in slowing CKD progression is seen even in those whose pretreatment plasma bicarbonate level is within the normal range.

Monitor Serum Creatinine in Patients Receiving a Proton Pump Inhibitor

Four large retrospective studies[45] have shown an association between PPI use and incident CKD. The comparison groups were those receiving no PPI or histamine-2 (H_2) receptor blockers. However, because the treatment groups were not the results of randomization, confounding is a concern. In addition, the risk for incident CKD was low (approximately one case of CKD for each 100 persons followed for 10 years). Nevertheless, the association of PPI with incident CKD should not be ignored. It would seem sufficient to monitor serum creatinine in PPI patients twice yearly.

Correct Vitamin D Deficiency

Severe deficiency of 25-OH vitamin D is common in CKD, and vitamin D influences the activation of more than 200 genes.[46] Although some have argued against routine vitamin D supplementation in CKD based on a paucity of evidence of benefit from randomized trials, there are some encouraging signs of benefit of adequate vitamin D levels in CKD.[47,48] Vitamin D_3 supplementation is relatively inexpensive and safe. The goal is to raise serum vitamin D levels to the normal range (>30 mg/ml). Vitamin D_3 doses of 1000 or 2000 IU daily or 50,000 IU monthly will usually restore 25-OH vitamin D levels to normal. Note that serum vitamin D levels are on average about one third lower in Blacks than Whites.[49] Most of this difference is accounted for by lower vitamin D binding protein in Blacks. However, biologically active vitamin D is at normal levels. This should be considered when deciding whether vitamin D replacement is adequate. For example, if the target is a vitamin D level of 40 to 60 mg/ml, a lower level within the range might be the appropriate target for those of African ancestry.

Avoid or Minimize Nonsteroidal Antiinflammatory Drug Use

In those with normal or near-normal kidney function, fewer than 1% experience renal events during 2 years of treatment while receiving nonsteroidal antiinflammatory drugs (NSAIDS) at average daily doses of celecoxib 200 mg, naproxen 850 mg, or ibuprofen 2600 mg.[50] However, clinical experience suggests that, if these were CKD patients, many if not most would show an increase in serum creatinine after only a few weeks of NSAIDS at these doses. Also, celecoxib was dosed at relatively lower level than the naproxen or ibuprofen.[51]

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SELF-ASSESSMENT QUESTIONS

1. With respect to the chronic kidney disease (CKD) cohort in the SPRINT trial, each of the following is correct *except:*
   - **A.** The SPRINT CKD cohort is regarded as elderly. The definition of elderly is older than 65 years of age.
   - **B.** The SPRINT CKD cohort manifested low-level proteinuria (maximum 24-hour urine was 1.0 g).
   - **C.** The Intensive blood pressure (BP) goal was a systolic BP less than 120 mm Hg. The Standard BP goal was a systolic BP less than 140 mm Hg with the target of a systolic BP of 135 to 139 mm Hg.
   - **D.** The Intensive BP intervention resulted in a significant reduction in proteinuria.
   - **E.** The Intensive BP intervention slowed estimated glomerular filtration rate (eGFR) decline and protected the patient from episodes of acute kidney injury (AKI).
2. In comparing the risks and benefits of angiotensin-converting enzyme (ACE) inhibitor therapy compared with angiotensin receptor blocker (ARB) therapy in the management of hypertension, each of the following is correct *except:*
   - **A.** Based on the randomized trials, ACE inhibitors cause angioedema; ARB therapy does not cause angioedema.
   - **B.** Those of African ancestry are particularly susceptible to developing angioedema on ACE inhibitor therapy.
   - **C.** ACE inhibitor–induced cough is an intractable problem.
   - **D.** Both ACE inhibitor therapy and ARB therapy are effective in slowing GFR decline in CKD.
   - **E.** Based on recent meta-analyses of randomized trials that compared ACE inhibitor to placebo or ARB to placebo, ACE inhibitor therapy was associated with a significant reduction in mortality but ARB therapy was not associated with a significant reduction in mortality.
3. With respect to the merits of monitoring proteinuria by measuring albuminuria or total proteinuria (albumin plus nonalbumin protein), each of the following is correct *except:*
   - **A.** At total 24-hour proteinuria less than 500 mg, albuminuria is more sensitive than total proteinuria in identifying change.
   - **B.** At 24-hour proteinuria greater than 500 mg, albuminuria and total proteinuria generally change in parallel.
   - **C.** The cost of measuring total proteinuria is less than the cost of measuring albuminuria.
   - **D.** In a given individual, urine protein-to-creatinine ratio (uPCR) varies widely over a given 24-hour period. Single-void (spot) uPCR reveals this variability. By contrast, the uPCR of an intended 24-hour urine collection conceals this variability. The rationale is that the uPCR of an intended 24-hour urine collection ratio is the integrated mean of the uPCR during the entire collection.
   - **E.** In individual CKD patient management, spot uPCR and the uPCR of an intended 24-hour urine collection are equally reliable in assessing proteinuria magnitude.

80

Clinical Evaluation and Management of Chronic Kidney Disease

Laurie A. Tomlinson, David C. Wheeler

Although many patients with chronic kidney disease (CKD) progress to end-stage renal disease (ESRD) and require renal replacement therapy (RRT), the majority die of nonrenal causes, particularly premature cardiovascular (CV) events.[1] Early diagnosis of CKD is therefore important because it provides opportunities to delay progression of CKD (see Chapter 79) and prevent CV complications (see Chapter 81).

DEFINITIONS

Chronic kidney disease is defined as abnormalities of kidney structure or function, present for at least 3 months, with implications for health (Table 80.1). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend classification of CKD based on cause, category of glomerular filtration rate (GFR), and albuminuria (see Fig. 79.1).[2] Because of the impracticalities of using radioisotopes and 24-hour urine collections, the KDIGO classification system recommends that kidney function be assessed by estimating GFR (eGFR) from the serum creatinine concentration using an appropriate equation, except in circumstances in which eGFR estimations are known to be less accurate, such as when there is significant muscle wasting. Initially, the Modification of Diet in Renal Disease (MDRD) equation was used, but this has predominantly been replaced by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which more accurately categorizes the risk for mortality and progression to ESRD (see Chapter 3).[3] Although staging systems for CKD based on eGFR have limitations, they have proved useful in many clinical settings and are now deeply embedded in guidelines developed for CKD management and research.

The evidence base for the management of CKD is constantly evolving. Although every effort has been made to ensure this chapter reflects current recommendations, the reader is advised to check for any relevant guideline updates.

CLINICAL PRESENTATION

CKD is usually asymptomatic until late stage G4 or stage G5 and is commonly detected by routine blood testing. Symptoms of CKD are nonspecific and need to be asked about directly (Table 80.2). There is some evidence that early diagnosis with appropriate management may slow the rate of decline of kidney function and reduce CV risk.[4] Screening of the general population for CKD is not recommended, but in the United Kingdom the National Institute for Health and Care Excellence (NICE) proposes offering testing to people with conditions associated with an increased prevalence of CKD—those with diabetes, hypertension, previous acute kidney injury (AKI), CV disease (CVD), structural renal tract disease, renal calculi, prostatic hypertrophy, multisystem diseases with potential kidney involvement (e.g., systemic lupus erythematosus), a family history of category G5 CKD, or hereditary kidney disease—and after opportunistic detection of hematuria or proteinuria.[5]

Evaluation of Chronic Kidney Disease

Establishing Chronicity

When eGFR of less than 60 ml/min/1.73 m^2 is detected, careful attention should be paid to previous blood and urine test results and the clinical history to determine if this is a result of AKI; that is, an abrupt decrease in kidney function or CKD that has been present but asymptomatic for some time.

A detailed medical history covering issues, including other medical conditions, family history of kidney disease, prescribed medication, and recreational drug use, may suggest an underlying cause. There may be hints of a history of kidney problems (e.g., hypertension, proteinuria, microhematuria) or symptoms suggestive of prostatic disease. The physical examination findings are not usually helpful, although skin pigmentation, scratch marks, left ventricular hypertrophy, and hypertensive fundal changes favor a chronic presentation (Fig. 80.1). Details of the social and personal circumstances are also crucial, particularly for patients with progressive kidney disease in whom RRT is likely to be required.

Blood tests for other conditions can be helpful because they may indicate evidence of an acute illness that could be the cause of kidney failure, such as systemic vasculitis or multiple myeloma. A normochromic normocytic anemia is usual in CKD, but also may be a feature of acute systemic illnesses and therefore is not discriminatory. Low serum calcium and raised phosphate levels also have little discriminatory value, but normal levels of parathyroid hormone (PTH) are more in keeping with AKI. Patients with grossly abnormal biochemical values—for example, blood urea nitrogen higher than 140 mg/dl, serum creatinine above 13.5 mg/dl (>1200 μmol/l), or blood urea greater than 300 mg/dl (>50 mmol/l)—who appear relatively well and are still passing normal volumes of urine are much more likely to have CKD than AKI.

Assessment of Glomerular Filtration Rate

For patients in whom the distinction between AKI and CKD is unclear, repeat testing of kidney function should be performed within 2 weeks of the initial finding of an eGFR below 60 ml/min/1.73 m^2. However, if previous results confirm that this is a chronic finding, or if repeated blood test results over a 3-month period are consistent, CKD is confirmed. Other tests (such as cystatin C or an isotope-clearance measurement of GFR) may be required for confirmation of CKD in circumstances in which eGFR based on serum creatinine is known to be less accurate.

TABLE 80.1 Criteria for Definition of Chronic Kidney Disease (CKD)

CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. These may include the following:	
Markers of kidney damage	Albuminuria (AER ≥30 mg/24 h; uACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities caused by tubular disorders Abnormalities detected through histology Structural abnormalities detected through imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2

From reference 2.
AER, Albumin excretion rate; *GFR,* glomerular filtration rate; *uACR,* urinary albumin-to-creatinine ratio.

TABLE 80.2 Symptoms and Signs of Severe Chronic Kidney Disease

Symptoms	Signs
Difficulty sleeping	Altered respiration including Kussmaul breathing and Cheyne-Stokes respiration
Nocturia	Icteric sclera or "red eye" due to calcium deposition
Headache	Muscle weakness
Restless leg syndrome	Oral lesions including gingival bleeding or petechiae, xerostomia, periodontitis, and candidiasis
Metallic taste in the mouth	Pericardial and/or pleural rub
Shortness of breath on exertion or at rest, paroxysmal nocturnal dyspnea	Pulmonary and peripheral edema
Fatigue, often profound	Skin changes including xerosis (abnormal dryness), scratch marks, pallor, sallow coloration or hyperpigmentation
Muscle cramps and twitches	Uremic flap (asterixis)
Seizures	Uremic fetor: Ammonia or urine-like odor to the breath
Lack or loss of appetite for food, abdominal pain, nausea, vomiting, and weight loss	Uremic frost: Crystallized urea deposits that can be found on the skin
Itch, particularly on the trunk and worse at night	

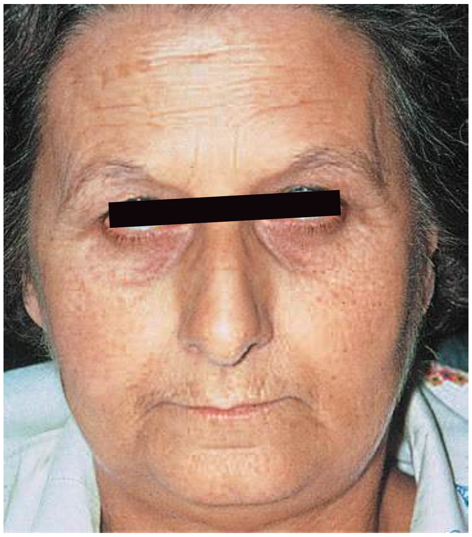

Fig. 80.1 Uremic pigmentation. Diffuse brown pigmentation as seen here suggests chronic kidney disease rather than acute kidney injury.

Assessment of Proteinuria

Dipstick testing of the urine and urine culture is important.[6] This may reveal microhematuria, which can be a useful pointer toward an underlying diagnosis. Workup of hematuria is discussed in Chapters 4 and 59. Whether or not proteinuria is detected by dipstick, there should be a further measurement of urinary protein excretion. Proteinuria is an important diagnostic and prognostic marker, and its presence indicates a higher risk for both progression of kidney disease and CV complications.[7] KDIGO guidelines recommend that the preferred method of assessing proteinuria is by measurement of the urinary albumin-to-creatinine ratio (uACR) using an early morning urine sample.[2] The degree of albuminuria is graded by the A1 to A3 category system, replacing previous terms such as *microalbuminuria* (see Fig. 79.1). However, it is important to be aware that some patients will excrete proteins other than albumin, and a urine protein-to-creatinine ratio (uPCR) may be more useful for certain conditions.[8] Serial uPCR measurements may be particularly useful in glomerular disease because of the higher variability of uACR and the greater cost of determining albumin in urine. Where appropriate, urine tests for Bence Jones protein (immunoglobulin light chains) may be required because this is not detected by standard proteinuria or albuminuria testing.

Kidney Imaging

Imaging of the kidneys with ultrasound is useful for a number of reasons. Small kidneys with reduced cortical thickness, showing increased echogenicity, scarring, or multiple cysts, suggest a chronic process. Structural abnormalities such as autosomal dominant polycystic kidney disease (ADPKD), hydronephrosis caused by obstruction, or coarse renal scarring may be detected. NICE guidelines propose that kidney ultrasound scanning is important only in certain circumstances and suggests counseling patients if ADPKD is suspected before imaging.[5] In some situations, imaging with computed tomography, magnetic resonance, or angiography may be useful, taking into account the risks of administering contrast media (see Chapter 5).

Further Investigations

Establishing the cause of CKD is important whenever possible, and further specific testing, as indicated by the history and results of initial investigations, may be required. There may be an underlying treatable condition that requires appropriate management, or there may be a genetic cause such as ADPKD, for which counseling should be offered. Furthermore, some kidney diseases may recur after transplantation (see Chapter 108) and an accurate diagnosis may therefore influence later management. Despite thorough investigation, however, the cause of CKD is often unclear, with an unhelpful medical history, minimal abnormalities on urinalysis, and small kidneys on ultrasound. In such patients, investigation should not be pursued relentlessly because the implications for treatment are often minimal. Attempting to obtain biopsy material from small kidneys is associated with risk, and even if a biopsy is performed, histologic assessment may simply show nonspecific chronic scarring rather than diagnostic features that explain the cause of kidney damage.

PREDICTING PROGNOSIS

With the cause of CKD established if possible, the GFR and the level of proteinuria measured, and other comorbidities categorized, it may be possible to estimate the risk for CKD progression and likely future need for RRT. KDIGO recommends consideration of the GFR and the albuminuria categories according to a "heatmap" of risk (see Fig. 79.1).[2] Other factors associated with CKD progression will help inform prognosis. These include the cause of CKD, age, sex, ethnicity, dyslipidemia, smoking, obesity, history of CVD, ongoing exposure to nephrotoxic agents, and degree of control of hypertension and hyperglycemia. However, often the best guide to future change in kidney function is the previous pattern of decline, highlighting the importance of considering results of previous blood and urine testing during the initial assessment.

Monitoring and Defining Progression

Once CKD has been identified, arrangements should be made to ensure regular monitoring of kidney function and proteinuria. In patients at low risk for rapidly declining eGFR, this can be done annually. However, assessment should be undertaken more regularly if the trajectory of the disease is not clear and in patients at higher risk for progression.

Determining a true change in kidney function may be difficult because small fluctuations in eGFR are common and not necessarily indicative of progression. They may be caused by reversible factors, such as intravascular depletion or high meat intake, so repeat testing may be required. Both NICE and KDIGO guidelines define accelerated progression as a sustained decrease in GFR of 25% or more and a change in GFR category within 12 months.[2,5] In addition, the NICE guidance refers to accelerated progression as a sustained decrease in GFR of 15 ml/min/1.73 m^2 per year.[2] In patients with CKD progression, consideration should be given to detection of reversible causes (e.g., renal tract obstruction) and specialist referral may be required.

When to Refer to the Nephrologist

Chronic management of patients with early nonprogressive CKD is becoming the responsibility of primary care physicians in many well-developed health care systems, with follow-up in secondary care for those likely to progress to ESRD and require RRT. However, early assessment by nephrologists is useful for all patients newly diagnosed with CKD in whom a treatable underlying cause is suspected, even in those with advanced disease at presentation to rule out treatable causes. Timely referral of those with progressive CKD allows preparation for dialysis, kidney transplantation, or initiation of a palliative approach if more appropriate. Substantially similar criteria for referral have been developed by NICE and KDIGO (Table 80.3). Such criteria are not absolute but should provide a guide to the primary care physician as to which patients are likely to benefit from specialist care. For example, many patients with stable category G4 CKD are successfully managed in the community, often after initial assessment by or with advice from secondary care colleagues.

Unfortunately, a substantial proportion of patients with advanced CKD are referred late, often when they need dialysis. Late referral is often avoidable, although in some cases, patients may have had a truly silent illness or an acute presentation of a disease with rapid decline in kidney function.[9] Over recent years the introduction of routine reporting of eGFR in some health care systems has facilitated better communication between primary and secondary care providers and has led to a substantial fall in late referrals.[10]

Late presentation is disadvantageous to the patient because it limits the time to select the mode of dialysis or to be listed for "preemptive" kidney transplantation. There may be increased psychological stress, making it difficult for the patient to come to terms with the illness. Furthermore, because an arteriovenous fistula takes several weeks to mature, patients presenting late start hemodialysis with central venous catheters. Catheters are prone to infectious complications and inevitably

TABLE 80.3 **Suggested Criteria for Referral of Patients With Chronic Kidney Disease to a Nephrologist**

	NICE 2014	KDIGO 2012
Advanced CKD	Category G4 and G5 CKD	Category G4 and G5 CKD
Proteinuria	*High proteinuria:* uACR ≥70 mg/mmol unless known to be caused by diabetes and appropriately treated	*Consistent proteinuria:* uACR ≥300 mg/g (≥30 mg/mmol)
Hematuria	Proteinuria (uACR ≥30 mg/mmol) together with hematuria	Urinary red cell casts, RBCs >20 per high-power field sustained; not readily explained
Progression of CKD	Rapidly declining eGFR: Sustained decrease in GFR of 25% or more, and a change in GFR category within 12 mo Sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 mo	Progression of CKD: Sustained decrease in GFR of 25% or more, and a change in GFR category within 12 mo Sustained decrease in GFR of 5 ml/min/1.73 m^2 or more within 12 mo
Uncontrolled hypertension	Hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses	CKD and hypertension refractory to treatment with four or more antihypertensive agents
Hereditary kidney disease	Known or suspected rare or genetic causes of CKD	Hereditary kidney disease
Other conditions	Suspected renal artery stenosis	Recurrent or extensive nephrolithiasis Persistent abnormalities of serum potassium

Data from references 2 and 5.

CKD, Chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *KDIGO,* Kidney Disease: Improving Global Outcomes; *NICE,* National Institute for Health and Care Excellence; *PTH,* parathyroid hormone; *RBC,* red blood cell; *uACR,* urinary albumin-to-creatinine ratio.

damage central veins, leading to thromboses and stenoses, which may manifest at a later stage when venous return from one or the other arm is increased by the subsequent construction of an arteriovenous fistula (see Chapter 91).[11] Late presentation of CKD also precludes effective treatment of complications such as hypertension and anemia, which may contribute to CV damage and ultimately limit life span.[12] Most important, late referral is associated with greater subsequent costs of medical care and a worse prognosis.[13]

PREVENTION OF CHRONIC KIDNEY DISEASE PROGRESSION

Management of CKD should be aimed at slowing the rate of decline of kidney function and minimizing the effects of other complications. Except for specific management of the underlying kidney disease where possible, the most effective intervention is control of blood pressure (BP), including (in patients with albuminuria) use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (see Chapter 79). Control of glycemia for patients with diabetes and CKD is covered in Chapter 32.

Hypertension

Hypertension is very common in patients with CKD, and the level of BP is associated with the rate of loss of kidney function[14] while control slows the rate of decline (see Chapter 79). BP targets have changed to reflect the available evidence, from a focus on “the lower, the better” toward less-intensive and individualized BP control.[15] With the results of the SPRINT trial, the pendulum may be swinging back again to lower BP goals.[16] Guidelines by both NICE and KDIGO have considered management of hypertension in patients with CKD in depth.[5,17] Both sets of guidelines emphasize the importance of considering coexistent CVD, other comorbidities, and side effects when choosing medications and BP targets, particularly for elderly patients. Lifestyle modifications should be encouraged, including maintenance of a healthy weight, reductions in salt and alcohol intake, and regular exercise (see Chapter 35).

Although current recommendations are based on office BP recordings, recent studies suggest that readings obtained from home and ambulatory monitoring correlate better with CV and kidney outcomes.[18] It is alarming to note that up to 30% of CKD patients who were thought to have hypertension have normal BPs at home, and 40% of patients who were thought to be normotensive (or to have adequately treated hypertension) were hypertensive at home.[19] Although ambulatory monitoring is not yet universally recommended, there should be a very low threshold for undertaking 24-hour monitoring or asking patients to undertake self-measurements at home if they prefer.

Target BP levels and antihypertensive therapy in CKD patients are discussed in Chapter 79. ACE inhibitors or ARBs are recommended as first-line agents for patients with evidence of proteinuria, but usually multidrug regimens are required to obtain good control. Patients with CKD are vulnerable to drug side effects, particularly during intercurrent illness, when they may develop hyperkalemia and AKI.[20] The KDIGO guidelines recommend the temporary discontinuation of potentially nephrotoxic drugs and those excreted by the kidney (including ACE inhibitors, ARBs, aldosterone inhibitors, direct renin inhibitors, diuretics, nonsteroidal antiinflammatory drugs, metformin, lithium, and digoxin) in patients with a GFR below 60 ml/min/1.73 m^2 (CKD categories G3a to G5) who have serious intercurrent illness.

Dietary Advice

Detailed dietary advice and education, along with ongoing support from an appropriately trained professional, are important in the management of patients with CKD. Obesity is associated with a more rapid decline of kidney function, so in early CKD, weight loss may be appropriate. However, in advanced CKD, malnutrition is common (see Chapter 86). The causes are multifactorial but include anorexia, acidosis, insulin resistance, inflammation, oxidative stress, and urinary protein loss. Biochemical indicators may demonstrate a decrease in serum albumin, transferrin, and cholesterol. Weight should be monitored in patients who progress to CKD categories G4 and G5. Serum creatinine concentrations, which in part reflect muscle mass, may stop rising despite a progressive loss of kidney function, because of compromised nutritional status.

In light of this, recommendations to restrict protein intake have been controversial. Although there is evidence that reduced protein intake may slow progression of decline of kidney function, many patients develop protein-calorie malnutrition on a low-protein diet.[21] KDIGO has recommended that protein intake should be lowered to 0.8 g/kg/day in adults with CKD and GFR below 30 ml/min/1.73 m^2, whereas high protein intake (>1.3 g/kg/day) should be avoided in adults with CKD at risk for progression. When this recommendation is followed, detailed dietary assessment and supervision are needed to ensure that malnutrition is prevented.

One of the earliest effects of CKD is to limit the ability of the kidney to compensate for large changes in sodium and water intake (see Chapter 7). Salt and water retention are major factors contributing to hypertension in CKD patients and, in more advanced stages, to morbidity and mortality through systemic or pulmonary edema. Therefore sodium intake ideally should be restricted to less than 90 mmol/day (5 g/day of sodium chloride), except in salt-wasting conditions. Advice about optimal fluid intake at each stage of CKD is needed to prevent volume overload. Salt substitutes containing potassium should be avoided because of the risk for hyperkalemia. In categories G4 and G5 CKD, education and advice about restriction of potassium and phosphate may be required.

MANAGEMENT OF COMPLICATIONS OF CHRONIC KIDNEY DISEASE

A detailed discussion of the complications of CKD is provided in Chapters 81 to 88. With the exception of hypertension, there are usually few clinical manifestations associated with CKD categories G1 and G2 (GFR >60 ml/min/1.73 m^2). Other complications (discussed in the following sections) tend to develop progressively as GFR declines below 60 and in particular below 30 ml/min/1.73 m^2 (i.e., during CKD categories G4 and G5).

Anemia

Anemia is common in CKD categories G3a to G5 and is caused by a relative deficiency of erythropoietin, although reduced availability of iron and chronic inflammation are frequent contributory factors (see Chapter 82). Anemia may have multiple adverse effects, including worsening cardiac dysfunction by increasing cardiac output and exacerbating left ventricular hypertrophy, exacerbating the decline of kidney function, and reducing cognition and concentration. However, clear evidence that reversal of anemia using erythropoiesis-stimulating agents (ESAs) is associated with improved clinical outcomes is lacking, and randomized trials have suggested that in some circumstances these agents may cause harm. A promising new avenue for the treatment of renal anemia is the development of oral small-molecule stabilizers of hypoxia inducible factor. These offer the possibility of simple and cheaper therapy compared with ESAs, with potential benefits beyond increases in hemoglobin (Hb) level.[22]

The relevant KDIGO guideline recommends that all patients identified as having CKD categories G3a and below should have their Hb levels monitored annually, increasing to twice a year for categories G4 and G5.[2] Anemia in adults is diagnosed when the Hb concentration falls below 13.0 g/dl in men and below 12.0 g/dl in women. NICE recommends that management of anemia should be considered in patients with CKD when the Hb level is 11 g/dl or lower.[5] In anemic patients, investigations for other causes should be conducted, including measurement of iron stores, serum vitamin B_{12}, and folate levels. ESAs should not be started until treatment of iron deficiency or other underlying causes has been addressed and then only after considering the balance of benefits (from the reduced requirement for blood transfusions and abrogation of anemia-related symptoms) against the potential harms, which may include an increased risk for stroke and malignancy.

If anemia does not respond to correction of underlying causes, such as iron deficiency, KDIGO recommends that ESAs be commenced when Hb concentrations are below 10.0 g/dl, if indicated.[23] Hb target ranges are discussed in Chapter 82.

Bone and Mineral Metabolism

Hyperphosphatemia, together with a deficiency of 1,25-dihydroxyvitamin D_3, contribute to secondary hyperparathyroidism and ultimately to the development of renal bone disease. These biochemical and endocrine changes, in association with the closely related histologic abnormalities of bone and soft tissue calcification, are collectively termed the *CKD–mineral and bone disorder* (see Chapter 84).[24] Bone disease already may be manifested in CKD category G3b and is well established in ESRD, even though patients may remain asymptomatic. In addition to the need to prevent bone complications, active management of CKD–mineral and bone disorder may help prevent some of the CV complications of CKD.[25]

KDIGO recommends measuring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity in adults with GFR below 45 ml/min/1.73 m^2 (GFR categories G3b through G5). Determining the optimal level of PTH in CKD has been controversial. For patients with levels of intact PTH above the upper normal limit of the assay, efforts should be made to correct hyperphosphatemia, hypocalcemia, and vitamin D deficiency if present. KDIGO guidelines recommend that serum phosphate concentrations be maintained in the normal range according to local laboratory reference values,[26] whereas the United Kingdom Renal Association support a level between 0.9 and 1.5 mmol/l for patients with category G4 and G5 CKD.[27] Early advice on dietary phosphate management by a specialist dietician or other professional is important in helping patients achieve this. Phosphate-binding drugs may be required, and their choice is discussed in Chapter 84. Prescription of vitamin D supplements or analogues, in the absence of documented deficiency, to suppress elevated PTH concentrations in patients with CKD not on dialysis is not routinely recommended. Calcimimetics are a group of drugs that mimic the action of calcium on parathyroid glands by activation of the calcium sensing receptor and thus reduce the release of PTH. At present, because of cost restraints, cinacalcet (the sole clinically available oral calcimimetic) and etelcalcetide (which is given intravenously) are generally used for patients who are unfit for surgical parathyroidectomy. Whether these drugs have additional health benefits is not clear (see Chapter 84).

Metabolic Acidosis

The metabolic acidosis associated with CKD is caused by failure of hydrogen ion excretion and may be compounded by the accumulation of organic acids and bicarbonate loss, particularly in interstitial kidney diseases. Clinical symptoms resulting from acidosis are rare until patients reach CKD category G5, when dyspnea may occur as a result of respiratory compensation. Other causes of dyspnea in advanced CKD, such as anemia and pulmonary edema, should always be considered. Acidosis aggravates hyperkalemia, inhibits protein anabolism, and accelerates calcium loss from bone where the hydrogen ions are buffered.[28] Correction of metabolic acidosis may slow progression of kidney disease, although larger trials are required to confirm this.[29]

KDIGO recommends that in patients with CKD and serum bicarbonate concentrations below 22 mmol/l (NICE recommends a threshold of <20 mmol/l), oral bicarbonate supplementation should be given to maintain serum bicarbonate within the normal range, unless contraindicated. However, the associated sodium loading may aggravate hypertension and fluid retention, and severe metabolic acidosis associated with symptoms in a patient with CKD category G5 may be an indication to start dialysis.[2] Novel pipeline drugs include an oral polymer designed to remove acid from the body with high capacity and specificity. This raises the possibility of treatment of acidosis without the problems associated with increased sodium intake.

Cardiovascular Risk

Patients with CKD have an increased prevalence of CVD and are far more likely to die from a CVD-related cause than to progress to ESRD (see Chapter 81). Therefore appropriate management of existing CVD and minimization of future CV risk is vital for all patients with CKD.

Unfortunately, many trials of interventions for CVD have excluded patients with CKD,[30] and there is doubt about the relevance of existing standards of care of CVD to patients with CKD.[31] Nonetheless, the level of care for coronary heart disease offered to patients with CKD should not be prejudiced by their CKD. NICE suggests that antiplatelet drugs should be offered to patients with CKD for the secondary prevention of CVD, and some experts would extend this recommendation to primary prevention for those at risk for atherosclerotic events. However, there is an increased risk for minor bleeding, and a recent systematic review of antiplatelet agents for patients with CKD found that although the incidence of myocardial infarction is reduced, major bleeding is increased. Thus the risks may outweigh benefits among individuals with low risk for CV events, including those with early stages of CKD who do not have clinically evident occlusive arterial disease.[32]

For reduction of cardiovascular risk, KDIGO guidelines recommend that statin treatment be routinely offered to patients with CKD who are older than 50 years and to younger patients with additional risk factors, irrespective of baseline lipid values.[33] NICE recommends that all people with CKD should be offered atorvastatin 20 mg for the primary or secondary prevention of CVD.[34]

Risk for Infections

Infection is the second most common cause of death after CVD in patients with ESRD. This is in part because of defects in both cellular and humoral immunity, which make CKD a state of chronic immunosuppression (see Chapter 83).[35] T-cell responses to de novo antigens are deficient, partly because of impaired antigen presentation by monocytes. Neutrophil activation is defective, and although serum immunoglobulin levels are normal, antibody responses to immunization may be poor. Patients with CKD have an increased susceptibility to bacterial infection (particularly staphylococcal), increased risk for reactivation of tuberculosis (typically with a negative tuberculin skin test response), and failure to eliminate hepatitis B and C viruses after infection.

In view of these increased risks, the KDIGO guidelines recommend that all adults with CKD be offered annual vaccination with influenza vaccine unless contraindicated and that all adults with eGFR below 30 ml/min/1.73 m^2 (GFR categories G4 to G5) and those at high risk for pneumococcal infection (e.g., patients with nephrotic syndrome, with diabetes, or who are receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated.[2] Patients who have received pneumococcal vaccination are offered revaccination within 5 years. In addition, those at high risk for progression of CKD with eGFR below 30 ml/min/1.73 m^2 (GFR categories G4 and G5) should be immunized against hepatitis B and the response confirmed by appropriate serologic testing. This should happen as early as possible to maximize the chances of seroconversion.[36]

CARE OF THE PATIENT WITH PROGRESSIVE CHRONIC KIDNEY DISEASE

To optimize the care of patients with progressive CKD, management is provided in a multidisciplinary setting where a range of professionals are able to provide education and information about diet, different RRT modalities, transplant options, vascular access surgery, and social care. Psychological comorbidity is common among patients with CKD. Health care professionals working with patients with CKD should take account of the psychological aspects of coping with the condition and offer access to support groups, counseling, or a specialist nurse. The aim is to create an environment in which patients can become informed and proactive in their care.

Chronic Kidney Disease and Risk of Acute Kidney Injury

All patients with CKD are at increased risk for AKI, and AKI is associated with the development and progression of CKD.[37,38] Imaging studies that require iodinated radiocontrast media carry a risk for AKI, and the benefit of a diagnostic scan needs to be balanced against the risks. If the investigation is needed, the lowest dose of radiocontrast should be used, the patient should be adequately hydrated, and potentially nephrotoxic agents should be withdrawn before and after the procedure; however, the fear of radiocontrast-induced AKI should not prevent or impair a necessary diagnostic workup. The potential risk for nephrogenic systemic fibrosis from gadolinium-based contrast media and measures to reduce it are discussed in Chapter 5.

Many commonly used medications increase the risk for AKI, and the level of GFR should be considered when any drug is prescribed or its dosage determined. As discussed earlier, the need for temporary cessation of all medications should be considered during periods of severe intercurrent illness. Other causes of reduction in kidney perfusion can lead to AKI, including volume depletion from excessive diuretics, insufficient fluid intake in hot weather, diarrhea or vomiting, heart failure, myocardial infarction, and tachyarrhythmias. Severe hypercalcemia, resulting from either coadministration of high doses of vitamin D and calcium-containing phosphate binders or from underlying disease, also can cause AKI.

Clinicians should always consider whether acceleration of loss of kidney function is a result of relapse of the underlying disease or of a superimposed problem such as acute interstitial nephritis (see Chapter 60), obstructive uropathy (see Chapter 58), or renal vein thrombosis.

Timing the Initiation of Renal Replacement Therapy

Despite all attempts to optimize the management of CKD, many patients will progress to needing RRT. All patients with eGFR below 20 ml/min/1.73 m^2 and/or who are likely to progress to ESRD within 12 months should receive education and counseling, with the support of a multidisciplinary team, to aid their selection of the most appropriate RRT modality (see Chapter 90). If hemodialysis is the preferred option, an arteriovenous fistula should be constructed, remembering that it may take 8 to 12 weeks for veins to become adequately arterialized before needling can be attempted (see Chapter 91). Similar plans need to be made for preemptive insertion of a peritoneal dialysis catheter to allow time for healing and training before any acute need for commencement of dialysis (see Chapter 99). Peritoneal dialysis catheters can be inserted and completely buried subcutaneously some time before patients require dialysis, then superficialized for use once clinical circumstances dictate.

Early kidney transplantation may be associated with improved long-term outcome,[39] so patients should be assessed for their suitability and, when feasible, activated on the waiting list before dialysis is commenced. This maximizes the chances of the potential recipient remaining in reasonable health. The availability of a living donor should be explored to increase the chances of preemptive transplantation before the patient begins dialysis. The KDIGO guidelines recommend that living donor preemptive kidney transplantation in adults be considered when the GFR is below 20 ml/min/1.73 m^2 and there is evidence of progressive and irreversible CKD over the preceding 6 to 12 months.[2]

Planned early initiation of dialysis is not associated with improvement in outcomes compared with commencement when indicated by signs and symptoms of uremia.[40] KDIGO suggests that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or BP; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment.[2] These problems often but not invariably occur when the GFR is below 15 ml/min/1.73 m^2 (see Chapter 90).

Conservative Management

The potential burden of commencing RRT in terms of high short-term mortality rates, recurrent hospitalizations, time spent traveling, and limited improvement in quality of life for some elderly patients and those with multiple comorbid disease is increasingly recognized. This has led to the practice of offering patients approaching ESRD the additional option of choosing not to start dialysis, but to maintain ongoing follow-up and symptomatic support through conservative management. Although dialysis may offer longer survival, those choosing conservative management may have as many hospital free-days as those who choose hemodialysis.[41] The symptoms of advanced uremia can be distressing, and it is important to ensure that patients who choose this pathway have access to members of the multidisciplinary team with expertise in palliative care to facilitate a death free of suffering.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is the most common cause of death for people with chronic kidney disease (CDK) (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2)?
   A. Failure of dialysis access
   B. Sepsis
   C. Withdrawal from dialysis
   D. Cardiovascular disease
   E. Cerebrovascular disease
2. The equation recommended by Kidney Disease: Improving Global Outcomes (KDIGO) for estimating GFR is:
   A. The Modification of Diet in Renal Disease (MDRD) equation
   B. The Cockcroft-Gault formula
   C. The Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) formula
   D. The Mayo Clinic Quadratic formula
   E. The Schwartz formula
3. Which of the following variables is *not* needed to calculate eGFR from the CKD-EPI formula?
   A. Age
   B. Weight
   C. Race
   D. Sex
   E. Creatinine
4. Which of the following symptoms is suggestive of CKD, regardless of cause?
   A. Pain in the renal angle
   B. Nocturia
   C. Urinary frequency
   D. Tremor
   E. Anuria
5. In a well patient, which of the following biochemical or hematologic abnormalities is suggestive of CKD rather than acute kidney injury?
   A. Calcium 3.5 mmol/l
   B. Potassium 7.5 mmol/l
   C. Hemoglobin 10.7 g/dl
   D. Creatinine 13.5 mg/dl
   E. Sodium 132 mmol/l

81

Cardiovascular Disease in Chronic Kidney Disease

Peter Stenvinkel, Charles A. Herzog

Diminished estimated glomerular filtration rate (eGFR) and albuminuria are powerful graded, independent predictors of cardiovascular (CV) morbidity and mortality[1] and all-cause mortality (Fig. 81.1). Even subtle kidney dysfunction, as suggested by albuminuria, increases CV risk because it may reflect microvasculature health, including endothelial function. Patients with end-stage renal disease (ESRD) face an extraordinary risk for premature death, largely because of CV complications. However, patients with eGFR below 60 ml/min/1.73 m^2 are much more likely to die than to develop ESRD, reflecting the burden of cardiovascular disease (CVD) in this population. The most effective strategy for reducing CV morbidity and mortality would be to target patients with mildly reduced eGFR for prevention and treatment.

Patients with chronic kidney disease (CKD) were often excluded from randomized controlled trials (RCTs) targeting CVD, possibly reducing acceptance of evidence-based therapies (validated in nonrenal patients) and fostering "therapeutic nihilism" in clinicians who treat CKD patients. Thus novel treatment strategies are urgently needed to reduce the unacceptable high CV event rate.

Like conventional atheromatous occlusive vascular disease, CKD is characterized by generalized vasculopathy, with other characteristics, including left ventricular hypertrophy (LVH), vascular calcification, and vascular noncompliance. Numerous CVD risk factors are specific to CKD and operate in addition to conventional risk factors found in the general population.

EPIDEMIOLOGY

Prevalence of Cardiovascular Complications in Chronic Kidney Disease

Interpretation of epidemiologic studies of CVD is problematic because of the difficulty in defining cause of death. Unexpected sudden death most likely results from arrhythmia, but a subarachnoid hemorrhage, massive embolic stroke, or aortic dissection might be indistinguishable from a primary arrhythmic event without an autopsy. Defining "coronary heart disease" (CHD) is also problematic: in the general population, sudden cardiac death is a primary complication of CHD, but this is unlikely to be true for dialysis patients. A history of angina cannot reliably classify a patient as having CHD because angina (resulting from supply-demand mismatch) can occur in patients with LVH and angiographically pristine coronary arteries. This probably relates to the increased myocardial fibrosis, diminished relative capillary density, and increased thickening of the intramyocardial vessel walls in uremia. At lower levels of eGFR (especially in dialysis patients), the burden of nonatherosclerotic (vs. atherosclerotic) CVD is relatively increased (Fig. 81.2).[2] Although occlusive CHD is common in CKD, acute myocardial infarction (AMI) accounts for only 14% of cardiac deaths; 66% of cardiac deaths in the U.S. Renal Data System (USRDS) database are attributable to arrhythmias.

Of incident dialysis patients, 75% have LVH and 75% to 85% have hypertension. Hypertension, anemia, vascular noncompliance, and volume overload contribute to LVH. Based on echocardiography, 85% to 90% of patients have a left ventricular (LV) ejection fraction (EF) of 50% or higher, despite frequent congestive heart failure (CHF), that is, heart failure with preserved EF (HFpEF), not heart failure with reduced EF (HFrEF), characterizes most CHF episodes. Therefore, many volume overload episodes in dialysis patients may be attributable to diastolic dysfunction or circulatory congestion. Fig. 81.3 provides a snapshot of CVD event rates in prevalent dialysis patients.

Cardiovascular Disease Is Present Before the Start of Renal Replacement Therapy

In elderly CKD patients at stage 2 or 3, traditional risk factors seem to be the major contributors to CV mortality. Atherosclerosis Risk in Communities (ARIC) data suggest that both traditional and novel risk factors are relevant at CKD stage 4, and novel risk factors are far more prevalent in dialysis patients than in the general population (Fig. 81.4).[3] The Framingham predictive instrument does not accurately predict coronary events in CKD. Mild to moderate CKD is associated with increased risk for venous thromboembolism, supporting the concept of hypercoagulability in CKD. Fig. 81.5 shows the burden of CVD in elderly patients with CKD. Because the incidence of CV events is much higher in the first weeks after hemodialysis (HD) initiation, concerns have been raised that the dialysis procedure per se may trigger CV events.[4]

Racial and International Differences in Cardiovascular Disease Prevalence

In the United States, survival is better for African American than for White dialysis patients. However, overall CV mortality among dialysis patients from the United States is significantly greater than is observed in Japan and Europe, even after adjustment for standard risk factors and dialysis dose. Higher mortality rates in U.S. dialysis patients may be related to higher prevalence of sicker or diabetic patients, differences in dialysis practice patterns, cultural habits, differences in diet, or genetic variations.

Reverse Epidemiology

Reverse epidemiology (preferably called *confounded epidemiology*) refers to the paradoxical observation that the association among hypercholesterolemia, hypertension, obesity, and poor outcomes, including CV death, in the general population does not exist and may be reversed in CKD. Patients with wasting and inflammation appear to mostly account for poor survival and confounded epidemiology.

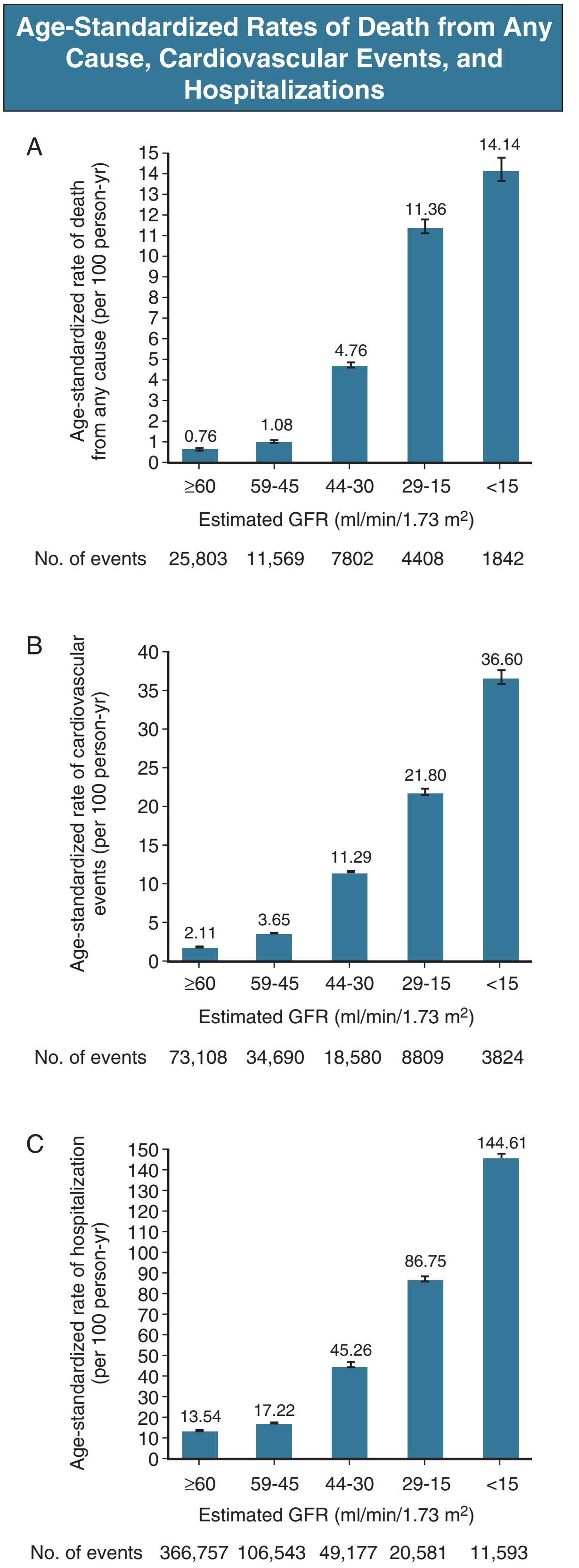


Fig. 81.1 **Age-standardized rates of death from any cause (A), cardiovascular events (B), and hospitalization (C) according to estimated glomerular filtration rate *(GFR)* among 1,120,295 ambulatory adults.** A cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, or peripheral arterial disease. Error bars represent 95% confidence intervals. The rate of events is listed above each bar. (From reference 1.)

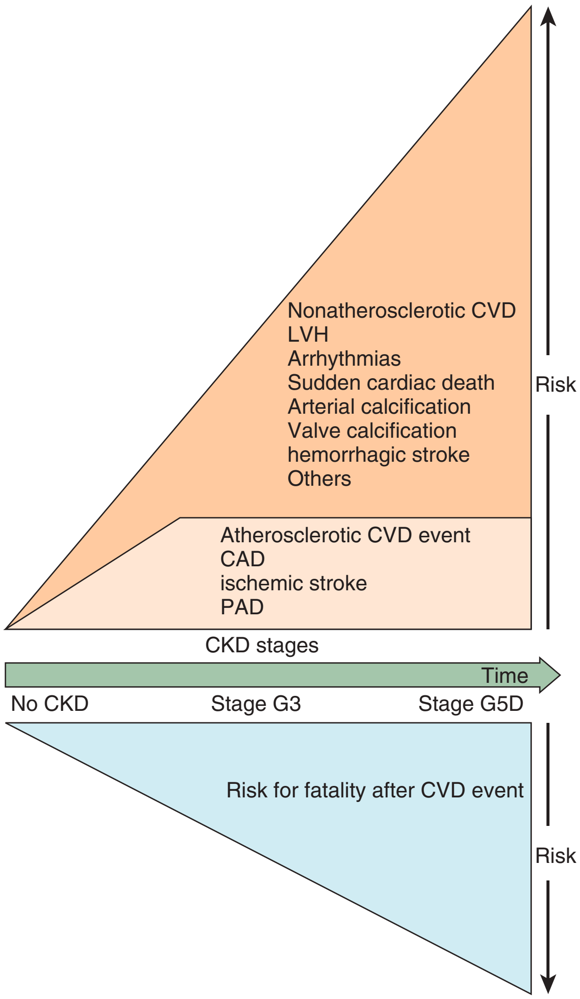

Nonatherosclerotic CVD
LVH
Arrhythmias
Sudden cardiac death
Arterial calcification
Valve calcification
hemorrhagic stroke
Others
Risk
Atherosclerotic CVD event
CAD
ischemic stroke
PAD
CKD stages
Time
No CKD
Stage G3
Stage G5D
Risk for fatality after CVD event
Risk

Fig. 81.2 **Change in cardiovascular risk during chronic kidney disease *(CKD)* progression.** Cardiovascular disease *(CVD)* event *(upper triangle),* contributions of atherosclerotic CVD *(tan),* nonatherosclerotic CVD *(orange),* and risk for fatality after CVD event *(blue). PAD,* Peripheral artery disease. (From reference 2.)

ETIOLOGY AND RISK FACTORS

Traditional Risk Factors

Age, Gender, and Smoking

The U.S. National Health and Nutrition Examination Surveys (NHANES) show the prevalence of CV factors and CVD prevalence in relation to age and CKD stage. In the United States, the average age at renal replacement therapy (RRT) initiation is 63 years, when CVD is common. An individual-level meta-analysis including more than 2 million participants showed that low eGFR and high albuminuria were independently associated with mortality and ESRD regardless of age. Female gender is associated with a 4% independent increased risk for mortality in incident dialysis patients and smoking with a 52% increased risk for death in dialysis patients.

Diabetes Mellitus

Diabetes accounted for 44% of incident U.S. ESRD patients in 2010[5] and is the most common cause of ESRD in many countries. Diabetic patients starting RRT have numerous CV risk factors, including dyslipidemia, hypertension, persistent inflammation, increased oxidative stress, and protein-energy wasting. Diabetes at dialysis initiation is a

Event Rates of Cardiovascular Diagnoses and Procedures by Modality

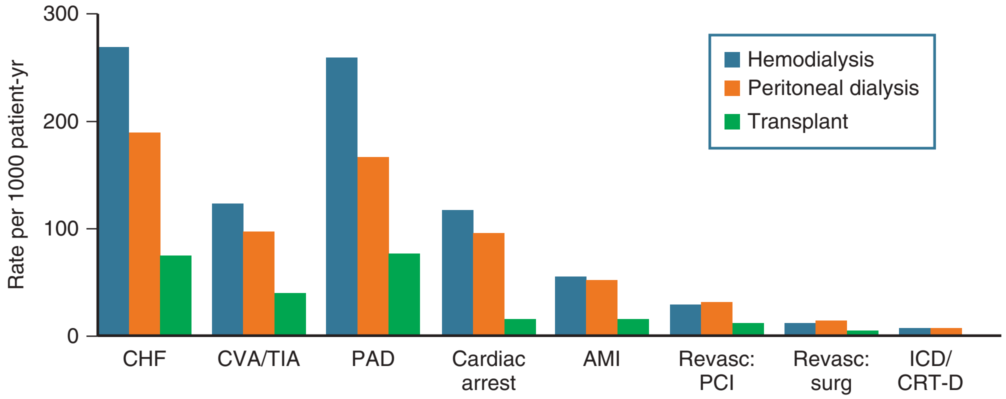


Fig. 81.3 Event rates of cardiovascular diagnoses and procedures by modality. Point prevalent end-stage renal disease (ESRD) patients on January 1, 2005, age 20 and older, with Medicare as primary payer and survival for 90 days after ESRD diagnosis. *AMI,* Acute myocardial infarction; *CHF,* congestive heart failure; *CRT-D,* cardiac resynchronization therapy defibrillator; *CVA,* cerebrovascular accident; *ICD,* implantable cardioverter-defibrillator; *PAD,* peripheral arterial disease; *PCI,* percutaneous coronary intervention; *TIA,* transient ischemic attack. (From U.S. Renal Data System. USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2009.)

TABLE 81.1 **Lipid Abnormalities in Renal Disease**

Lipid Abnormalities in Renal Disease. Common Patterns of Hyperlipidemia in Different Stages of Renal Disease, Compared With the Healthy Population.

	CHOLESTEROL LEVELS			
Stage of Renal Disease	**Total**	**High-Density Lipoproteins**	**Low-Density Lipoproteins**	**Triglycerides**
Nephrotic syndrome	↑↑↑	↓	↑↑	↑
Chronic kidney disease	No change	↓	No change*	↑↑
Hemodialysis	No change	↓	No change*	↑↑
Peritoneal dialysis	↑	↓	↑	↑
Transplantation	↑↑	No change	↑	↑

*Composition altered.

potent independent risk factor for all-cause and CVD-related deaths, including after coronary revascularization or AMI. Nevertheless the rate of incident AMI is even higher for patients with CKD stages 3b to 4 without diabetes than for patients with diabetes and CKD stages 1 or 2.

Hypertension

Hypertension is common but variably treated in CKD patients. Of NHANES subjects with CKD stages 3 to 4, 80% had a blood pressure (BP) of 130 or greater/80 or greater mm Hg, and only 20% were aware of it and had BP adequately controlled. In CKD stages 1 and 2, 63% were hypertensive and only 11% were adequately controlled. Recent NHANES data suggest modest improvement in hypertensive people with CKD stages 3 or 4.[6] Hypertension predicts mortality in CKD patients before or at dialysis initiation. Isolated systolic hypertension with increased pulse pressure is by far the most prevalent BP anomaly in dialysis patients, resulting from arterial medial sclerosis with secondary stiffening. Stiff vessels cause increased pulse wave velocity, resulting in increased systolic BP (SBP) peak pressure by a prematurely reflected pulse wave, progressive LV dysfunction, and finally CHF. At this stage, mean arterial and diastolic pressure may decrease. The relationship between BP and mortality is U shaped; isolated systolic hypertension and increased pulse pressure probably indicate high long-term risk in dialysis patients, whereas low mean and diastolic BPs (DBPs) predict early mortality. CKD patients are frequently "nondippers" and experience sleep apnea and sympathetic nervous system activation.

Dyslipidemia

The relationship between hypercholesterolemia, CVD, and mortality in CKD is weak because some CV abnormalities, such as cardiomyopathy and arteriosclerosis, may be less dependent on dyslipidemia than on other factors. Low rather than high serum cholesterol level is associated with poor survival in HD patients, likely related to confounding by protein-energy wasting and inflammation. After adjustment for C-reactive protein (CRP) levels, high cholesterol level predicts risk in noninflamed ESRD patients.

Progressive CKD leads to changes in blood lipids typically associated with vascular disease, including decreased apolipoprotein A (apoA)-containing lipoproteins and increased apoB-containing lipoproteins (Table 81.1). Serum triglycerides are elevated in most ESRD patients, whereas

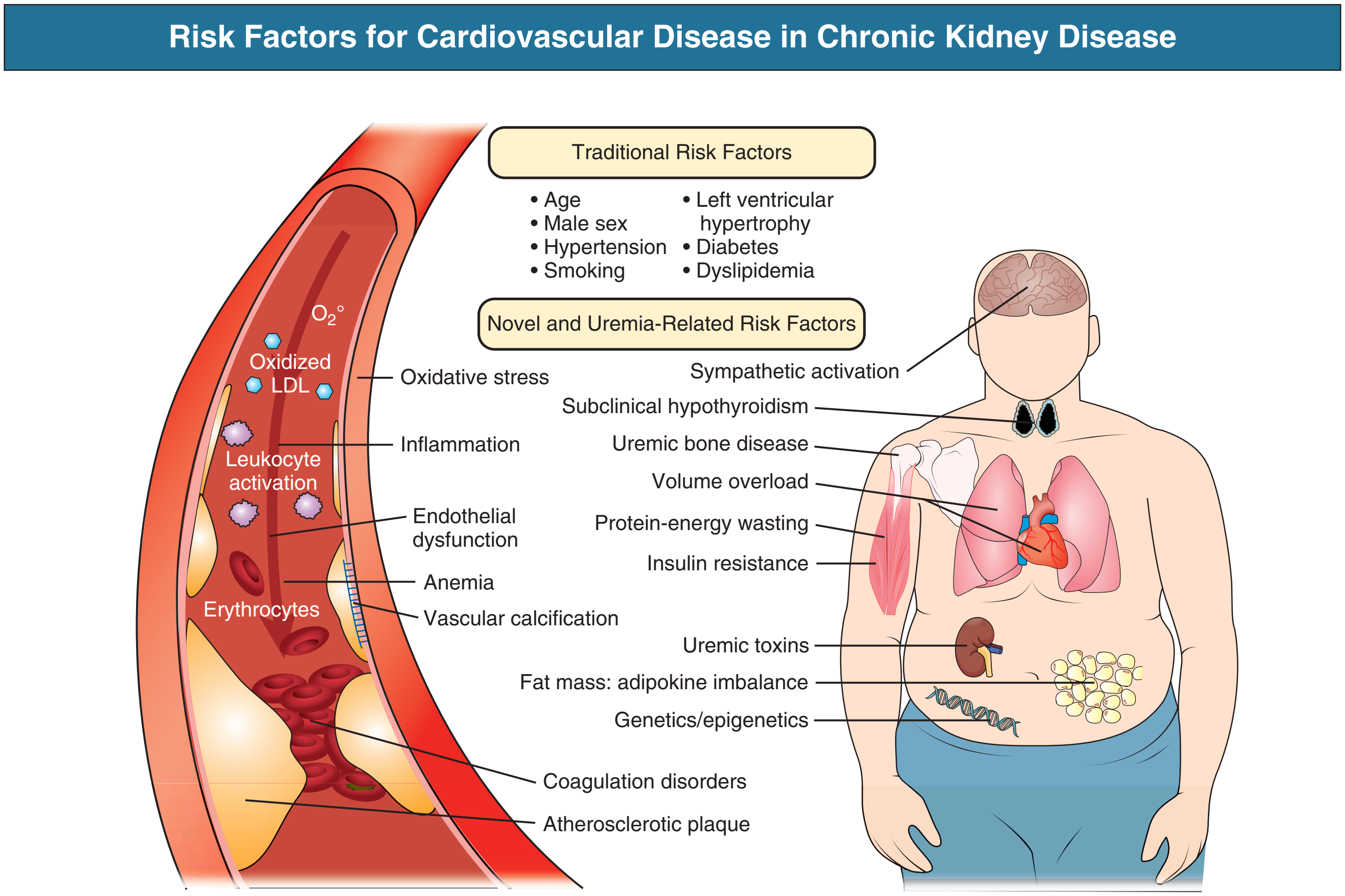

Risk Factors for Cardiovascular Disease in Chronic Kidney Disease
Traditional Risk Factors
• Age
• Male sex
• Hypertension
• Smoking
• Left ventricular hypertrophy
• Diabetes
• Dyslipidemia
Novel and Uremia-Related Risk Factors
O2°
Oxidized LDL
Leukocyte activation
Erythrocytes
Oxidative stress
Inflammation
Endothelial dysfunction
Anemia
Vascular calcification
Coagulation disorders
Atherosclerotic plaque
Sympathetic activation
Subclinical hypothyroidism
Uremic bone disease
Volume overload
Protein-energy wasting
Insulin resistance
Uremic toxins
Fat mass: adipokine imbalance
Genetics/epigenetics

Fig. 81.4 **Risk factors for cardiovascular disease in chronic kidney disease.** Overview of traditional (i.e., Framingham) risk factors and novel and uremia-related risk factors. *LDL,* Low-density lipoprotein. (From reference 3.)

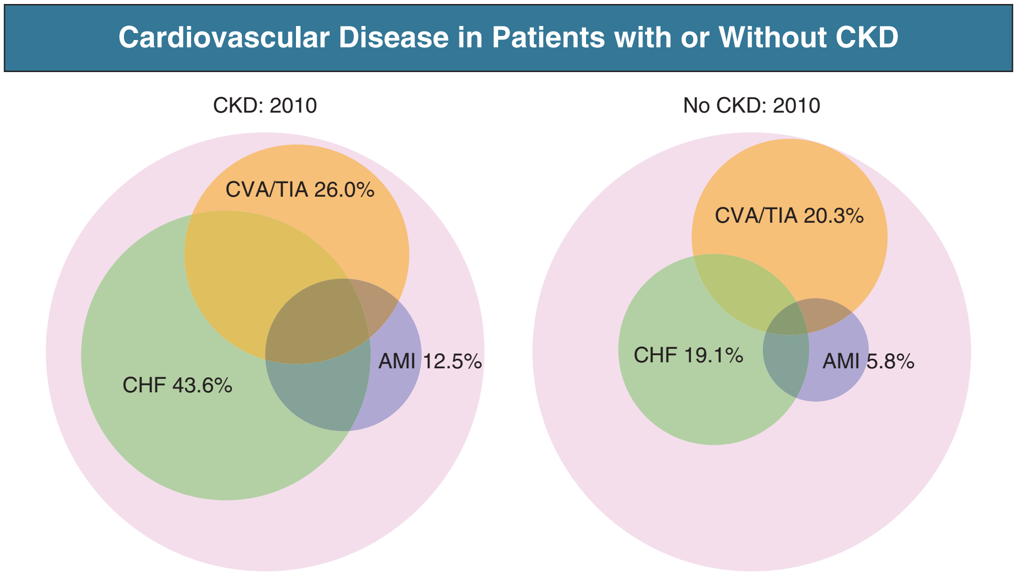


Fig. 81.5 **Cardiovascular disease in patients with or without chronic kidney disease *(CKD),* 2010.** Relative frequency of cardiovascular disease in Medicare enrollees, age 66 and older, with or without CKD. *AMI,* Acute myocardial infarction; *CHF,* congestive heart failure; *CVA,* cerebrovascular accident; *TIA,* transient ischemic attack. (From reference 5.)

total serum cholesterol is variable, depending on nutritional status and presence of inflammation. High-density lipoprotein (HDL) cholesterol is typically reduced, and low-density lipoprotein (LDL), intermediate-density lipoprotein, and very low-density lipoprotein cholesterol, as well as lipoprotein(a) levels, tend to be increased. Because of altered molecular composition, the antiinflammatory activity of HDL is reduced in the uremic milieu. Compared with long-term HD patients, peritoneal dialysis (PD) patients more often have both hypercholesterolemia and hypertriglyceridemia. Both groups are characterized by low HDL and elevated oxidized LDL cholesterol levels; elevated lipoprotein(a) levels are associated with increased CVD mortality.

Insulin Resistance and Atherosclerosis

In the general population, impaired insulin-stimulated glucose disposal in muscle is often part of a metabolic syndrome that includes dyslipidemia, hypertension, endothelial dysfunction, and sympathetic overactivity. Many of these abnormalities are present in CKD. Although insulin resistance was found to be an independent predictor of CV mortality in dialysis patients, its magnitude of contribution in CKD mortality is uncertain.

Nontraditional and Uremia-Specific Risk Factors

Even mild CKD is an independent risk factor for CVD, and similar in magnitude to diabetes and hypertension. The uremic milieu may affect both quality and quantity of the atherosclerotic plaques. Coronary lesions in uremic patients, compared with nonrenal controls, are characterized by increased media thickness, infiltration and activation of macrophages and marked media calcification. The mechanism(s) by which a uremic milieu may promote vascular senescence and accelerate premature vascular aging[7] are not well established, but prevalence and magnitude of several nontraditional risk factors, such as oxidative stress, inflammation, and advanced glycation end-products (AGEs), increase as renal function deteriorates. Other uremic retention solutes, such as asymmetric dimethylarginine (ADMA), guanidine, indoxyl sulfate, and *p*-cresol, which accumulate in CKD, may have proatherogenic properties.[8] Finally, failing kidneys produce fewer substances that may inhibit CVD and atherogenesis—for example, renalase, a soluble monoamine oxidase that regulates cardiac function and BP.

Oxidative Stress

Oxidative stress may be implicated in the pathogenesis of atherosclerosis, the increased risk for atherosclerotic CV events, protein-energy wasting, and anemia. Increased production of reactive oxygen species in the vascular wall characterizes atherosclerosis. Moderate CKD, and in particular uremia, is a prooxidant state resulting from reduced antioxidant systems (vitamin C and selenium deficiency, reduced intracellular vitamin E levels, reduced glutathione system activity), and increased prooxidant activity associated with advanced age, diabetes, chronic inflammation, retained uremic solutes, and dialysis membranes and solutions. Four oxidative stress pathways can be hypothesized in CKD: carbonyl stress, nitrosative stress, chlorinated stress, and classic oxidative stress (Fig. 81.6).

Inflammation

Most dialysis patients are in a state of chronic inflammation. Inflammatory biomarkers, such as CRP, interleukin 6 (IL-6), pentraxin 3 (PTX3), fibrinogen, and white blood cell count, are independent predictors of mortality in CKD patients. Hypoalbuminemia, strongly associated with systemic inflammation, is another strong outcome predictor in CKD. Whereas both dialysis-related factors and non–dialysis-related factors (infection, comorbidity, genetic factors, hypogonadism, diet, renal function loss) may contribute to chronic inflammation, its primary causes are not always evident. The senescence-associated secretory phenotype caused by increased numbers of senescent vascular cells also may be a significant contributor to uremic inflammation. Whether the acute-phase response reflects only established atherosclerotic disease or is involved in the initiation and progression of atherosclerosis is unclear. Some inflammatory biomarkers, such as IL-6, PTX3, and tumor necrosis factor, may have proatherogenic properties, such as promoting vascular calcification, oxidative stress, and endothelial dysfunction (Fig. 81.7). Evidence suggests associations between inflammation and development of albuminuria. Persistent inflammation may change the risk factor profile for traditional risk factors, such as cholesterol and obesity.[9] The link between septicemia and subsequent increased risk for death and CV events, including AMI, further supports inflammation as a trigger for CV events.

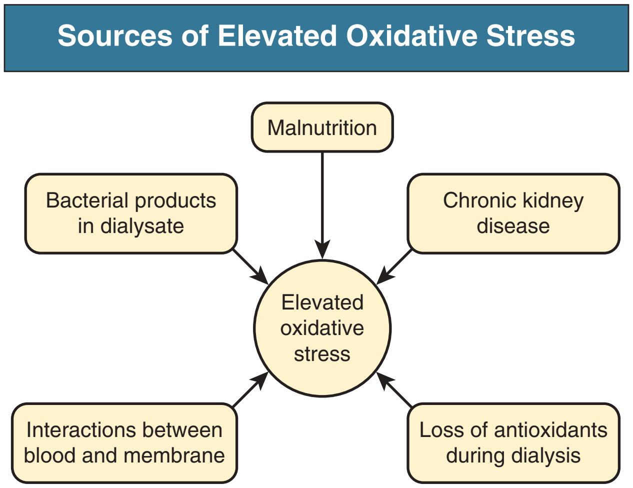

Sources of Elevated Oxidative Stress
Malnutrition
Bacterial products in dialysate
Chronic kidney disease
Elevated oxidative stress
Interactions between blood and membrane
Loss of antioxidants during dialysis

Fig. 81.6 Sources of elevated oxidative stress.

Gut Dysbiosis

The uremic milieu affects the intestinal microbiota and the integrity of the intestinal wall, possibly contributing to inflammation and increased production of uremic toxins such as proatherogenic indoxyl sulfate, phenylacetic acid, and *p*-cresol sulfate. The uremic milieu and volume retention may damage the intestinal wall, promoting increased leakiness of endotoxins and translocation of intestinal bacteria. The microbial metabolite trimethylamine N-oxide contributes to the development of atherosclerotic heart disease and is related to adverse CV outcomes in the general population[10] and in CKD patients.

Endothelial Dysfunction

Endothelial dysfunction (as evaluated by impaired endothelium-dependent vasodilation) is common in CKD. Reasons include inflammation, ADMA retention, oxidative stress, elevated fibroblastic growth factor-23 (FGF-23), dyslipidemia, hyperglycemia, and hypertension. Serum ADMA concentrations are associated with endothelial function in uremic resistance vasculature. Surrogate markers of endothelial dysfunction, such as ADMA, PTX3, and adhesion molecules, independently predict death.[3] Detached circulating endothelial cells are potential markers of endothelial damage and have prognostic value in HD patients.[3] Normally, in response to an ischemic insult and cytokine stimulation, endothelial progenitor cells are mobilized from the bone marrow to repair endothelial injury, and this seems to be impaired in CKD.

Anemia

Anemia is a major cause of LVH and LV dilation in CKD. Although partial correction of anemia with erythropoiesis-stimulating agents

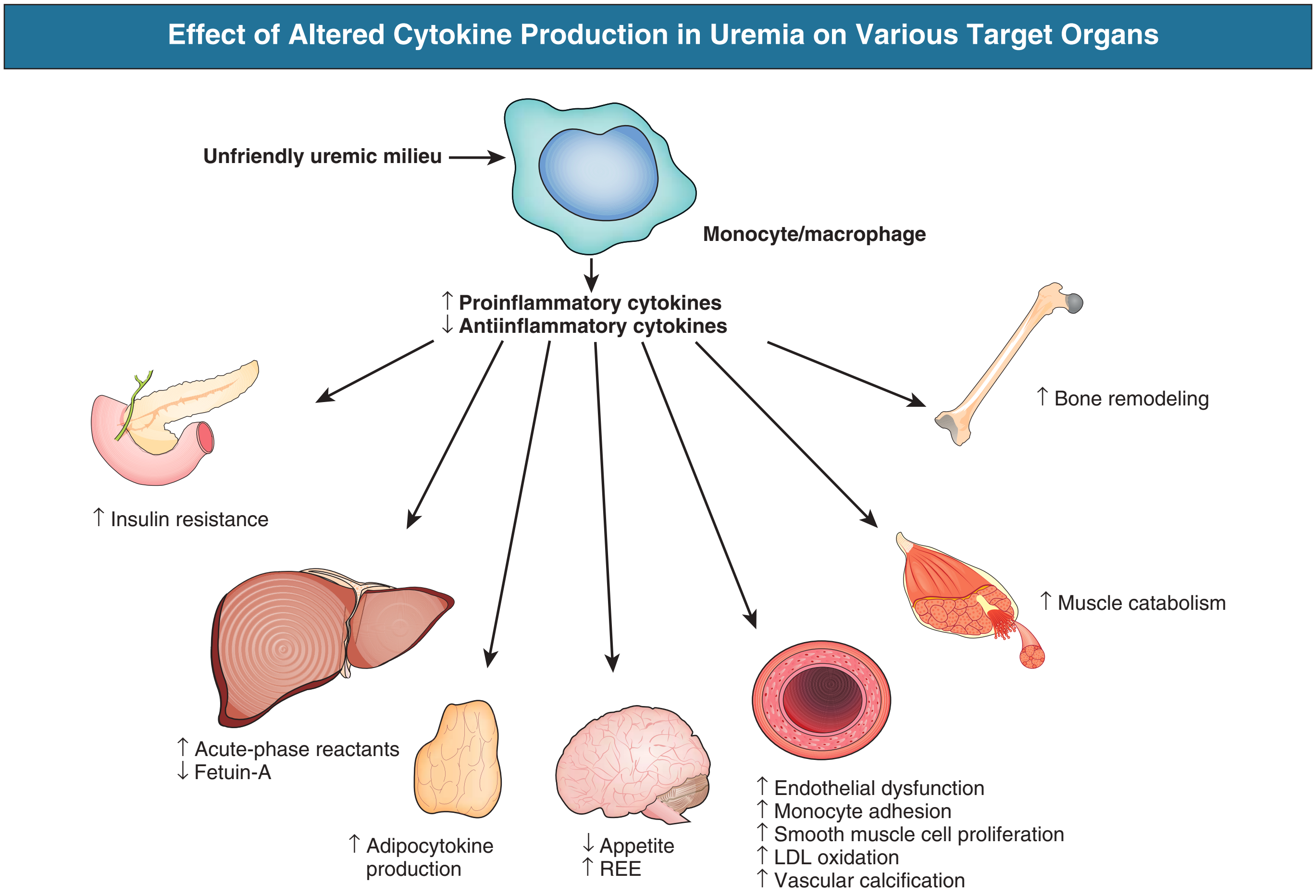

Effect of Altered Cytokine Production in Uremia on Various Target Organs

Fig. 81.7 Potential mechanisms by which elevated circulating levels of proinflammatory and antiinflammatory cytokines may promote accelerated atherosclerosis, other uremic complications, and wasting. *LDL*, Low-density lipoprotein; *REE*, resting energy expenditure. (From reference 8.)

(ESAs) results in LVH regression, current information suggests no CV outcome benefit of normalized hemoglobin (see Chapter 82).

Secondary Hyperparathyroidism and Mineral Metabolism

Disturbances of calcium and phosphate metabolism might accelerate calcifying atherosclerosis and arteriosclerosis (see also Chapter 85). Recent evidence suggests that chronically elevated FGF-23 levels contribute directly to high rates of LVH, atrial fibrillation (AF), and mortality. In registry data, a strong independent mortality risk is predicted by hyperphosphatemia, an intermediate risk by elevated serum calcium levels, and a weak risk by high or low serum intact parathyroid hormone (PTH) levels. The overall mortality risk prediction attributable to mineral metabolism disorders is estimated to be about 17% in HD patients.

Cardiovascular Calcification

CV calcification may affect the arterial media, atherosclerotic plaques, myocardium, and heart valves. Medial calcification causes arterial stiffness and, consequently, increased pulse pressure. The pathophysiologic role of plaque calcification is less clear because soft plaques are assumed to rupture and cause AMI; atherosclerotic calcification is a potent risk marker for CV events, but its utility as a risk marker for clinical management of CKD patients remains controversial. Valvular calcification mostly affects the aortic and mitral (annulus) valves in dialysis patients and contributes to progressive stenosis and associated morbidity and mortality. In dialysis patients, extensive vascular, especially coronary artery, calcification can occur at young ages. Calciphylaxis (calcific uremic arteriolopathy) is discussed in Chapter 88.

Vascular calcification is not derived only from passive calcium and phosphate precipitation. Rather, it involves differentiation of vascular smooth muscle cells toward osteoblasts induced by phosphate, calcium, and other factors, such as calcitriol and proinflammatory cytokines. Uremic bone disease and protein-energy wasting may be additional risk factors for vascular calcification.[11] One way by which chronic inflammation promotes vascular calcification may involve downregulation of fetuin-A, the most potent circulating inhibitor of extraosseous calcification and a component of calciprotein particles. Apart from fetuin-A, other inhibitors, such as magnesium, probably counteract unwanted calcification. Leptin, matrix GLA protein, FGF-23, pyrophosphates, bone morphogenic proteins (e.g., BMP-2 and BMP-7), and osteoprotegerin may be related to accelerated vascular calcification in ESRD. Deficiency of vitamin K and/or treatment with vitamin K antagonists (warfarin) may accelerate the vascular calcification process in the uremic milieu.

Advanced Glycation End-Products

AGEs accumulate in CKD patients as a result of nonenzymatic glycation, oxidative stress, intestinal food components, and diminished clearance of AGE precursors. Stable AGE residues of long-lived proteins are biomarkers of cumulative metabolic, inflammatory, and oxidative stress; carbonyl stress is speculated to contribute to tissue aging and long-term CKD complications. Whether AGE inhibition may affect CV disease in CKD is unknown.

Dialysis Modality

Reports from dialysis registries are inconsistent regarding whether HD or PD is associated with better outcomes. Valid mortality comparisons between HD and PD modalities are not available because this would require stratification of patients according to underlying ESRD cause, age, and level of baseline comorbidity. Cardiac arrhythmias, such as AF, seem to occur more often on the day of HD compared with PD.

CLINICAL MANIFESTATIONS AND NATURAL HISTORY

Fig. 81.8 shows survival of patients with CV diagnoses and procedures, by RRT modality.

Chest Pain, Coronary Heart Disease, and Acute Myocardial Infarction

AMI in dialysis patients is associated with poor long-term survival. The unadjusted 2-year mortality rate is not changing: 71% in 1977 to 1984 and 72% in 2008,[12] despite dramatic improvements in AMI outcomes in the general population (Fig. 81.9). Significant improvement has occurred only in patients with ST-segment elevation myocardial infarction (STEMI), specifically related to in-hospital mortality. Rates of non-STEMI (NSTEMI) mortality or postdischarge mortality have not improved.[12] In-hospital deaths increase with decreasing GFR.[13] This poor outcome has been attributed to underrecognition resulting from atypical presentations, underuse of appropriate diagnostic investigations, and undertreatment (therapeutic nihilism).[14] A U.S. registry of dialysis patients hospitalized for AMI found the following[14]:

- 45% of dialysis, versus 21% of nondialysis patients, were diagnosed incorrectly with respect to acute coronary syndrome (ACS).
- 44% of dialysis, versus 68% of nondialysis patients, experienced chest pain.
- 19% of dialysis, versus 36% of nondialysis patients, had ST-segment elevation.
- After other clinical exclusions, only 10% of dialysis, versus 25% of nondialysis patients, were eligible for acute coronary reperfusion.
- Of those who were eligible, 47% of dialysis and 75% of nondialysis patients actually received reperfusion.
- In-hospital death was 21% for dialysis and 12% for nondialysis patients. In-hospital cardiac arrest occurred twice as frequently in dialysis as in nondialysis patients (11% vs. 5%).

Similar findings occur across the CKD spectrum; the likelihood of increased mortality and lower prevalence of both STEMI and chest pain are correlated with severity of non–dialysis-dependent CKD in

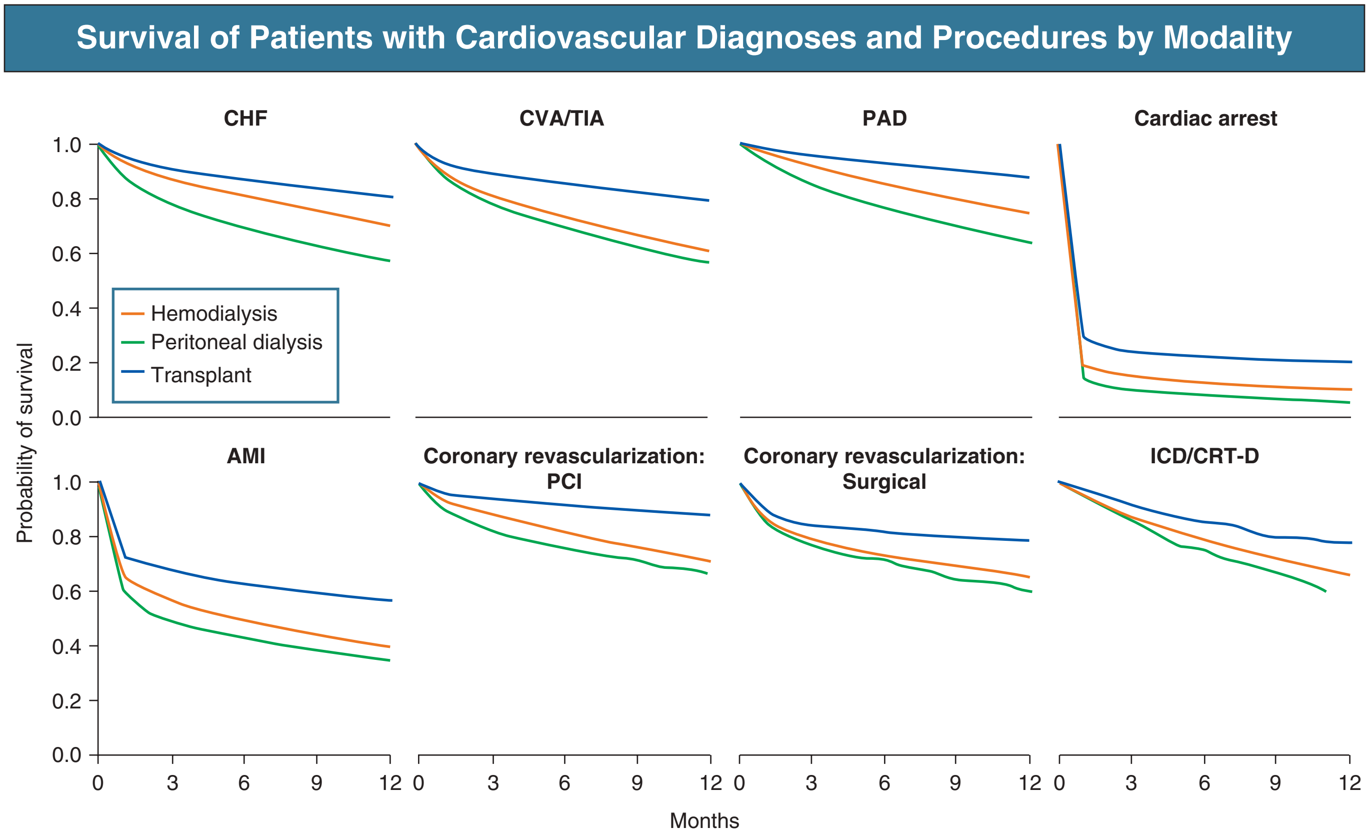


Fig. 81.8 **Survival of patients with cardiovascular diagnoses and procedures, by modality.** January 1, 2005, point prevalent end-stage renal disease patients, age 20 and older, with a first cardiovascular diagnosis or procedure in 2005-2007. *AMI,* Acute myocardial infarction; *CHF,* congestive heart failure; *CRT-D,* cardiac resynchronization therapy defibrillator; *CVA,* cerebrovascular accident; *ICD,* implantable cardioverter-defibrillator; *PAD,* peripheral arterial disease; *PCI,* percutaneous coronary intervention; *TIA,* transient ischemic attack. (Modified from U.S. Renal Data System. USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2009.)

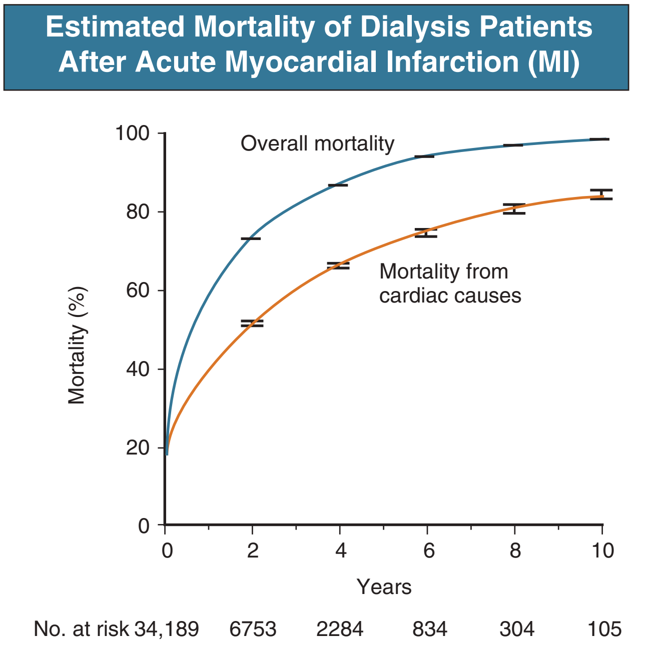


Fig. 81.9 Estimated mortality of dialysis patients after acute myocardial infarction. (Reprinted with permission from Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998;339:799-805.)

patients with AMI.[13,15] Patients with eGFR below 45 ml/min/1.73 m^2 are three times as likely to present with AMI as the initial manifestation of CHD, rather than stable angina.

Peripheral Arterial Disease

Risk for peripheral arterial disease (PAD) is highest for dialysis patients with diabetes or preexisting atherosclerosis. In HD patients, PAD is also associated with time on dialysis, hypoalbuminemia, low PTH levels, and low predialysis DBP. Vascular medial calcification of large peripheral arteries may not indicate occlusive disease, and peripheral gangrene is often caused by diabetic or other small-vessel disease or rarely by calcific uremic arteriolopathy (see Chapter 88). PAD is associated with increased mortality; outcomes after revascularization are worse than for the general population, in part reflecting advanced vasculopathy. Although one fourth of CKD patients and half of HD patients have PAD,[5,16] knowledge gaps regarding their treatment are large.[17]

Cerebrovascular Disease and Atrial Fibrillation

Cognitive impairment is severe in more than a third of dialysis patients, and only 15% have normal cognition. Cognitive impairment prevalence increases approximately 10% per 10 ml/min/1.73 m^2 of eGFR less than 60 ml/min/1.73 m^2. Microalbuminuria and stage 3 CKD increased stroke risk 1.5-fold to 2-fold in a multivariate model and stroke risk increases to 6-fold in incident dialysis patients; 11% of stroke hospitalizations in dialysis patients were attributed to hemorrhagic stroke. Silent cerebral microbleeds occur in 20% of CKD patients, predict CVD,[18] and may explain the fourfold to sevenfold increase in stroke incidence that immediately follows dialysis initiation.[19] Stroke accounts for 3% of ESRD deaths in the USRDS registry[5] (see Chapter 86 for more details).

AF is the most common dysrhythmia in CKD patients, and its incidence is increasing in older patients initiating dialysis in the United States.[20] Incident AF is an independent risk factor for development of ESRD in CKD.[21] Prevalence among dialysis patients is 15% to 20%, and this increased to 27% (58% of these episodes were paroxysmal AF[22]) and 40% in small series employing implantable loop recorders. Among AF patients with stage 3 CKD, adjusted-dose warfarin was associated with a 76% reduction in the relative risk for ischemic stroke or systemic embolism.[23] In AMI patients with AF, warfarin treatment was associated with a lower 1-year risk for the composite outcome of death, AMI, and ischemic stroke without a higher risk for bleeding, irrespective of CKD severity. In contrast, the usefulness of warfarin for primary prevention of stroke in dialysis patients with AF is controversial; some observational studies suggest harm, and current Kidney Disease: Improving Global Outcomes (KDIGO) recommendations do not include routine warfarin therapy for primary prevention of stroke in AF patients with CKD stage 5D (however, warfarin for secondary prevention of stroke is recommended).[17,24]

The therapeutic approach to primary prevention of stroke in ESRD remains controversial. There are few data on the safety and efficacy of novel oral anticoagulants (NOACs), and warfarin use is made challenging by the difficulty of maintaining dialysis patients in optimal anticoagulation range and the potential for accelerated vascular calcification with vitamin K antagonists. The case favoring NOACs rather than warfarin in moderate CKD is less controversial, based on post hoc analysis of RCTs (Fig. 81.10). No data support the sole use of aspirin for prevention of stroke in CKD patients with AF.

Left Ventricular Remodeling and Hypertrophy

LVH occurs early in progressive CKD, probably because of high hypertension prevalence, including frequent nocturnal hypertension. Pressure overload, caused by hypertension and arterial stiffness, results in concentric hypertrophy. Volume overload manifests as eccentric hypertrophy. LV dilation strongly predicts poor outcome. It may be an end result of severe LVH, diffuse ischemic damage, or recurrent volume overload; a high-output arteriovenous fistula may contribute. Diastolic dysfunction is strongly associated with LVH and with increased risk for intradialytic hypotension because relatively small reductions in left atrial filling significantly affect cardiac output in these stiff, hypertrophied preload-sensitive hearts, together with the Bezold-Jarisch reflex activation through stimulation of LV posterior wall stretch receptors in underfilled, hypercontractile, hypertrophied ventricles.

The term *uremic cardiomyopathy* is misleading; *cardiomyopathy of advanced CKD* more accurately describes the structural heart disease that occurs before ESRD onset. There is no change in LV mass index in patients with eGFR below 20 ml/min/1.73 m^2 (not on dialysis) serially imaged with echocardiograms and subsequently imaged after dialysis initiation (i.e., after incident ESRD).[25] Dialysis initiation was associated with a small drop in LVEF in some but not all studies. In patients with stage 4 CKD (and no clinical heart failure), 75% had LVH and only about 10% had normal LV geometry.[26]

Conventional HD delivery can produce repetitive myocardial injury, leading to global and segmental reduction in LV systolic function; the occurrence of HD-induced myocardial stunning is associated with increased 1-year mortality. Even pediatric HD patients can experience HD-induced myocardial stunning, indicating that large-vessel obstructive CHD is not a prerequisite for this pathologic finding. Biofeedback dialysis or reduced dialysate temperature both help reduce intradialytic hypotension and severity of HD-induced myocardial stunning.

Extracellular Volume Overload

Extracellular volume overload resulting from loss of sodium excretory capacity is the major cause of hypertension in dialysis patients. Whether prevention of recurrent hypervolemia reduces CV morbidity and mortality remains unproved. If adjustments are made for comorbidity and advanced age, a strong, incremental risk for all-cause and CV mortality is associated with interdialytic weight gains. Recurrent hypervolemia may result in LVH and LV dilation, peripheral or pulmonary edema,

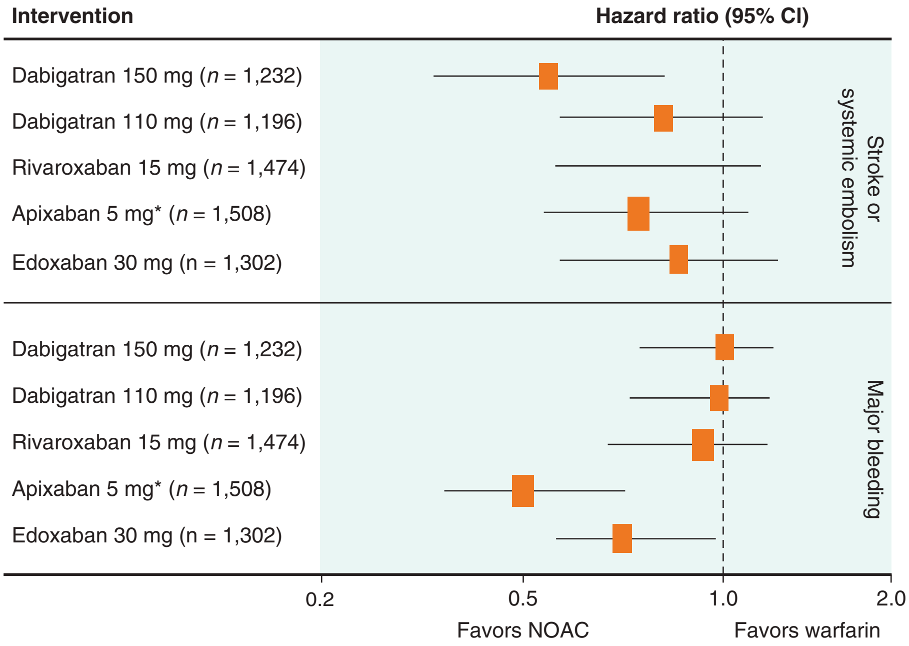


Fig. 81.10 **Efficacy and safety of novel oral anticoagulants *(NOACs)* versus warfarin in the subgroup of patients with moderate chronic kidney disease from randomized, clinical trials in atrial fibrillation.** (From Qamar A, Bhatt DL. Stroke prevention in atrial fibrillation in patients with chronic kidney disease. *Circulation* 2016;133(15):1512-1515.)

raised jugular vein pulse, or a third heart sound, or it may be largely asymptomatic. Tolerance of large ultrafiltration volumes may indicate that the dry weight target (see Chapter 96) has not been reached. Reaching an optimal dry weight, however, does not necessarily lead to immediate BP correction; a lag phase of some weeks can precede improvement.

Pericarditis

Dialysis-associated pericarditis may be related to intercurrent illnesses (including viral infections), fistula recirculation leading to underdialysis, or underlying diseases such as systemic lupus. Fever with pericardial pain or a rub on heart auscultation, unexplained cardiomegaly on chest films, or hemodynamic instability should prompt echocardiography. An effusion causing overt hemodynamic compromise (i.e., pericardial tamponade) or large pericardial effusions judged unlikely to resolve with conservative measures require echocardiographically guided or computed tomography (CT)-guided pericardiocentesis or surgical drainage. Intensive dialysis is indicated for true uremic pericarditis; the optimal treatment of dialysis-associated pericarditis is much less clear in patients without hemodynamic compromise. Citrate-based anticoagulation is preferred given the risk for hemorrhage-induced pericardial tamponade.

Autonomic Dysfunction

There is decreased baroreflex sensitivity in CKD, which has been linked to increased risk for sudden death. Increased sympathetic nerve activity, including secondary to sleep apnea, is a common alteration in CKD patients and associated with adverse outcome.

Valvular Disease

The rate of progression of calcific aortic stenosis is approximately three times faster in dialysis patients than in the general population. Annual echocardiography is recommended for asymptomatic dialysis patients with an aortic valve area of 1.0 cm^2 or less[27] who are suitable candidates for valve replacement. A meta-analysis of dialysis patients undergoing valve replacement surgery found no difference in survival for patients receiving tissue versus mechanical valves and fewer valve-related complications with tissue valves. The overall mortality is high, with in-hospital mortality about 20% (four times higher than in non-CKD patients) and 2-year survival of 40%. Transcatheter aortic valve replacement may be appropriate in dialysis patients with symptomatic aortic stenosis who are not good candidates for surgery. In kidney transplant recipients, in-hospital mortality was 11% for tissue and 15% for mechanical valve patients, and 2-year mortality rates were 62% and 60%, respectively. In the entire cohort of kidney transplant patients, the rate of endocarditis after valve surgery was 5% per year.[28]

Infective Endocarditis

Estimated incidence of infective endocarditis in U.S. dialysis patients is 267 cases per 100,000 patient-years. Vascular access, including temporary and semipermanent catheters, is an important source of infection; heightened risk for bacteremia related to HD therapy is likely an important aspect of endocarditis risk. Dialysis patients with bacterial endocarditis have poor in-hospital and long-term survival. One-year survival for U.S. dialysis patients with endocarditis who subsequently received valve replacement surgery was about 50%.[29] A risk model for operative mortality may be helpful in managing these high-risk patients.

Sudden Cardiac Arrest

In the USRDS database, two thirds of all cardiac deaths and one quarter of all-cause mortality in dialysis patients are attributable to arrhythmias.[5] The reported rate of cardiac arrest in HD centers is 3.8 to 7.1 events per 100,000 dialysis sessions. Strong predictors of sudden cardiac death are history of CHD, PAD, diabetes, elevated inflammatory biomarkers, and reduced LVEF. Even a modest reduction in LVEF to 40% to 50% is prognostically important in both HD[30] and PD patients. Myocardial fatty acid imaging might identify patients at risk for sudden death. Factors probably contributing to the special vulnerability of ESRD patients to sudden cardiac arrest include LVH; rapid electrolyte shifts and hyperkalemia in HD; autonomic dysfunction and sympathetic overactivity, including sleep apnea; and abnormalities in myocardial ultrastructure and function, including endothelial dysfunction, interstitial fibrosis, decreased perfusion reserve, and diminished ischemia tolerance.[31] Low-potassium dialysate (<2 mmol/l) doubles the risk for cardiac arrest.[32] The rate of cardiac arrest is 50% higher for HD than for PD patients 3 months after dialysis initiation but is higher for PD patients at 3 years. The highest rate of sudden cardiac death occurs in the first 2 months after HD initiation.[33] In cardiac arrests occurring in HD centers, the predominant rhythm is ventricular fibrillation (66%), followed by pulseless electrical activity (23%), and asystole (10%).

In women with CHD, eGFR below 40 ml/min/1.73 m^2 was associated with a 2.3-fold increased risk for sudden cardiac death. Despite a graded, incremental risk for arrhythmic death and impaired renal function, the overall magnitude of risk in stage 3 CKD patients is small compared with that in dialysis patients.

Onsite defibrillation capability in HD centers (preferably with automatic external defibrillators) was recommended in a U.S. practice guideline in 2005.[27] The role that implantable cardioverter-defibrillators (ICDs) may play in reducing mortality in CKD patients is controversial, particularly regarding primary prevention. CKD may attenuate the survival advantage of ICDs, but older age and medical comorbidity should not routinely exclude patients from receiving ICDs. In dialysis patients who survived cardiac arrest, ICD implantation was associated with a 14% to 42% reduction in long-term mortality.[34] The role of ICDs in dialysis patients is uncertain: the Wearable Cardioverter Defibrillator in Hemodialysis Patients (WED-HED) trial (clinicaltrials.gov, NCT02481206) was a prospective RCT, testing wearable defibrillators for prevention of sudden cardiac death in incident HD patients who do not qualify for ICDs under current guidelines. Unfortunately, the trial was terminated in 2017 due to low enrollment.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Key issues in the diagnosis of CVD are underrecognition of symptoms, underuse of appropriate diagnostic investigations, and interpretation of those investigations.

Blood Pressure Measurements

Outcome prediction by ambulatory BP monitoring is not necessarily better than by office BP measurements. However, ambulatory monitoring is useful to identify high-risk nondippers and inverted dippers, allowing consequent treatment adjustments.

Electrocardiography and Echocardiography

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for CVD in dialysis patients recommend an electrocardiogram at dialysis initiation and then annually.[27] Diabetic HD patients presenting without sinus rhythm (11% of the cohort) were 89% more likely to die and 164% more likely to sustain a stroke. CKD patients (eGFR <60 ml/min/1.73 m^2) with increased QRS duration had 15% greater risk for incident CHF, 13% greater risk of incident CHD, and 17% greater risk for mortality per 10-ms increase; prolongation of the QT interval was independently associated with adverse outcome.

KDOQI guidelines recommend echocardiography in all dialysis patients after they achieve "dry weight" targets, preferably 1 to 3 months after dialysis initiation on an interdialytic day for HD patients and at 3-year intervals thereafter.[27] The rationale for this guideline is that diminished LV systolic function, an important independent risk factor for CVD and mortality,[27] is not accurately diagnosed by history, physical examination, or chest radiography. Detection of unsuspected cardiomyopathy is also important, given that carvedilol therapy in such patients improved LV systolic function, decreased hospitalization, and reduced mortality. As in the general population, CKD patients with LVEF below 40% should be evaluated for CHD (exceptions are pediatric or young adult patients with nondiabetic CKD and other patients known to be at low risk for CHD).

A new classification scheme for CHF staging specifically targeted for dialysis patients has been proposed by the Acute Dialysis Quality Initiative (ADQI) XI Workgroup.[35] The three key elements are as follows:

1. Standardized echocardiographic evidence of structural and/or functional cardiac abnormalities.
2. Dyspnea occurring in the absence of primary lung disease, including isolated pulmonary hypertension (i.e., not secondary to elevated pulmonary capillary wedge pressure).
3. Improvement of congestive symptoms after RRT/ultrafiltration.

The justification for the KDOQI 2005 Guidelines (recommending echocardiograms in incident dialysis patients) *and* the validity of the first element of the proposed ADQI XI heart failure staging scheme (standardized echocardiographic evidence of structural and/or functional heart disease) are both supported by the finding that right ventricular dysfunction was associated with a 66% increased risk for death.[36]

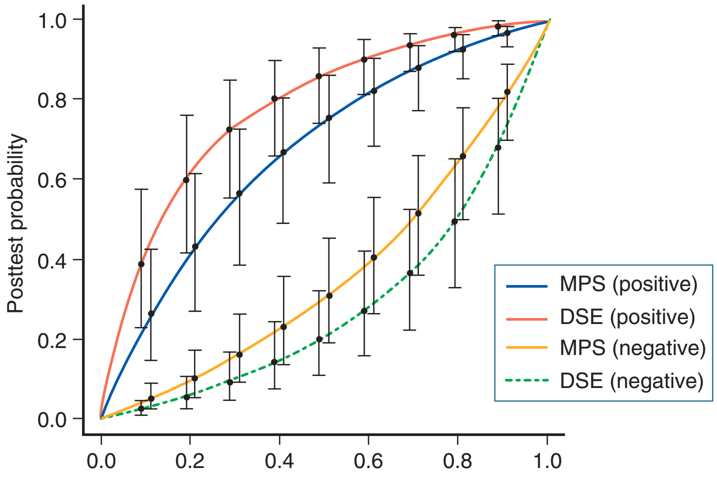
Stress Tests and Screening Renal Transplant Candidates

ESRD patients are poorly suited for conventional exercise stress electrocardiography because of limited exercise tolerance and frequent resting electrocardiographic abnormalities. Accuracies of pharmacologic stress echocardiographic and nuclear scintigraphic techniques are remarkably variable across the world; they are operator dependent, and the approach of individual sites to cardiac screening should rely on institutional expertise. Moreover, prediction of the likelihood of future events may differ considerably from prediction of coronary anatomy. In severe CKD, dobutamine stress echocardiography is an independent predictor of long-term mortality. Sensitivities and specificities for detection of CHD in renal transplant candidates have been reported to range from 44% to 90%. A meta-analysis concluded that presence of inducible myocardial ischemia by any stress-imaging test is independently predictive of increased AMI risk and cardiac death, whereas a fixed or resting defect or abnormality is predictive of cardiac death but not AMI. A subsequent meta-analysis by the Cochrane Collaboration (Fig. 81.11) concluded that dobutamine stress echocardiography is probably more accurate than myocardial stress nuclear scintigraphy for noninvasive detection of CHD in renal transplant candidates.[37]

The major problem with "screening" is use of test results for clinical management. The evidence for prophylactic revascularization of asymptomatic renal transplant candidates (or any other patient group) is weak.[38] The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease Trial (ISCHEMIA-CKD; clinicaltrials.gov, NCT01985360) is a prospective RCT testing the comparative efficacy of a conservative versus invasive strategy for treatment of stable CHD in patients with eGFR less than 30 ml/min/1.73 m^2, including dialysis patients. The best observational data supporting the usefulness of preemptive coronary revascularization showed 3-year cardiac event–free survival of 90% for wait-listed revascularized patients.[39] Optimal medical therapy (which should constitute the treatment strategy for all patients) may potentially attenuate the putative benefit of prophylactic coronary revascularization. One algorithm for screening and management of CHD in renal transplant candidates is presented in Fig. 81.12.

Coronary Angiography

Coronary angiography should be considered in stable ESRD patients with evidence for inducible myocardial ischemia, unstable patients with ACS (performed urgently for STEMI), and patients with LVEF below 40%. In



Post-test probability			
Test	**Pretest probability of (%) coronary artery disease**	**Posttest probability (%) after positive result**	**Posttest probability (%) after negative result***
Dobutamine Stress Echocardiography (DSE)	Low risk (10-29)	42-72	3-10
	Intermediate risk (30-59)	73-90	10-27
	High risk (60-90)	91-98	28-70
Myocardial Perfusion Scintigraphy (MPS)	Low risk (10-29)	24-54	5-15
	Intermediate risk (30-59)	55-81	16-38
	High risk (60-90)	81-96	39-79

Fig. 81.11 Accuracy of dobutamine stress echocardiography versus myocardial perfusion scintigraphy for diagnosing coronary artery disease coronary artery disease in renal transplant candidates. (From reference 67.)

CKD and dialysis patients with residual renal function, fear of contrast nephropathy may restrain use of coronary angiography (see Chapter 70 for preventive measures); one retrospective study of 76 nondialysis patients with mean eGFR of 12.5 ml/min/1.73 m^2 found no significant postangiographic deterioration in renal function. However, patients sustaining acute kidney injury (AKI) after coronary angiography are at heightened risk for long-term mortality, ESRD, and hospitalization.[40] However, fear of AKI should not deter clinically mandated coronary angiography. Echocardiography should be performed before any nonemergent coronary angiography in CKD patients to diagnose clinically unsuspected valvular disease or cardiomyopathy, to gauge preprocedure volume status, and to assess LV function (to avoid excessive exposure to radiocontrast media through unwarranted ventriculography).

Noninvasive coronary CT angiography (CCTA) may be problematic in dialysis patients because of medial calcification interfering with angiographic interpretation. Nevertheless, noninvasive CCTA has diagnostic sensitivity to detect obstructive CHD nearly comparable to invasive coronary angiography and markedly superior to noninvasive nuclear single-photon emission computed tomography imaging.[41] Generalizability of these findings must be interpreted in the context of individual institutional expertise. Noninvasive gadolinium-based magnetic resonance angiographic imaging in patients with severe CKD remains problematic because of lingering concerns about nephrogenic fibrosing dermopathy; the usefulness of imaging without contrast media is uncertain.

Imaging of Vascular Calcification

Vascular calcification can be visualized by conventional x-ray techniques and by multislice spiral CT or electron-beam CT. Valvular and large-artery calcification can be visualized by ultrasound techniques, and (if present) predicts worse outcome in dialysis patients, although the value of coronary artery calcification in dialysis patients as a surrogate for CHD severity has been questioned.

Biomarkers

Plasma brain natriuretic peptides (BNP and NT-proBNP), cardiac troponins (cTnT, cTnI), and high-sensitivity (hs) CRP are prognostic risk markers in the evaluation of heart disease in ESRD.[42] BNP reflects cardiac filling pressures (not limited to the left heart), troponins reflect myocardial cell death (but not necessarily ischemia), and hsCRP reflects inflammation. Elevation of cTnT occurs even in pediatric CKD patients and is associated with cardiac dysfunction. Elevated levels of serum troponin in ESRD patients should not be uncritically attributed to myocardial ischemia caused by obstructive coronary artery disease. Elevated levels of cTnT are associated with the presence and severity of HD-induced myocardial stunning.[43] The cardiac biomarker–based diagnosis of ACS requires a time-appropriate rise and fall of the biomarker. The most cost-effective combination of biomarkers for risk stratification in dialysis patients might be high-sensitivity cardiac troponin and a natriuretic peptide, but this is speculative. A recent study underscored the robustness of IL-6 as a classifier of clinically overt CVD and predictor of

Algorithm for Management of Coronary Artery Disease in Renal Transplant Candidates

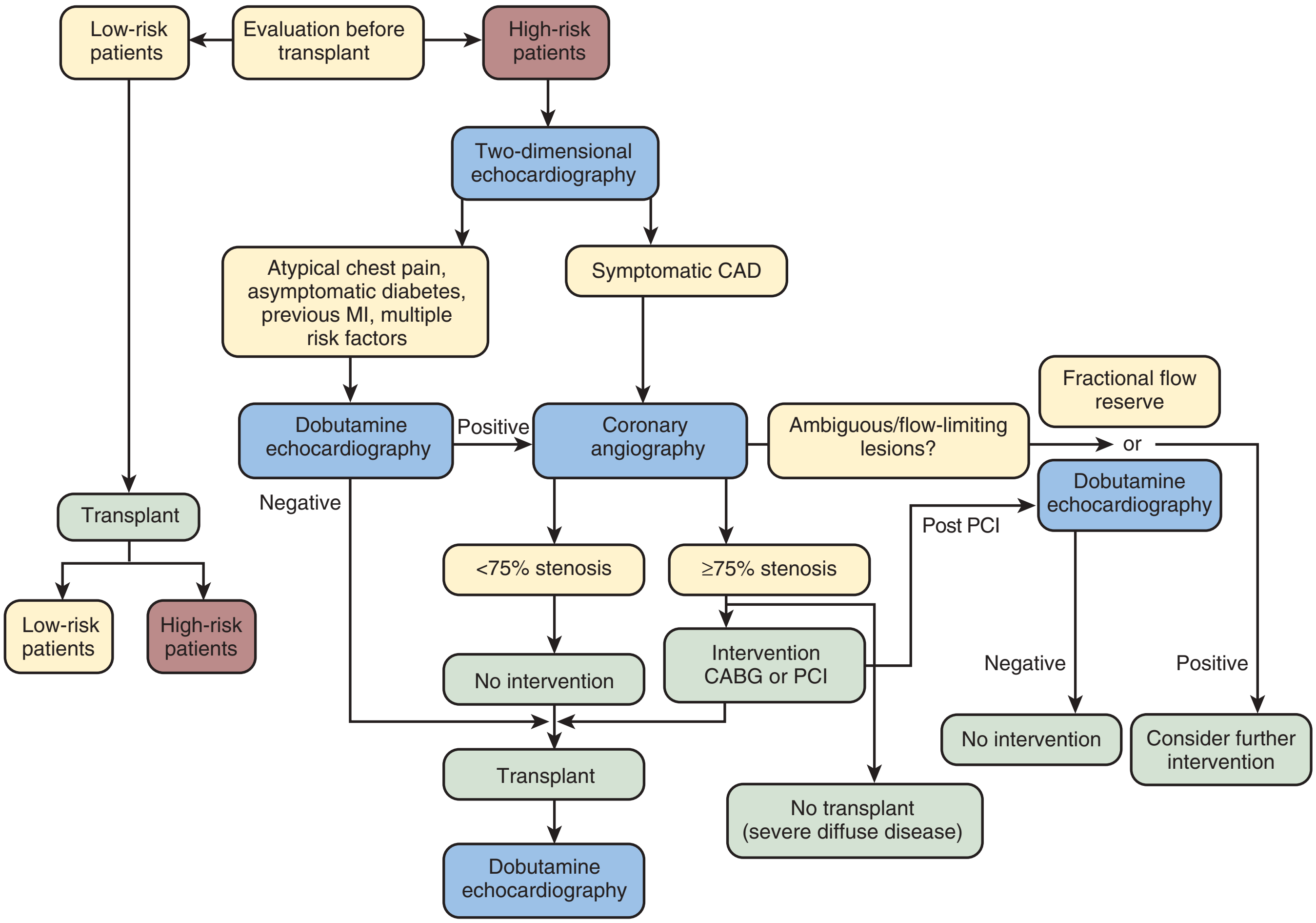

Low-risk patients
Evaluation before transplant
High-risk patients
Two-dimensional echocardiography
Atypical chest pain, asymptomatic diabetes, previous MI, multiple risk factors
Symptomatic CAD
Fractional flow reserve
Dobutamine echocardiography
Positive
Coronary angiography
Ambiguous/flow-limiting lesions?
or
Dobutamine echocardiography
Negative
Transplant
Post PCI
<75% stenosis
≥75% stenosis
Low-risk patients
High-risk patients
Intervention CABG or PCI
Negative
Positive
No intervention
No intervention
Consider further intervention
Transplant
No transplant (severe diffuse disease)
Dobutamine echocardiography

Fig. 81.12 Algorithm for management of coronary heart disease in renal transplant candidates. *CABG,* Coronary artery bypass graft surgery; *CAD,* coronary artery disease; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention. (Modified from Herzog CA. Acute MI in dialysis patients: How can we improve the outlook? *J o Critical Illness* 1999;14(11):613-621.)

all-cause mortality in CKD stage 5.[44] In CKD, NT-proBNP and BNP are equivalent predictors of decompensated heart failure, but NT-proBNP is a better predictor of survival. Fig. 81.13 graphically displays the relationship of cTnT and cTnI levels in asymptomatic dialysis patients and long-term survival. On the basis of these data, the U.S. Food and Drug Administration approved the measurement of cTnT in dialysis patients for risk stratification (mortality prediction).[27]

High-sensitivity cardiac troponin (hs-cTn) assays, which offer the advantage of high precision, serve dual, complementary (but distinct) roles: the diagnosis of AMI, which now includes cardiac biomarkers and risk stratification based on detection of hs-cTn in an asymptomatic, nonischemic setting (e.g., perhaps a marker for apoptosis). Hs-cTn–based risk stratification should employ reference change values over time, rather than simple thresholds, particularly when data are inconclusive regarding acceptable normal values in special populations, such as dialysis patients, known to have chronically elevated cardiac troponin levels.[45]

FGF-23 has also proven to be a strong outcome predictor in CKD patients, but further studies are needed to demonstrate its role as an additional clinical biomarker.

An improved CV prediction risk score was recently developed for use in HD patients (http://aro-score.askimed.com/).[46]

TREATMENT AND PREVENTION OF CARDIOVASCULAR DISEASE

Risk Factor Reduction

Lifestyle Factors and Smoking

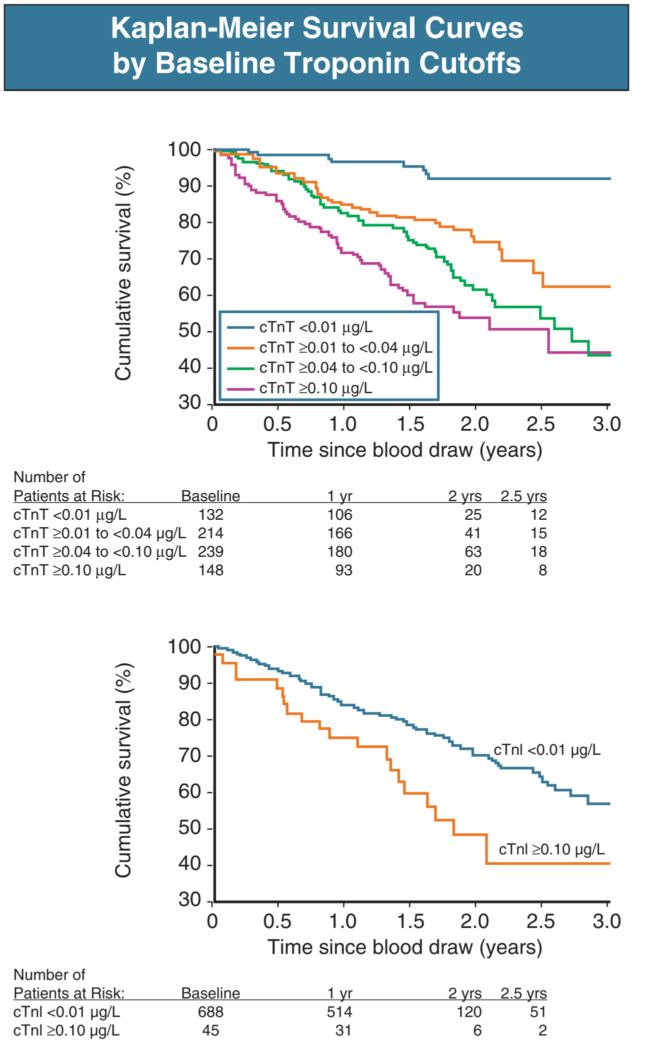
Because physical inactivity is associated with albuminuria and CV mortality, CKD patients should be advised to stay as physically active as possible and to avoid smoking.

Weight and Diet

Lifestyle changes, including balanced diets with regard to saturated fat and carbohydrates (in diabetic patients), probably reduce CV morbidity and should be encouraged. However, in all CKD stages, protein-energy wasting must be avoided; especially in dialysis patients, increased body mass index has been associated with improved outcomes, possibly reflecting confounded epidemiology; thus the obesity paradox only exists in HD patients with inflammation.[9]

Hypertension and Coronary Heart Disease

BP targets for CKD patients, in particular those with diabetes or proteinuria greater than 1 g/day, are discussed in Chapter 79. A goal of



Number of Patients at Risk:	Baseline	1 yr	2 yrs	2.5 yrs
cTnT <0.01 µg/L	132	106	25	12
cTnT ≥0.01 to <0.04 µg/L	214	166	41	15
cTnT ≥0.04 to <0.10 µg/L	239	180	63	18
cTnT ≥0.10 µg/L	148	93	20	8

Number of Patients at Risk:	Baseline	1 yr	2 yrs	2.5 yrs
cTnI <0.01 µg/L	688	514	120	51
cTnI ≥0.10 µg/L	45	31	6	2

Fig. 81.13 **Kaplan-Meier survival curves by baseline troponin cutoffs.** *cTnI,* Cardiac troponin I; *cTnT,* cardiac troponin T. (From reference 42.)

therapy is volume control (see Chapter 79) and prevention of sodium overload, particularly through dietary sodium restriction. Longer or more frequent HD sessions may be beneficial in controlling hypertension. Because of their parallel cardioprotective effects, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and vasodilating β-blockers (e.g., carvedilol) are the first-line drugs to treat CKD- and ESRD-related hypertension. Calcium channel blockers and most other antihypertensive drugs, including centrally acting sympathetic inhibitors, are useful in combination with first-line agents. Pure vasodilators (e.g., minoxidil) should be avoided because they may increase volume overload or occasionally cause pericardial effusion. Novel approaches to drug-resistant hypertension, such as renal sympathetic denervation, have become controversial in view of recent trials. Because sleep-disordered breathing occurs in about 50% of CKD stage 4 and 5 patients and is associated with hypertension, sleep apnea should be considered in therapy-resistant hypertension.

CHD and CHD-related events should be treated with the same medications and active interventions indicated in the general population in the absence of convincing CKD-specific data to the contrary. Medical treatment includes use of antiplatelet agents, ACE inhibitors, ARBs, β-blockers, nitroglycerin, and statins. There is no rationale for a less aggressive therapeutic approach in CKD than in the nonrenal population.

Diabetes Mellitus

Optimal glycemic control (see Chapter 32), reaching BP target levels, and lipid monitoring (with subsequent dyslipidemia treatment) are crucial in managing diabetic CKD patients. CHD and other CVD should be treated aggressively in this high-risk group. Because the harm associated with severe hypoglycemia might counterbalance the potential benefit of intensive glucose-lowering treatment, treating to a hemoglobin A_{1c} (HbA_{1c}) level below 7.0% (53 mmol/mol) is not recommended in CKD stages 3 to 5.[47]

Dyslipidemia

Because CKD, like diabetes and hypertension, is considered a CV risk equivalent, CKD patients should be treated to achieve the guideline goal for secondary prevention for LDL cholesterol (<100 mg/dl [2.6 mmol/l]). This goal is not supported by clinical trials targeting dialysis patients. Post hoc subgroup analyses in the Heart Protection Study, Cholesterol and Recurring Events (CARE) study, and Treating to New Targets (TNT) study, together with a meta-analysis, provide inferential support for the role of statins in improving outcomes in CKD stages 1 and 2. The Study of Heart and Renal Protection (SHARP) showed that reducing LDL cholesterol with simvastatin 20 mg/day plus ezetimibe 10 mg/day safely reduced the incidence of major atherosclerotic events in patients with advanced CKD.[48] Thus statin treatment is recommended in CKD patients older than 20 years, with LDL cholesterol level goals below 130 mg/dl (3.4 mmol/l) or below 100 mg/dl (2.6 mmol/l) for secondary prevention; however, the negative results from the 4D study and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) do not support this guideline in dialysis patients. The possibility that statins have a procalcifying effect in the uremic milieu deserves further attention.[49]

Volume

In predialysis CKD, sodium restriction and diuretics are important to counteract fluid retention. In ESRD, longer and more frequent HD sessions may permit more effective volume control. In the HD center in Tassin, France, more than 90% of patients were normotensive with 8 hours of dialysis three times per week, with dietary salt restriction and no antihypertensive drugs. In the Frequent Hemodialysis Network (FHN) trial, frequent (six times per week) HD (vs. conventional three times per week) led to better hypertension control, a drop in LV mass index over 12 months,[50,51] and less myocardial stunning.[50,51] Episodes of dialysis-related hypotension should prompt reevaluation of dry weight, antihypertensive treatment, and exclusion of pericardial effusions, valvular disease, cardiomyopathy, and silent myocardial ischemia (see Chapter 98).

Anemia

Partial correction of severe anemia with ESAs results in regression of LVH. Treatment of severe anemia is also associated with fewer ischemic symptoms in CHD patients. However, evidence for reduction of CV mortality by ESAs is based on observational data only. To date, RCTs in HD and CKD patients have shown no benefit of normalized anemia on mortality as a primary end-point (see Chapter 82). Thus anemia correction in patients with advanced CKD to a hemoglobin level of 10 to 12 g/dl appears logical.

Inflammation

Data from statin trials in dialysis patients (4D, AURORA) showed lower CRP levels in the statin arms but no association with fewer CV events. A careful search for infectious processes, such as periodontal disease, is recommended in dialysis patients with inflammation. Restriction of catheter use is also important; short daily dialysis with better fluid status was associated with decreasing CRP levels compared with conventional HD. Volume status should be carefully monitored to avoid inflammation. Altered intestinal microbial flora as a potential risk factor for systemic uremic inflammation merits further study. It was recently demonstrated that medium cut-off dialysis membranes reduce uremic inflammation[52]; thus larger trials with longer treatment periods are encouraged.

Oxidative Stress

Two placebo-controlled interventional studies showed that vitamin E and *N*-acetylcysteine decreased the number of CV events in HD patients. Unfortunately, both studies were small and of limited duration, so adequately powered randomized trials are warranted. A recent meta-analysis showed that use of ultrapure dialysate results in decreased markers of inflammation and oxidative stress in HD patients.[53] However, administration of mixed tocopherols and α-lipoic acid did not influence biomarkers of inflammation and oxidative stress or the erythropoietic response in a recent randomized trial in HD patients.[54] Because CKD 4 patients allocated to the antioxidant synthetic triterpenoid bardoxolone experienced excessive CVD and especially CHF,[55] the beneficial effects of antioxidant treatment strategies in this patient group remains to be proven.

Chronic Kidney Disease–Mineral Bone Disorder

Recent meta-analyses and the updated KDIGO CKD-MBD guidelines (www.kdigo.org) conclude that calcium-free phosphate binders such as sevelamer reduce CV events, calcifications, and mortality compared with calcium-containing binders (see Chapter 85). Thus, these agents should be preferred for CKD patients with significant life expectancy, particularly patients on the transplant waiting list, independent of the presence or absence of calcifications.

Because vitamin D treatment is associated with improved survival in dialysis patients, vitamin D insufficiency should be considered. However, results from the Dialysis Outcomes and Practice Patterns Study (DOPPS) call into question the survival advantage for HD patients taking vitamin D. In the Paricalcitol Capsules Benefits Renal Failure Induced Cardiac Morbidity in Subjects With Chronic Kidney Disease Stage 3/4 (PRIMO) study, 48 weeks of paricalcitol therapy did not alter LV mass index or improve measures of diastolic dysfunction.[56]

The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) study[57] showed that cinacalcet only reduced the risk for death or major CV events in dialysis patients with moderate-severe secondary hyperparathyroidism after adjustment for age. In a second trial in similar dialysis patients, cinacalcet plus low-dose vitamin D sterols tended to attenuate vascular and cardiac valve calcification compared with an exclusively vitamin D sterol–based approach.[58]

FGF-23, a bone hormone, is cardiotoxic and induces LVH but does not induce vascular calcification.[59] In a post-hoc analysis of EVOLVE data, treatment of secondary hyperparathyroidism with cinacalcet was associated with reduced FGF-23 levels and patients with a 30% or 50% drop in FGF-23 levels experienced significantly fewer CV events.[60]

Revascularization

CKD is a strong risk factor for death after coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[61,62] Coronary revascularization complicated by AKI is associated with excess mortality; operative mortality for non-ESRD patients who require acute dialysis after cardiac surgery is 44%.

Observational studies suggest lower mortality in CKD (including dialysis) patients undergoing coronary revascularization compared with no revascularization. A post hoc analysis of CKD patients in the Fast Revascularization During Instability in Coronary Artery Disease (FRISC II) trial indicated a superior outcome with an early invasive strategy in ACS compared with conservative management. However, the optimal coronary revascularization method in CKD remains controversial. A post hoc analysis of CKD patients enrolled in the Arterial Revascularization Therapies Study (ARTS) found similar outcomes for coronary artery bypass grafting (CABG) or multivessel percutaneous coronary intervention (PCI) with non–drug-eluting stents (DESs) for death, myocardial infarction, or stroke. In elderly non–dialysis-dependent CKD patients, the incidence of ESRD is lower after PCI (5.4% at 3 years vs. 6.8% for CABG), but long-term risk for death (28% 3-year mortality with CABG, 33% with PCI) or the combined event of death or ESRD is lower after CABG. The relative survival advantage of CABG (vs. PCI) occurs only more than 6 months after revascularization.[63] Dialysis patient survival after CABG is better than after PCI with non-DESs[64] and DESs,[65] but 2-year mortality remains high at 44% (vs. 52% for PCI).[64] Based on three large observational studies,[64-67] we recommend the following strategy for dialysis patients who do not require acute reperfusion therapy for STEMI, which would typically be treated with emergent PCI first:

1. Patients with multivessel CHD (including the left anterior descending coronary artery [LAD]) who are anatomically suitable candidates for internal mammary artery grafts should undergo CABG surgery; concomitant ACS additionally favors CABG surgery.
2. The CABG survival advantage occurs more than 6 months after revascularization. Patients with limited life expectancy or who are concerned about perioperative morbidity (higher with CABG) might choose PCI (better outcomes at less than 6 months).
3. If the left internal mammary graft (to the LAD) is not part of the surgical strategy, CABG likely provides no advantage.

In the general population, advantages of DESs (compared with non-DESs) include lower incidence of in-stent restenosis and improved survival.[67] In dialysis patients, reliance on clinical surrogates (e.g., chest pain) leads to underestimation of the true restenosis incidence. The most complete angiographic follow-up of DESs noted a 22% to 31% incidence of restenosis with DESs and 24% to 43% with non-DESs. Clinically silent restenosis is a rationale for surveillance stress imaging (see Fig. 81.12).

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is *not* an established risk factor for cardiovascular disease in patients with advanced chronic kidney disease?
   - **A.** Inflammation
   - **B.** Smoking
   - **C.** Dyslipidemia
   - **D.** Hyperhomocysteinemia
   - **E.** Diabetes
2. What is *not* true about cardiovascular complications in end-stage renal disease patients?
   - **A.** Left ventricular hypertrophy is present in about 75% of the patients.
   - **B.** In dialysis patients the incidence of atrial fibrillation is about 15% per year.
   - **C.** Low levels of cholesterol predict death.
   - **D.** In dialysis patients, extensive vascular, especially coronary artery, calcification can occur even at young ages.
   - **E.** The calcific aortic stenosis progression rate is only slightly higher in dialysis patients compared to the general population.
3. What is the *most* common cause of death in dialysis patients?
   - **A.** Congestive heart failure
   - **B.** Infection
   - **C.** Arrhythmic death
   - **D.** Stroke
   - **E.** Valvular heart disease
4. Which drug has been shown to reduce mortality in dialysis patients with dilated cardiomyopathy and systolic heart failure?
   - **A.** Atorvastatin
   - **B.** Digoxin
   - **C.** Carvedilol
   - **D.** Metoprolol
   - **E.** Atenolol

82

Anemia in Chronic Kidney Disease

Iain C. Macdougall, Kai-Uwe Eckardt

Anemia is an almost universal complication of chronic kidney disease (CKD). It contributes considerably to reduced quality of life of patients with CKD and has been associated with a number of adverse clinical outcomes. Before the availability of recombinant human erythropoietin (rHuEPO, or epoetin), patients on dialysis frequently required blood transfusions, exposing them to the risks of iron overload, transmission of viral hepatitis, and human leukocyte antigen (HLA) sensitization, which reduced the chances of successful transplantation. The advent of rHuEPO in the late 1980s changed this situation completely. The ability to correct anemia has had consequences beyond simply an improvement in general fatigue and reduced physical capacity, to impact on a broad spectrum of physiologic functions. Thus there is a strong rationale for managing anemia in CKD patients, and yet the optimal treatment strategies are still incompletely defined. Apart from therapy with erythropoiesis-stimulating agents (ESAs), iron replacement is essential for anemia management. It is important to note that CKD patients on dialysis require target thresholds of iron parameters different from those for normal individuals to ensure optimal rates of red blood cell (RBC) production. The costs of anemia management are considerable, and it has become apparent that full anemia correction may cause harm; therefore a rational and careful consideration of the risks and benefits is mandatory.

PATHOGENESIS

Renal anemia is typically an isolated normochromic, normocytic anemia with no leukopenia or thrombocytopenia. Both RBC life span and the rate of RBC production are reduced, but the latter is more important. The normal bone marrow has considerable capacity to increase the rate of erythropoiesis, and compensation normally could be easily made for the reduction in erythrocyte life observed in association with CKD. However, this EPO-induced compensatory increase in erythrocyte production is impaired in CKD. Serum EPO levels remain within the normal range and fail to show the inverse exponential relationship with blood oxygen content characteristic of other types of anemia. EPO is normally produced by interstitial fibroblasts in the renal cortex, in close proximity to tubular epithelial cells and peritubular capillaries.[1,2] In addition, hepatocytes and perisinusoidal, or Ito, cells in the liver can produce EPO (Fig. 82.1). Hepatic EPO production dominates during fetal and early postnatal life but does not compensate for the loss of renal production in adult organisms. Subtle changes in blood oxygen content induced by anemia, reduced environmental oxygen concentrations, and high altitude stimulate the secretion of EPO through a widespread system of oxygen-dependent gene expression.[2-4] Central to this process is a family of hypoxia-inducible transcription factors (HIFs). The two most important members of this family, HIF-1 and HIF-2, are composed of an oxygen-regulated α subunit (HIF-1α or HIF-2α) and a constitutive β subunit. The production of HIF-1α and HIF-2α is largely independent of oxygen, but their degradation is related to cellular oxygen concentrations. Hydroxylation of specific prolyl and asparagyl residues of HIF-α, for which molecular oxygen is required as a substrate, determines proteasomal destruction of HIF and inhibits its transcriptional activity. Apart from EPO, several hundred HIF target genes have been identified. HIF-2, rather than HIF-1, is the transcription factor primarily responsible for the regulation of EPO production.[5,6]

The role of renal EPO production in the pathogenesis of renal anemia is supported by the particularly severe anemia in anephric individuals. However, the mechanisms impairing renal EPO production in diseased kidneys remain poorly understood. The production capacity for EPO remains significant, even in end-stage renal disease. Thus patients with anemia and CKD can respond with a significant increase in EPO production to an additional hypoxic stimulus.[1] The main problem therefore appears to be a failure of EPO production to increase in response to chronically reduced hemoglobin (Hb) concentrations. In line with this view, endogenous EPO production can be induced in CKD patients by pharmacologic inhibition of HIF degradation (see later discussion).

EPO is a glycoprotein hormone consisting of a 165–amino acid protein backbone and four complex, heavily sialylated carbohydrate chains.[1] The latter are essential for the biologic activity of EPO in vivo because partially or completely deglycosylated EPO is rapidly cleared from the circulation. This is why rHuEPO has to be manufactured in mammalian cells; bacteria lack the capacity to glycosylate recombinant proteins.

EPO stimulates RBC production by binding to homodimeric EPO receptors, which are primarily located on early erythroid progenitor cells, the burst-forming units erythroid (BFU-e) and the colony-forming units erythroid (CFU-e). Binding of EPO to its receptors salvages these progenitor cells and the subsequent earliest erythroblast generation from apoptosis, thereby permitting cell division and maturation into RBCs.[7] Inhibition of RBC production by yet unknown uremic inhibitors of erythropoiesis may contribute to the pathogenesis of renal anemia, and dialysis per se can improve renal anemia and the efficacy of ESAs. Moreover, the interindividual dose requirements for ESAs vary significantly among CKD patients, and the average weekly dose is much higher than estimated production rates of endogenous EPO in healthy individuals. An alternative view to the accumulation of inhibitors of erythropoiesis in CKD is that in many patients there is overlap between renal anemia and the anemia of chronic disease, which is characterized by inhibition of EPO production and EPO efficacy, as well as by reduced iron availability, mediated through inflammatory cytokines.[8] The hepatic release of hepcidin, the key regulator of iron metabolism, is upregulated in states of inflammation; it simultaneously blocks iron absorption from the gut and promotes iron sequestration in macrophages.[9]

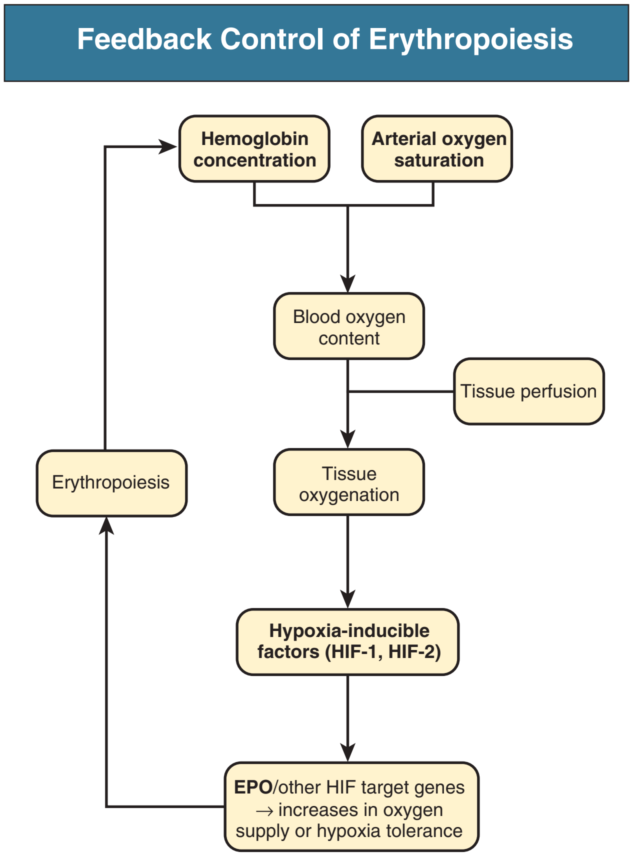
Feedback Control of Erythropoiesis
Hemoglobin concentration
Arterial oxygen saturation
Blood oxygen content
Tissue perfusion
Tissue oxygenation
Erythropoiesis
Hypoxia-inducible factors (HIF-1, HIF-2)
EPO/other HIF target genes → increases in oxygen supply or hypoxia tolerance

Fig. 82.1 Feedback control of erythropoiesis. *EPO,* Erythropoietin.

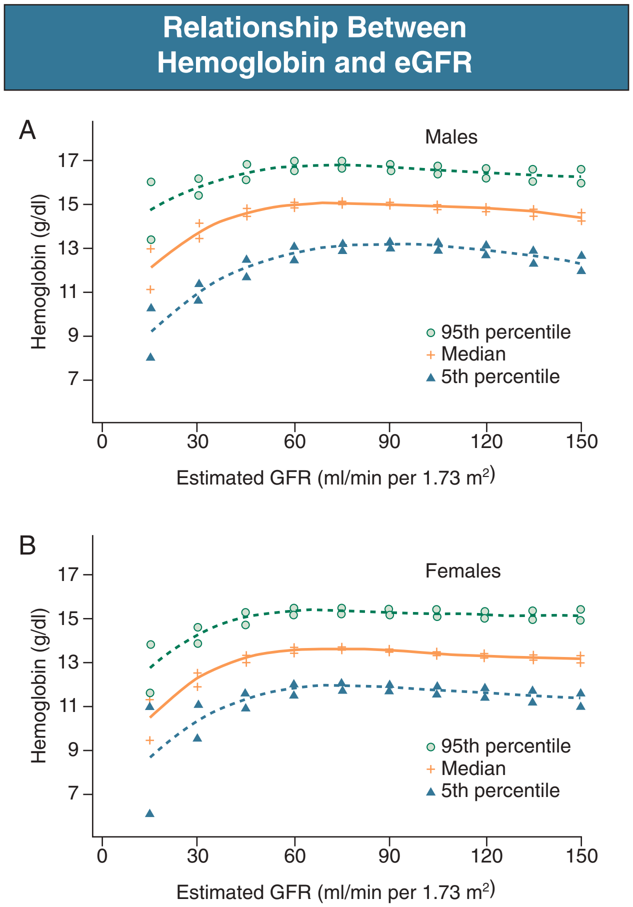
Relationship Between Hemoglobin and eGFR

Fig. 82.2 Relationship between hemoglobin (Hb) concentration and estimated glomerular filtration rate *(GFR).* Data are from a cross-sectional survey of individuals randomly selected from the general U.S. population (Third National Health and Nutrition Examination Survey [NHANES III]). Results and 95% confidence interval are shown for males (A) and females (B) at each estimated GFR interval. (From reference 11.)

EPIDEMIOLOGY AND NATURAL HISTORY

In general, there is a progressive increase in the incidence and severity of anemia with declining renal function. The reported prevalence of anemia by CKD stage varies significantly and depends to a large extent on the definition of anemia and whether study participants are selected from the general population, are at high risk for CKD, are diabetic, or are already under the care of a nephrologist. Data from the National Health and Nutrition Examination Survey (NHANES) showed that the distribution of Hb levels starts to fall at an estimated glomerular filtration rate (eGFR) of less than 75 ml/min/1.73 m^2 in men and 45 ml/min/1.73 m^2 in women (Fig. 82.2).[10] The prevalence of Hb values below 13 g/dl increases below an eGFR of 60 ml/min/1.73 m^2 in men and 45 ml/min/1.73 m^2 in women in the general population. Among patients under regular care for CKD, the prevalence of anemia was found to be much greater, with mean Hb values of 12.8 (CKD stages 1 and 2), 12.4 (CKD stage 3), 12.0 (CKD stage 4), and 10.9 (CKD stage 5).[11] Although anemia develops largely independently of the cause of kidney disease, there are two important exceptions. Diabetic patients develop anemia more frequently, at earlier stages of CKD, and more severely at a given level of renal impairment.[12,13] Conversely, in patients with polycystic kidney disease, Hb is on average higher than in other patients with similar degrees of renal failure, and polycythemia may occasionally develop.

With the advent of rHuEPO and its derivatives, Hb values in patients with CKD have changed. In particular, in patients on dialysis, average Hb values have steadily increased for many years and then declined again in view of new evidence suggesting lower target levels.[12] The average Hb value still varies considerably among countries, reflecting variability in practice patterns (Table 82.1).[13] Moreover, Hb values vary considerably among patients in the same treatment setting as well as within patients over time, mainly reflecting persistent and time-dependent changes in responsiveness (see later discussion).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of anemia and the assessment of its severity are best made by measuring the Hb concentration rather than the hematocrit (Hct). Hb is a stable analyte that is measured directly in a standardized fashion, whereas the Hct is relatively unstable, indirectly derived by automatic analyzers, and lacking standardization. Within-run and between-run coefficients of variation in automated analyzer measurements of Hb are half and one third those for Hct, respectively.[12]

There is considerable variability in the Hb threshold used to define anemia. According to the most recent definition in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, anemia should be diagnosed at Hb concentrations of less than 13.0 g/dl in men and less than 12.0 g/dl in women.[14] These values represent the World Health Organization definition of anemia. In children, age-dependent differences in the normal values have to be taken into account. Normal Hb values are increased in high-altitude residents. It is important to note

TABLE 82.1 **Hemoglobin Levels in Patients on Dialysis**

	AMONG PATIENTS ON DIALYSIS FOR LONGER THAN 180 DAYS			AMONG PATIENTS NEW TO ESRD, AT START OF DIALYSIS		
Country	**n**	**Mean Hb (g/dl)**	**Hb <11 g/dl (% of patients)**	**n**	**Mean Hb (g/dl)**	**Hb <11 g/dl (% of patients)**
Sweden	456	12.0	23	168	10.7	55
United States	1690	11.7	27	458	10.4	65
Spain	513	11.7	31	170	10.6	61
Belgium	442	11.6	29	213	10.3	66
Canada	479	11.6	29	150	10.1	70
Australia and New Zealand	423	11.5	36	108	10.1	70
Germany	459	11.4	35	142	10.5	61
Italy	447	11.3	38	167	10.2	68
United Kingdom	436	11.2	40	93	10.2	67
France	341	11.1	45	86	10.1	65
Japan	1210	10.1	77	131	8.3	95

Mean hemoglobin (Hb) levels and percentage of patients with Hb levels below 11 g/dl who have been on dialysis therapy for more than 180 days and at the time of starting dialysis, by country.

Data are from the Dialysis Outcomes and Practice Patterns Study, Phase II (DOPPS 2), and are derived from 308 randomly selected, representative dialysis facilities. Note that there are marked differences among countries, but at least one fourth and up to three fourths of dialysis patients, and, in most countries, more than two thirds of patients starting chronic dialysis have Hb values below the recommended lower target of 11 g/dl.

ESRD, End-stage renal disease.

Modified from reference 13.

that thresholds for the diagnosis of anemia and evaluation of the causes should not be interpreted as being thresholds for treatment of anemia.[14]

In addition to the Hb value, the evaluation of anemia in CKD patients should include a complete blood count with RBC indices (mean corpuscular Hb concentration [MCHC], mean corpuscular volume [MCV]), white blood cell count (including differential), and platelet count. Although renal anemia is typically normochromic and normocytic, deficiency of vitamin B_{12} or folate may lead to macrocytosis, whereas iron deficiency or inherited disorders of Hb formation (such as thalassemia) may produce microcytosis. Macrocytosis with leukopenia or thrombocytopenia suggests a generalized disorder of hematopoiesis caused by toxins, nutritional deficit, or myelodysplasia. Hypochromia probably reflects iron-deficient erythropoiesis. An absolute reticulocyte count, which normally ranges between 40,000 and 50,000 cells/μl of blood, is a useful marker of erythropoietic activity.

Iron status tests should be performed to assess the level of iron in tissue stores or the adequacy of iron supply for erythropoiesis. Although serum ferritin is the only available marker of storage iron, several tests reflect the adequacy of iron for erythropoiesis, including transferrin saturation (TSAT), the percentage of hypochromic red blood cells (PHRC), the reticulocyte hemoglobin content (CHr), the MCV, and the MCHC. Storage time of the blood sample may elevate PHRC, and MCV and MCHC are below the normal range only after long-standing iron deficiency; in clinical practice, TSAT remains the most frequently used parameter.

It is important to identify anemia in CKD patients because it may signify nutritional deficits, systemic illness, or other conditions that warrant attention. Moreover, even at modest degrees, anemia reflects an independent risk factor for hospitalizations, cardiovascular disease (CVD), and mortality.[12] The diagnosis of renal anemia, that is, anemia caused by CKD, requires careful judgment of the degree of anemia in relation to the degree of renal impairment and exclusion of other or additional causes. Because there is significant variability in the degree of anemia in relation to the impairment in renal function, no simple diagnostic criteria can be applied. Causes of anemia other than EPO deficiency should be considered when (1) the severity of anemia is disproportionate to the impairment of renal function, (2) there is evidence of iron deficiency, or (3) there is evidence of leukopenia or thrombocytopenia. Concomitant conditions such as sickle cell disease may exacerbate the anemia, as can drug therapy. For example, inhibitors of the renin-angiotensin system may reduce Hb levels by (1) direct effects of angiotensin II (Ang II) on erythroid progenitor cells,[15] (2) accumulation of *N*-acetyl-seryl-lysyl-proline (Ac-SDKP), an endogenous inhibitor of erythropoiesis in patients treated with angiotensin-converting enzyme (ACE) inhibitors,[16] and (3) reduction of endogenous EPO production, possibly because of the hemodynamic effects of Ang II inhibition. Myelosuppressive effects of immunosuppressants may further contribute to anemia.[17] The measurement of serum EPO concentrations is usually not helpful in the diagnosis of renal anemia because there is relative rather than absolute deficiency, with a wide range of EPO concentrations for a given Hb concentration that extends far beyond the normal range of EPO levels in healthy, nonanemic individuals. Abnormalities of other laboratory parameters should be looked for, such as a very low MCV or MCHC, a high MCV, or an abnormal leukocyte or platelet count, and further tests should be performed as indicated to explore these potential contributory causes (see earlier). However, when there are no such pointers to other confounding causes of anemia, and iron deficiency has been excluded, a trial with rHuEPO or its derivatives is warranted, even when the eGFR is only moderately reduced.

CLINICAL MANIFESTATIONS

In the early clinical trials of rHuEPO performed in the late 1980s, the mean baseline Hb concentration was about 6 to 7 g/dl, and this progressively increased to about 11 or 12 g/dl after treatment. Patients subjectively felt much better, with reduced fatigue, increased energy levels, and enhanced physical capacity, and there were also objective improvements in cardiorespiratory function.[18] Thus it is now clear that many of the symptoms previously attributed to the "uremic syndrome" may have been caused by severe anemia associated with CKD (Boxes 82.1 and 82.2). Although the avoidance of blood transfusions and improvement in quality of life are obvious early changes, there are also possible effects on the cardiovascular system (see Box 82.1). The physiologic consequences of long-standing anemia are an increase in cardiac output and a reduction in peripheral vascular resistance. Anemia is associated with the development of left ventricular hypertrophy in CKD patients and is thought to exacerbate left ventricular dilation. Sustained correction of severe anemia in CKD patients tends to reverse most of these CV abnormalities, with the notable exception of left ventricular dilation (although anemia correction may prevent further dilation in some patients[19]). Other effects of anemia correction reported in clinical trials include improvements in quality of life, cognitive function, sleep patterns, nutrition, sexual function, menstrual regularity, immune responsiveness, and platelet function. The majority of these trials, however, were not placebo-controlled, so the spectrum and extent of possible benefits remain uncertain.

Over the years, there has been considerable debate about the optimal target range of Hb in CKD patients. A presumed improvement in quality of life and expectations of positive effects on CV function and renal disease progression with increasing Hb concentrations led to suggestions of a level above 10 to 11 g/dl in all CKD patients,[12,13] but several studies have indicated increased risks associated with attempts to completely correct anemia. In particular, no survival benefit is evident at a higher level of anemia correction,[20-23] and attempts to normalize Hb concentrations have shown various risks, including increased rates of thromboembolic events, strokes, and possibly death. Thus there is a possible tradeoff among improved quality of life, reduced transfusion requirements, and risk for harm (see discussion later), and a target Hb level of above 13 g/dl should be avoided.[12,14]

BOX 82.1 Cardiovascular Effects Resulting from Anemia Correction

- Reduction in high cardiac output
- Reduced stroke volume
- Reduced heart rate
- Increase in peripheral vascular resistance
- Reduction in anginal episodes
- Reduction in myocardial ischemia
- Regression of left ventricular hypertrophy
- Stabilization of left ventricular dilation
- Increase in whole blood viscosity

BOX 82.2 Other Effects of Anemia Correction

Beneficial

- Reduced blood transfusions
- Increased quality of life
- Increased exercise capacity
- Improved cognitive function
- Improved sleep patterns
- Improved immune function
- Improved muscle function
- Improved depression
- Improved nutrition
- Improved platelet function

Adverse

- Hypertension
- Vascular access thrombosis
- Increased risk for stroke

TREATMENT

Erythropoiesis-Stimulating Agents

Epoetin Therapy

Manufacture of rHuEPO is achieved by gene transfer into a suitable mammalian cell line such as Chinese hamster ovary (CHO) cells. The early clinical trials of rHuEPO were conducted with both EPO alfa and EPO beta, both produced in CHO cells. Like the endogenous hormone, rHuEPO consists of a 165–amino acid backbone with one *O*-linked and three *N*-linked glycosylation chains. Invariably, however, there are some differences in the glycosylation pattern among different preparations of rHuEPO and the endogenous hormone. "Biosimilar" EPO preparations have been licensed in Europe after demonstration of their efficacy and safety in an abbreviated trial program.[24] Many other "copy" EPOs are available in several parts of the world, which are not necessarily produced to the same regulatory standards.

Before 1998, EPO alfa in Europe was formulated with human serum albumin, but this was replaced with polysorbate 80. EPO beta is formulated with polysorbate 20, along with urea, calcium chloride, and five amino acids as excipients. The importance of the formulation of the EPO products was highlighted in 2002 with an upsurge in cases of antibody-mediated pure red cell aplasia (PRCA) in association with the subcutaneous use of EPO alfa after its change of formulation. Patients affected by this complication develop neutralizing antibodies against both rHuEPO and the endogenous hormone, which result in severe anemia and transfusion dependence.[25] The cause of this serious complication in which there is a break in B cell tolerance remains obscure, although it seems likely that factors such as a breach of the cold storage chain are relevant, and the subcutaneous application route is a prerequisite; circumstantial evidence also suggests that rubber stoppers of prefilled syringes used in one of the albumin-free EPO alfa formulations may have released organic compounds that acted as immunologic adjuvants.[26] Although this unfortunate combination of adverse factors was specific for one compound, the development of neutralizing anti-EPO antibodies was subsequently also observed during a clinical trial with an epoetin alfa biosimilar[27] and a low rate of PRCA also occurs with EPO beta and darbepoetin alfa.

The EPOs are administered either intravenously or subcutaneously. The bioavailability after intraperitoneal administration (in peritoneal dialysis [PD] patients) is too low. The earliest clinical trials of EPO used intravenous injections two or three times per week. This was partly because of the short half-life of EPO (6 to 8 hours after intravenous administration)[28] and partly because of the convenience for the patient on dialysis. With use of this regimen, 90% of patients show a significant increase in Hb concentration. Good iron management is pivotal for the success of EPO therapy (see later discussion). Although the bioavailability of subcutaneous EPO is 20% to 30%, the prolonged half-life after subcutaneous administration compared with intravenous administration allows less frequent injections. Furthermore, the dose required to achieve the same Hb response is about 30% lower with subcutaneous than with intravenous administration.[28] There appears to be little difference in efficacy among the thigh, arm, or abdomen as injection sites.

Darbepoetin Alfa

Darbepoetin alfa is a second-generation ESA that is a supersialylated analogue of EPO, possessing two extra *N*-linked glycosylation chains. This property confers a lower clearance rate in vivo, and the elimination half-life of this compound in humans after a single intravenous administration is 25.3 hours versus 8.5 hours for epoetin alfa. Thus this agent can generally be given less frequently than the standard epoetins, with administration intervals of once weekly and once every 2 weeks with similar dose requirements.[29] In contrast to the epoetins, dosage requirements for darbepoetin alfa in CKD patients are the same for intravenous and subcutaneous administration. The conversion factor for switching patients from epoetin alfa or beta to darbepoetin alfa is usually quoted as 200 : 1, but there may be considerable variability in this, depending on the patient population, the dose, and the route of administration.

Methoxy Polyethylene Glycol–Epoetin Beta (C.E.R.A.)

Alternative bioengineering techniques to prolong the half-life of EPO further resulted in the development of C.E.R.A., a pegylated derivative of epoetin beta with an elimination half-life of around 130 hours when administered either intravenously or subcutaneously. Phase III studies suggested that many patients are able to be maintained with once-monthly administration of C.E.R.A., and a superiority study suggested greater efficacy with this frequency of administration compared with once-monthly dosing of darbepoetin alfa when administered intravenously to hemodialysis (HD) patients.[30]

Adverse Effects of the Erythropoiesis-Stimulating Agents

Adverse effects of ESA therapy include a moderate increase in blood pressure and an increased rate of thromboembolic events, including vascular access thrombosis. Whereas these effects probably depend to a large degree on the increase in Hb concentration, there are some concerns that ESA therapy may enhance thrombogenicity and tumor growth in patients with malignant disease, as well as exacerbate vascular events in CKD independently of Hb concentrations. Thus attempts should be made to use the lowest doses of ESA possible to avoid the presumed pleiotropic effects of this class of drugs. Similarly, because no "safe" upper dose level has been determined, it is advisable to avoid repeated dose escalations.[14] In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), patients with a history of malignancy were found to have an increased rate of cancer-related deaths when treated with darbepoetin.[23] Although no study has investigated anemia management in patients with CKD and active cancer, ESAs should be used only with great caution in such patients, in particular when cure from cancer is the anticipated outcome.[14] Similarly, in patients with a history of stroke or recent venous thromboembolic event, careful consideration should be given to the benefit-to-risk ratio of using ESA therapy (see later discussion).

Peginesatide

Peginesatide (previously called *Hematide*) is an EPO-mimetic peptide, the amino acid sequence of which is completely unrelated to native or recombinant EPO,[24] although it shares the same functional and biologic properties as EPO. It has been shown to be an effective treatment for anti-EPO antibody–mediated pure RBC aplasia because of a lack of cross-reactivity with anti-EPO antibodies.[31] Peginesatide was also shown to be equivalent to epoetin and darbepoetin in raising Hb concentrations in dialysis and nondialysis patients, respectively, but in nondialysis patients, a higher rate of CV events was observed.[32,33] Approximately a year after its introduction, peginesatide had to be withdrawn from the market because of severe hypersensitivity reactions, including fatal anaphylactic events. Currently no EPO-mimetic peptide is available as rescue therapy for anti-EPO antibody–induced PRCA.

Hypoxia-Inducible Transcription Factor Stabilizers

The HIF stabilizers are competitive inhibitors of HIF prolyl hydroxylases [2,24,34] and asparagyl hydroxylase enzymes involved in the metabolism of HIF and its transcriptional activity. The HIF stabilizers, also referred to as *prolyl-hydroxylase domain protein inhibitors* (PHD-inhibitors) cause an increase in endogenous EPO production from both liver and the diseased, nonfunctioning kidneys.[34,35] Such compounds are orally active, and several of these drugs (e.g., roxadustat, daprodustat, vadadustat, and molidustat) are currently being tested in phase II and III clinical trials.[34] The results of phase II trials published so far have shown efficacy in terms of increasing or maintaining the Hb level in both dialysis-dependent and non–dialysis dependent CKD patients and revealed no evidence of acute adverse effects.[36-38] Levels of endogenous EPO induced by prolyl-hydroxylase inhibitors are lower than those observed under intravenous treatment with ESAs, potentially avoiding dose-dependent toxicity of ESAs. On the other hand, prolyl-hydroxylase inhibitors are likely to have a range of consequences additional to increasing levels of EPO through activation of other HIF-target genes or interference with other cellular pathways.[2,34] Such pleiotropic effects could be beneficial, for example, by improving iron availability or reducing lipid levels.[35] However, given the widespread biological role of HIF, including its effects on neoangiogenesis and vascular function, the long-term benefit-to-risk relationship is difficult to predict and can be assessed only through rigorous long-term observation.

Initiation of and Maintenance Therapy With Erythropoiesis-Stimulating Agents

Before ESA therapy is considered in CKD patients, it is essential to exclude and to correct causes of anemia other than EPO deficiency, such as iron and vitamin deficiencies (Fig. 82.3). If the serum ferritin concentration is below 100 ng/ml, the first therapeutic approach in anemic patients should be iron supplementation. Iron is best given by intravenous administration, although oral iron can be considered in patients not yet on dialysis.[39] Some patients may respond to intravenous iron alone (see later discussion). If the ferritin level is above 100 μg/l (in the absence of systemic inflammation) or there is a suboptimal response to iron, ESA therapy is an option. However, the Hb level at which ESAs should be initiated remains controversial, mainly because the topic has not been rigorously studied. In TREAT, the largest ESA trial performed so far, darbepoetin therapy (with a target Hb level of 13 g/dl) was compared with placebo, with a rescue protocol when a patient's Hb dropped below 9 g/dl.[23] In the darbepoetin arm, the number of patients transfused was lower and there was a small increase in quality of life, but the stroke rate was twice as high, so that the benefit-to-risk relationship was clearly negative. Whereas these data argue strongly against the initiation of ESA therapy in patients with mild anemia, there is only one, much smaller randomized controlled trial (RCT) (in HD patients) that tested two different target ranges of 9.5 to 11.0 g/dl and 11.5 to 13.0 g/dl against placebo in patients with severe anemia.[40] Patients in both EPO treatment arms experienced improved quality of life and exercise capacity, but there was no difference between the arms. Based on these findings, the KDIGO guidelines recommend use of ESAs to prevent the Hb level from falling below 9 g/dl.[14] However, individualization is possible, acknowledging the fact that some patients have improved symptoms at higher Hb levels and are prepared to take increased risks. A commonly used target Hb range is between 10 and 12 g/dl.

The usual intravenous or subcutaneous starting dose of epoetin is about 25 to 50 IU/kg (e.g., 2000 IU two or three times weekly), of darbepoetin alfa is 20 to 30 mcg once weekly, and of C.E.R.A. is 30 to 60 mcg once every 2 weeks. Within 3 to 4 days after treatment initiation, an increase in the reticulocyte count is seen, and within 1 to 2

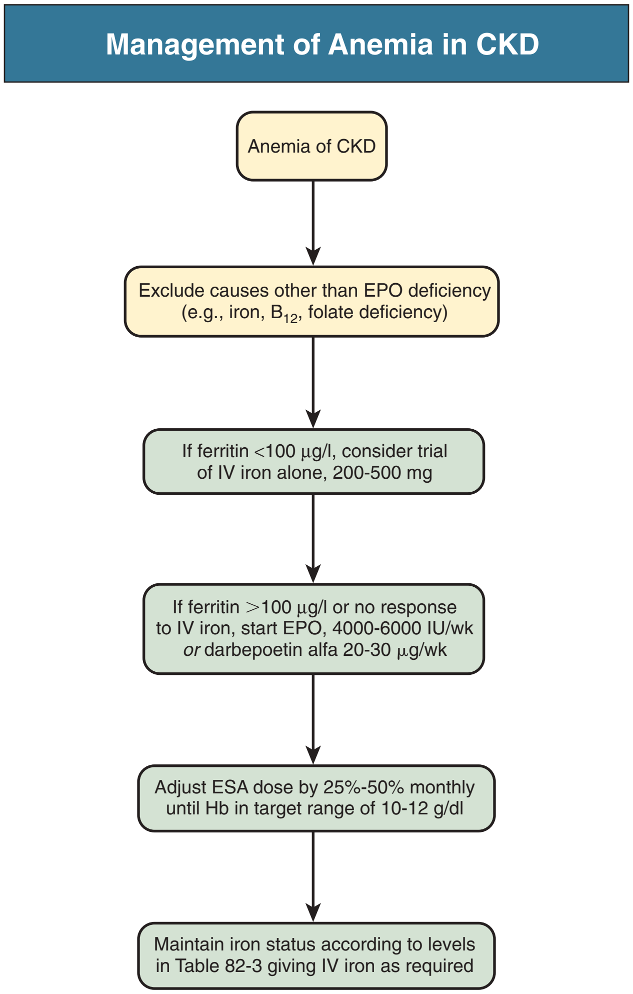
Management of Anemia in CKD
Anemia of CKD
Exclude causes other than EPO deficiency (e.g., iron, B_{12}, folate deficiency)
If ferritin <100 µg/l, consider trial of IV iron alone, 200-500 mg
If ferritin >100 µg/l or no response to IV iron, start EPO, 4000-6000 IU/wk *or* darbepoetin alfa 20-30 µg/wk
Adjust ESA dose by 25%-50% monthly until Hb in target range of 10-12 g/dl
Maintain iron status according to levels in Table 82-3 giving IV iron as required

Fig. 82.3 Management of anemia in patients with chronic kidney disease *(CKD). EPO,* Erythropoietin; *ESA,* erythropoiesis-stimulating agent; *Hb,* hemoglobin; *IV,* intravenous.

TABLE 82.2 Causes of a Poor Response to Erythropoiesis-Stimulating Agent Therapy

MAJOR (FREQUENT)	MINOR (LESS COMMON)
Iron deficiency	Poor compliance, poor adherence to ESA therapy
Infection, inflammation	Blood loss
Underdialysis	Hyperparathyroidism
	Aluminum toxicity (now rare)
	Vitamin B_{12} or folate deficiency
	Hemolysis
	Primary bone marrow disorders (e.g., myelodysplastic syndrome)
	Hemoglobinopathies (e.g., sickle cell disease)
	ACE inhibitors, angiotensin receptor blockers
	Carnitine deficiency
	Anti-EPO antibodies causing PRCA

ACE, Angiotensin-converting enzyme; *EPO*, erythropoietin; *PRCA*, pure red cell aplasia.

weeks, there is a significant rise in the Hb concentration, usually of the order of 0.25 to 0.5 g/dl/wk. Thus, over the course of 1 month, a significant increase of 1 to 2 g/dl in Hb concentration is usually achieved. If a patient fails to respond satisfactorily to ESAs, the dose is increased in stepwise upward titrations of 25% to 50%, and if there is still an inadequate response, causes of resistance to ESA therapy should be investigated (see later discussion).

Given the risks observed in trials aiming at Hb normalization, it is recommended that the Hb level should not be intentionally increased to 13 g/dl or higher and should generally not be maintained above 11.5 g/dl.

Hyporesponsiveness to Erythropoiesis-Stimulating Agents

According to the most recent guidelines, hyporesponsiveness to ESA therapy is identified when the Hb concentration does not increase from baseline after the first month of ESA treatment on appropriate weight-based dosages or if after treatment with stable doses, patients require two increases in ESA doses up to 50% beyond the dose at which their condition had previously been stable.[14] Patients who are hyporesponsive have a worse prognosis than those who do respond.[41] The causes of resistance to ESA therapy are listed in Table 82.2, and it is important to correct them when possible. The major causes include iron deficiency (see later discussion), infection or inflammation, and underdialysis.[12,14] If the patient is self-administering (e.g., for PD patients), poor adherence to or compliance with therapy must be excluded. If there is any doubt about the possibility of iron deficiency, a trial of intravenous iron may be useful. Vitamin B_{12}, folate, and thyroxine deficiency may be excluded easily by the appropriate laboratory tests, as may be severe hyperparathyroidism. Aluminum toxicity is no longer a significant cause of ESA resistance. Depending on the ethnic origin of the patient, a hemoglobinopathy should be excluded by performing Hb electrophoresis. Some patients taking ACE inhibitors or angiotensin receptor blockers may require higher doses of ESA therapy, although it is rarely necessary to stop these drugs. The possibility of a primary bone marrow disorder, such as myelodysplastic syndrome, should be investigated by a bone marrow examination (aspirate and trephine) if all other causes have been excluded. A bone marrow test also may be necessary in the diagnosis of antibody-mediated PRCA, although measurement of the reticulocyte count and anti-EPO antibodies may provide an earlier clue.[25] If a patient receiving ESA therapy has a high reticulocyte count, the bone marrow is generating more than adequate quantities of new RBCs and bleeding or hemolysis should be investigated by means of endoscopy or hemolysis screen (Coombs test, serum bilirubin, lactate dehydrogenase, and haptoglobin levels).

There is no defined upper dose limit of ESA, and doses of 60,000 IU of EPO per week have not uncommonly been used in the United States, but there is recent concern that high doses of ESA may increase side effects independently of Hb concentrations, as described earlier. In patients with acute illness requiring hospitalization, Hb frequently falls despite continued ESA therapy, indicating increased blood loss and temporary hyporesponsiveness. The optimal management of anemia under these conditions remains unclear. Whereas cost considerations may speak for withholding of ESA therapy until responsiveness is reestablished, it has been proposed that doses should be increased in an attempt to overcome hyporesponsiveness. Anecdotally, very high doses can be effective even in critically ill patients in intensive care units, but an RCT[42] failed to demonstrate a reduction in transfusion requirements and observed an increase in deep vein thrombosis. From a practical point of view, and pending evidence to the contrary, it seems sensible to continue the same dose of ESA.

Iron Management

Iron is an essential ingredient for heme synthesis, and adequate amounts of this mineral are required for the manufacture of new RBCs. Thus, under enhanced erythropoietic stimulation, greater amounts of iron are used, and many CKD patients (particularly those on HD) have inadequate amounts of available iron to satisfy the increased demands of the bone marrow.[43] Even before the introduction of ESA therapy, many CKD patients were in negative iron balance as a result of poor dietary intake, poor appetite, and increased iron losses from occult and overt blood losses (see Chapter 86). Losses in HD patients are up to 5 or 6 mg/day, compared with 1 mg in healthy individuals, and this may easily exceed the absorption capacity of the gastrointestinal tract, particularly when there is any underlying inflammation. Iron absorption capacity in patients with CKD is considerably lower than in nonuremic individuals, particularly in the presence of systemic inflammation, and this is mediated by hepcidin upregulation.[9] For this reason also, traditional oral iron therapy (e.g., with ferrous sulfate) is ineffective in many CKD patients, and parenteral iron administration is required, particularly in those receiving HD.[43] However, recently, a newer preparation of oral iron (ferric citrate) that shows greater absorption of iron from the gut has become available in the United States and Japan, and the role that ferric citrate may play in iron management in CKD awaits further elucidation.

An inadequate supply of iron to the bone marrow may be caused by an absolute or a functional iron deficiency.[43] Absolute iron deficiency occurs when there are low whole-body iron stores, as indicated by a serum ferritin level less than 30 ng/ml. Functional iron deficiency occurs when there is ample or even increased storage iron but the iron stores fail to release iron rapidly enough to satisfy the demands of the bone marrow. Several markers of iron status are available, but none of them is ideal (Table 82.3). Serum ferritin is a marker of storage iron but is spuriously raised in inflammatory conditions and liver disease. TSAT is a function of the circulating serum iron in relation to the total iron-binding capacity and is often regarded as a better measure of available iron; however, levels can be highly fluctuant because of significant diurnal variation in the measurement of serum iron.[43] The percentage of hypochromic RBCs and the CHr are RBC and reticulocyte parameters, respectively, that are indirect measures of how much iron is being incorporated into the newly developing or mature RBC. No one measure of iron status is usually adequate to exclude iron deficiency, and the recommended levels for these measures are based on limited scientific evidence. Functional iron deficiency is usually diagnosed when there is a normal or increased ferritin level and a reduced TSAT (<20%) or increased hypochromic RBCs (>10%). The KDIGO guidelines on renal anemia management suggest a trial of iron in CKD patients with anemia who are not on iron and ESA therapy and in whom an increase in Hb concentration is desired and in patients on ESA therapy in whom an increase in Hb concentration or a decrease in ESA dose is required when TSAT is 30% or lower and ferritin level is 500 ng/ml or lower[14] (see Table 82.3). Levels of ferritin above this threshold usually do not confer any clinical advantage and may exacerbate iron toxicity. The optimal TSAT is above 20% to 30% to ensure a readily available supply of iron to the bone marrow. No upper limits of ferritin or TSAT were specified in the KDIGO anemia guidelines, largely because there is no robust evidence to determine a threshold beyond which harm or loss of efficacy supervenes. However, until more informative data become available, the treating nephrologist would be well advised to exercise caution in administering intravenous iron to patients with ferritin levels above 800 ng/ml or TSAT above 30%. Several studies support maintaining the percentage of hypochromic RBCs at less than 6% and the CHr at greater than 29 pg/cell. Other measures of iron status, such as serum transferrin receptor levels and erythrocyte zinc protoporphyrin levels, are mainly research tools.

TABLE 82.3 Recommended Iron Status Levels in CKD

Test	Recommended Range
Serum ferritin	100-500 μg/l (CKD) 200-500 μg/l (HD)
Transferrin saturation	20%-40%
Hypochromic red cells	<10%
Reticulocyte hemoglobin content (CHr)	>29 pg/cell
Serum transferrin receptor	Not established
Erythrocyte zinc protoporphyrin	Not established

CKD, Chronic kidney disease; *HD,* hemodialysis.

Oral iron is generally poorly absorbed in uremic individuals, and there is a high incidence of gastrointestinal side effects. Intramuscular administration of iron is not recommended in CKD, given the enhanced bleeding tendency, the pain of the injection, and the potential for brownish discoloration of the skin. Thus intravenous administration of iron has become the standard of care for many CKD patients, particularly those receiving HD.[43] Several intravenous iron preparations are available worldwide, including iron dextran, iron sucrose, iron gluconate, and the newer iron preparations ferric carboxymaltose, ferumoxytol, and iron isomaltoside 1000. The last three iron preparations allow higher doses of intravenous iron to be administered more rapidly, without the need for a test dose. All of the iron preparations contain elemental iron surrounded by a carbohydrate shell, which allows them to be injected intravenously. The lability of iron release from these preparations varies, with iron dextran being the most stable and iron gluconate being the least stable. Iron is released from these compounds to plasma transferrin and other iron-binding proteins and is then taken up by the reticuloendothelial system.

In HD patients, it is easy and practical to give low doses of intravenous iron (e.g., 10 to 20 mg) at every dialysis session or, alternatively, 100 mg weekly. In PD and nondialysis CKD patients, however, such low-dose regimens are impractical and larger doses may be administered. The more stable the iron preparation, the larger the dose administration rate that can be used. For example, 1 g of iron dextran may be given by intravenous infusion, whereas the maximum recommended dose of iron gluconate is 125 mg. The usual dose of ferumoxytol is 510 mg, whereas up to 1 g of ferric carboxymaltose or iron isomaltoside 1000 may be given as a single administration. All intravenous iron preparations carry a risk for immediate hypersensitivity reactions, which may be characterized by hypotension, dizziness, and nausea. These reactions are usually short-lived and caused by too large a dose given in too short a time. Iron dextran also carries the risk for acute anaphylactic reactions because of preformed dextran antibodies, although this was largely a problem with the high molecular weight intravenous iron dextran preparations, which have now been withdrawn from the market. Other, longer term concerns about intravenous administration of iron include the potential for increased susceptibility to infections and oxidative stress. Much of the scientific evidence for this has been generated from in vitro experiments, the clinical significance of which is unclear.[43]

Despite these concerns, the lack of efficacy of traditional oral iron preparations in HD patients has resulted in the widespread use of intravenous iron to correct the negative iron balance in this patient population. In general, the greater the use of intravenous iron, the lower is the dose requirement of ESA therapy; however, the optimum balance between intravenous iron and ESA therapy remains unknown. This gap in knowledge may be partly addressed by the ongoing PIVOTAL RCT, which is comparing a more liberal use of intravenous iron versus a restrictive policy in 2141 HD patients recruited across 50 sites in the United Kingdom.[44]

In nondialysis patients, both oral and intravenous iron may be used and there are advantages and disadvantages for each route of administration, which have been compared in two recent RCTs. The FIND-CKD study showed that both routes of administration were effective in this patient population, although higher dose intravenous iron resulted in a faster and greater rise in Hb, with no safety concerns.[39] The REVOKE study, however, suggested that the rate of cardiovascular- and infection-related serious adverse events was greater in the intravenous iron treatment group compared with the oral iron group.[45] The reasons for these discrepant findings remain unknown. Thus the physician has to balance the low costs and convenience of oral iron treatment with known poor adherence to treatment, gastrointestinal side effects, and reduced efficacy; intravenous iron on the other hand requires special facilities and set-up for administration and carries a very small risk for hypersensitivity reactions and potential additional risks.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is *false* regarding the characteristics of renal anemia?
   - **A.** The red blood cells (RBCs) produced are usually normochromic and normocytic.
   - **B.** There is usually no associated leukopenia or thrombocytopenia.
   - **C.** The reticulocyte count is usually around 40,000 to 50,000/μl of blood.
   - **D.** Serum erythropoietin levels are usually within the normal range.
   - **E.** The RBC life span is usually normal.
2. Which of the following statements is *false*?
   - **A.** Dose requirements of epoetin are generally 20% to 30% less when the agent is administered subcutaneously compared with intravenously.
   - **B.** Erythropoiesis-stimulating agent (ESA) therapy should be used with caution in patients with previous or current malignancy.
   - **C.** Patients who are hyporesponsive to ESA therapy have a worse prognosis than those who do respond.
   - **D.** The defined upper dose limit of epoetin is 60,000 IU/wk because it is known that cardiovascular toxicity occurs above this dose level.
   - **E.** Angiotensin-converting enzyme (ACE) inhibitors may confer resistance to ESA therapy in some patients.
3. Which of the following statements is *false* regarding the TREAT study?
   - **A.** Patients receiving darbepoetin alfa were randomized to either a target hemoglobin (Hb) of 13 or a target Hb of 9 g/dl.
   - **B.** Patients randomized to a target Hb of 13 g/dl had a small increase in quality of life compared with the control arm.
   - **C.** There was a significant reduction in the use of RBC transfusions in patients randomized to a target Hb of 13 g/dl.
   - **D.** There was a doubling of the rate of stroke in patients randomized to a target Hb of 13 g/dl.
   - **E.** There was a significant increase in cancer-related mortality in the subset of patients with a history of malignancy who were randomized to a target Hb of 13 g/dl.
4. Which of the following statements is *true* regarding intravenous iron supplementation?
   - **A.** All intravenous iron preparations require a test dose before their first administration, as per their product label.
   - **B.** All the newer intravenous iron preparations (ferumoxytol, ferric carboxymaltose, and iron isomaltoside 1000) have the advantage that up to 1 g may be administered as a single dose.
   - **C.** Intravenous iron preparations vary in their lability and speed of iron release from the carbohydrate shell, with iron gluconate being the most stable and iron dextran the least stable compound.
   - **D.** Intravenous iron may improve the anemia of chronic kidney disease in up to 30% of patients not receiving ESA therapy who have a low ferritin level.
   - **E.** Hypersensitivity reactions are more common with low molecular weight iron dextrans than with high molecular weight iron dextran compounds.

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Other Blood and Immune Disorders in Chronic Kidney Disease

Matthias Girndt, Gunnar H. Heine

IMMUNE DYSFUNCTION

Patients with chronic kidney disease (CKD) have a high morbidity and mortality as a result of infection. This is in part directly caused by alterations in the immune system, although multiple other factors are involved.

Bacterial Infections

Infections are a major cause of hospitalization in patients with CKD; infection-related hospitalization rates are at least three to four times (nondialysis CKD) or eight times (dialysis) higher than in individuals with normal renal function.[1] The number of days spent in hospital for infections has slightly decreased over the last decade. Nevertheless, they are still higher than those for cardiovascular disease (4 vs. 2.2 days per patient year[1]). Infection is also an important cause of mortality, accounting for 8% of deaths in dialysis patients. Pulmonary infections and infections of the genitourinary system in particular increase with decreasing renal function. For example, patients with CKD stage 4 have a 15-fold higher risk for severe pulmonary infections compared with those with an estimated glomerular filtration rate (eGFR >60 ml/min/1.73 m^2). Furthermore, mortality from pneumonia is markedly enhanced by concurrent CKD.[2]

In hemodialysis (HD) patients, bloodstream infections are another major cause of infection-related hospitalization, particularly in patients with central venous catheters as dialysis access.[3] Catheter-based HD is among the major risk factors for the development of bacterial endocarditis. More than 50% of cases of bacteremia are caused by *Staphylococcus aureus*. Nevertheless, there is also a relevant rate of gram-negative bacteremias in dialysis patients, indicating that contamination or infection of the dialysis access is not the only cause for bloodstream infection.

The high incidence of bacterial infection in CKD patients may be one clinical consequence of immune dysfunction; another is atypical clinical presentations of infections such as the lack of fever in 20% to 40% of bacteremic patients. When bacteremia is suspected, blood cultures should be obtained frequently. Another aspect of immune dysfunction is the high rate of false-negative tuberculin (Mantoux) skin tests with anergic skin reactions in the presence of positive interferon-γ release assays (IGRA tests), indicating impaired T-lymphocyte function.[4]

However, other factors besides immune dysfunction also predispose to infection in persons with CKD. Thirty-nine percent of patients with end-stage renal disease reported by the U.S. Renal Data System are above 65 years of age,[1] and in other countries this fraction exceeds 50%. Besides their age, many CKD patients have underlying renal or extrarenal autoimmune disease that requires therapeutic immunosuppression and other comorbidities that facilitate infection such as diabetes or heart failure. Dialysis patients and patients with the cardiorenal syndrome often have excess pulmonary fluid, which may impair alveolar bacterial clearance and contribute to the risk for pneumonia. Repeated breaks in the skin barrier by cannulation provide opportunity for bacterial invasion. Finally, dialysis patients frequently receive intravenous iron preparations, and iron overload is a risk factor for bacterial infection as a result of inhibition of monocyte and macrophage function.

Viral Infections

Viral hepatitis has been a scourge of dialysis ever since renal replacement therapy (RRT) became a routine treatment. Only rigorous standard hygienic precautions and active vaccination against hepatitis B virus (HBV) made large-scale HD safe. However, impaired immune defense was only one among other causes for the high prevalence of viral hepatitis in this patient group. The viruses can be easily transmitted nosocomially in HD patients without proper precautions. Nevertheless, the early outbreaks of HBV infection showed an abnormal clinical course related to the immune defect in CKD.[5] The acute infection could sometimes only be detected by measurement of transaminases. The clinical syndrome of icterus, subfebrile temperatures, and malaise, which is typical for patients with normal renal function, was missing. The majority of affected dialysis patients developed chronic persistent infection, which occurs in only 10% of patients with intact renal function.

The clinical manifestations of HCV infection are not significantly influenced by the immune deficiency of renal failure. The infection usually runs a rather subclinical course and becomes chronic even in the absence of CKD.

Vaccinations in Chronic Kidney Disease

Immune deficiency leads to a high rate of nonresponse to hepatitis B vaccination. Dialysis patients should always receive double-dose vaccination and extended vaccination protocols (Fig. 83.1), but even with the most recent vaccines some 20% of patients do not develop protective antibody levels.[6] This impaired response led to the development of specifically adjuvanted vaccines or intracutaneous application protocols[7] with improved efficiency in former nonresponders.

Other vaccinations are also affected by the immune defect in CKD. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[8] recommend annual influenza vaccinations. Studies comparing vaccination efficiency in patients with CKD and healthy individuals have methodologic limitations; therefore the extent to which immune dysfunction compromises these vaccination results is not clear. Most likely, the efficacy is lower in dialysis patients. A recent systematic review on the protective effects with regard to hard end-points such as mortality or hospitalization pointed out that the universal recommendation to vaccinate—albeit very plausible—has a weak evidence base.[9]

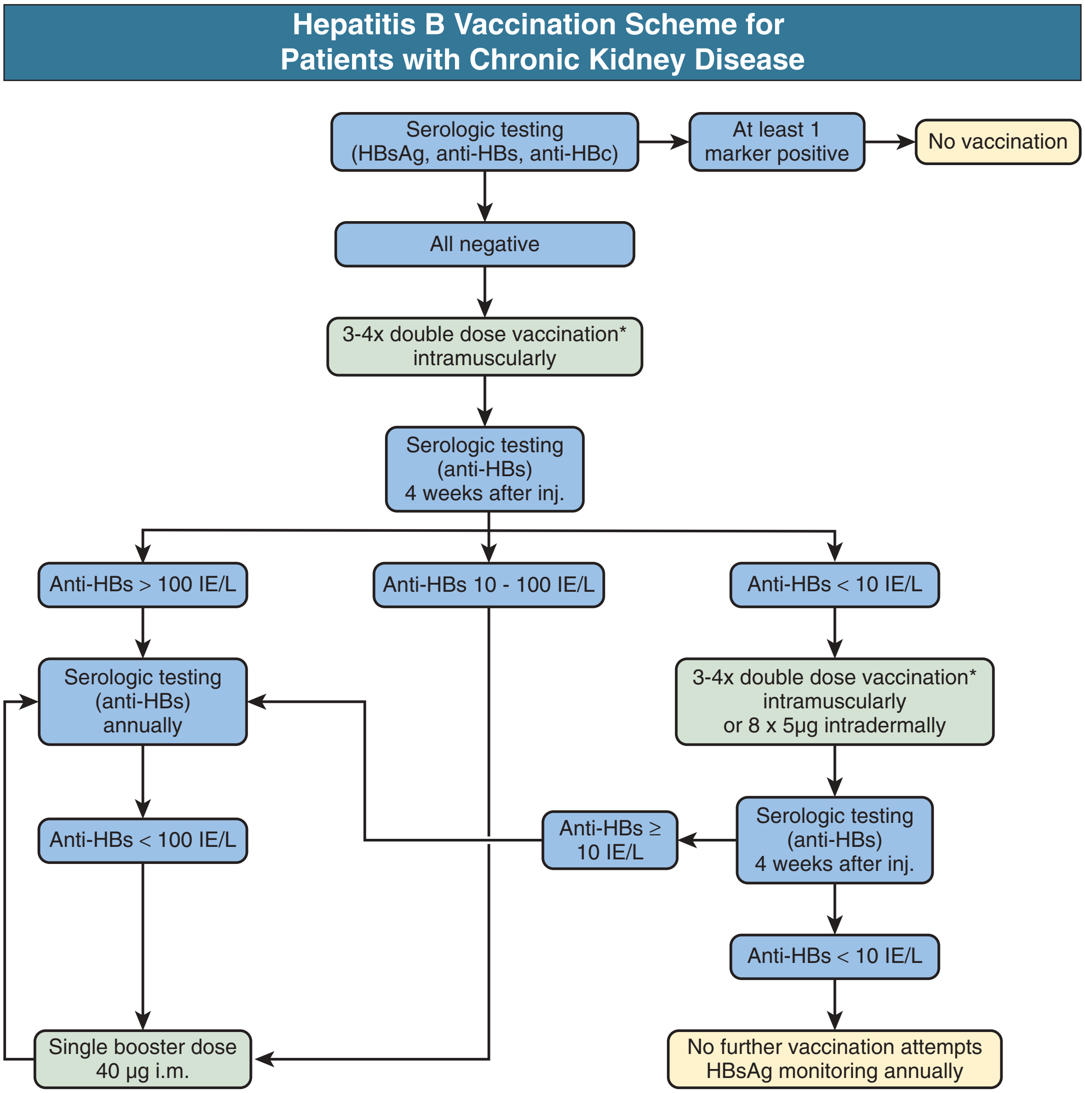
Hepatitis B Vaccination Scheme for
Patients with Chronic Kidney Disease
Serologic testing (HBsAg, anti-HBs, anti-HBc)
At least 1 marker positive
No vaccination
All negative
3-4x double dose vaccination* intramuscularly
Serologic testing (anti-HBs) 4 weeks after inj.
Anti-HBs > 100 IE/L
Anti-HBs 10 - 100 IE/L
Anti-HBs < 10 IE/L
Serologic testing (anti-HBs) annually
3-4x double dose vaccination* intramuscularly or 8 x 5µg intradermally
Anti-HBs < 100 IE/L
Anti-HBs ≥ 10 IE/L
Serologic testing (anti-HBs) 4 weeks after inj.
Anti-HBs < 10 IE/L
Single booster dose 40 µg i.m.
No further vaccination attempts HBsAg monitoring annually

Fig. 83.1 Hepatitis B vaccination scheme for patients with chronic kidney disease (CKD). *The schedule varies with different vaccine preparations.

In contrast to antiviral vaccinations, those against bacteria appear to be less influenced by CKD. Vaccination against pneumococcal infections is universally recommended[8] for adults with eGFR less than 30 ml/min/1.73 m^2. Evidence of efficacy in terms of antibody titers comes from very old studies or series with small patient numbers. Likely, maximum antibody titers are lower and protection lasts shorter in CKD patients,[10] but data on hospitalization or mortality can be derived only from observational studies.[11] Because multiple vaccine preparations are available, the congruence of local epidemiology and the vaccine coverage should be considered (Fig. 83.2). Newer conjugate vaccines have a rather narrow spectrum of serotype coverage while being highly effective in inducing seroprotection; thus there is an argument to vaccinate CKD patients sequentially with conjugate vaccine first, followed in 6 to 12 months by the broad polysaccharide vaccine. Revaccination with the polysaccharide vaccine is recommended after 6 years.

Further recommendations for vaccination in CKD are given in Table 83.1.

TABLE 83.1 Vaccination Recommendations for Adult Patients With Chronic Kidney Disease

Vaccination Against	Recommendation
Hepatitis B virus (HBV)	All patients susceptible to HBV infection, double dose (see Fig. 83.1)
Influenza	Annually according to WHO recommendation, standard dose
Streptococcus pneumoniae	All patients, conjugate vaccine, can be boostered by polysaccharide vaccine at 6 mo, revaccination after 6 y
Tetanus	All patients according to recommendations for general population, standard dose
Diphtheria	All patients according to recommendations for general population, standard dose
Hepatitis A	Not routinely indicated, can be given for travel

Modified from reference 49.
WHO, World Health Organization.

INFLAMMATION

Chronic inflammation is typical for patients with CKD 4 or 5 on RRT, and C-reactive protein (CRP) and plasma cytokines increase steadily

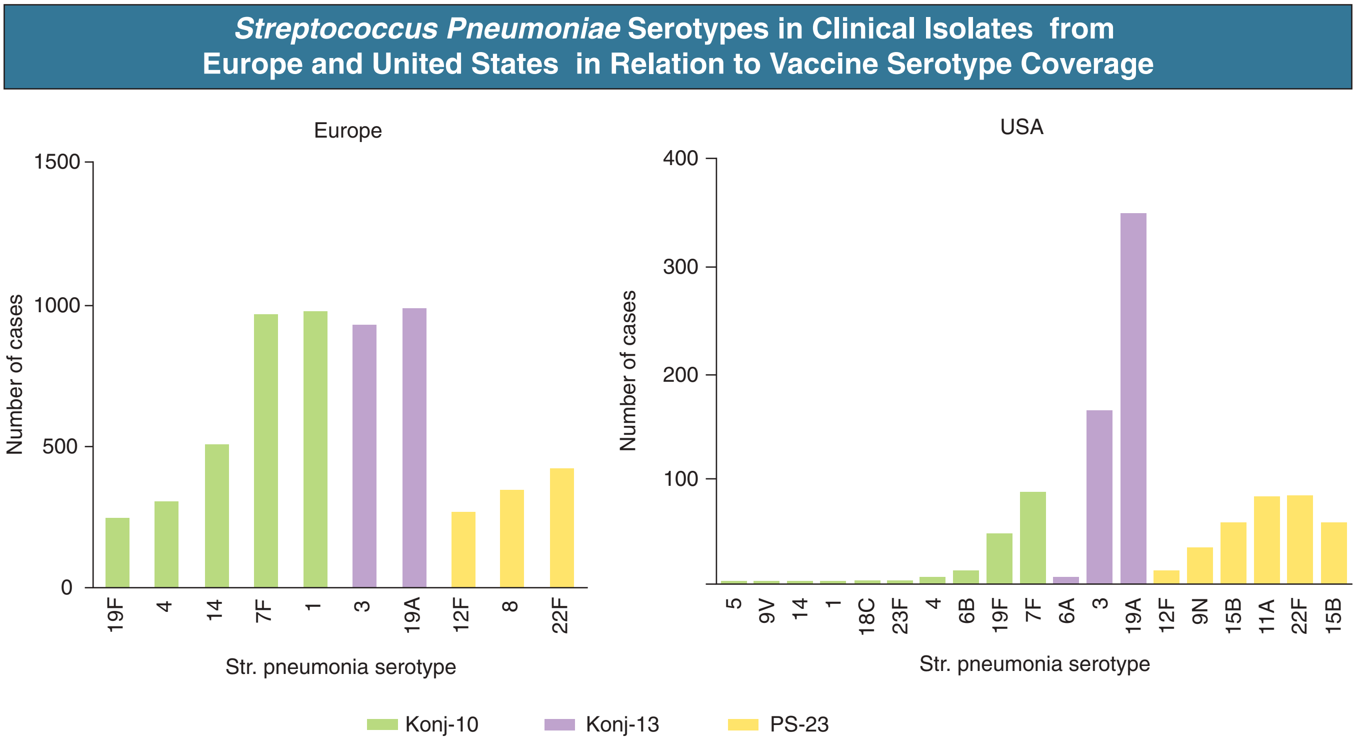

Fig. 83.2 *Streptococcus pneumoniae* **serotypes in clinical isolates (as of 2010) from Europe (European Center of Disease Control) and United States (Centers for Disease Control and Prevention) in relation to vaccine serotype coverage.** Conj-10: 10-valent conjugate vaccine; Conj-13: 13-valent conjugate vaccine; PS-23: 23-valent polysaccharide vaccine. Low isolate numbers for the serotypes covered by Conj-10 in the United States are result of successful vaccination programs.

with every stage of CKD. The majority of HD and peritoneal dialysis patients periodically or permanently have CRP values above the normal limit in the absence of clinical infection.[12]

Causes of Inflammation

Although early research in this field focused on dialysis membrane bioincompatibility, contamination of dialysis fluids, or vascular access as causes of inflammation, chronic inflammation also occurs in patients with CKD stages 3 and 4. One important reason may be the renal clearance of circulating proinflammatory cytokines.[13] Impaired kidney function leads to prolonged cytokine serum half-life, thus enhancing and prolonging inflammatory episodes that usually would have abated quickly.

At least 30% of patients with advanced CKD have diabetes mellitus, a comorbidity that promotes inflammation both by itself and through diabetic complications such as ulcers. In addition, many patients with CKD have poor dental health and periodontitis is associated with systemic inflammation.[14]

Whether inflammation is also related to classic uremic toxicity remains a matter of debate. Typical toxins with increased plasma levels are indoxyl sulfate, paracresyl sulfate, and trimethylamine N-oxide (TMAO). Across stages of CKD, plasma levels of TMAO show a positive correlation with inflammatory markers, and both decrease after renal transplantation.[15] Several studies show that serum levels of indoxyl sulfate or paracresyl sulfate increase with renal dysfunction in parallel with inflammatory markers; however, a causal relationship remains to be proven.

The extent of inflammation is at least in part controlled by the genetic predisposition of the individual. This may be clinically relevant in patients with CKD because inherited single-nucleotide polymorphisms in the gene of the antiinflammatory cytokine interleukin-10 (IL-10) influence the quantity of its production in response to inflammatory stimuli and thus the way a patient can contain and limit inflammation.[16]

Consequences of Inflammation

Inflammation is closely associated with the occurrence of CV complications (reviewed in Chapter 81) and immune dysfunction. When using the response to HBV vaccination as a surrogate for clinical immune function, there is a close correlation between inflammation and decreased immunity. This is confirmed by the finding that the IL-10 gene polymorphism, which influences the extent of inflammation, also predicts vaccination responses in dialysis patients.[16]

IMMUNE CELL ABNORMALITIES

Monocytes

Monocytes are bone marrow–derived cells with specific functions in immune surveillance and antigen presentation. During their differentiation, they briefly circulate in the blood, produce cytokines, and then migrate into tissues to become macrophages.[17] Injury and infection lead to rapid enhancement of circulating monocyte numbers, which then migrate to the site of tissue injury and initiate the local immune response. Monocyte-derived macrophages are constituents of atherosclerotic plaques, and imaging studies have revealed that monocytes patrol along the vascular endothelium, where they detect endothelial defects.[18]

Monocyte subpopulations are defined by the expression of the lipopolysaccharide (LPS) receptor CD14 and the immunoglobulin Fcγ receptor CD16.[19] The classic monocytes only express CD14 and account for some 80% of all circulating monocytes in healthy individuals;

intermediate monocytes express both CD14 and CD16 (~5% to 7%), and nonclassic monocytes express high levels of CD16 while showing limited staining for CD14 (~10% to 12%). Genetic analysis revealed that $CD14^{++}CD16^{+}$ intermediate monocytes particularly express markers related to antigen presentation, inflammation, and angiogenesis.[20]

In CKD, the intermediate and nonclassic monocyte subtypes are significantly expanded. This finding is related to the CV risk[21]; patients with the highest rate of $CD14^{++}CD16^{+}$ monocytes in blood had the lowest CV event-free survival.

Mouse models confirm differences between monocyte subpopulations in their ability to invade atherosclerotic plaques.[22] In CKD the expansion of proinflammatory monocyte subsets and their epidemiologic association with CV events make a causal role of these cells for atherosclerotic disease likely. Furthermore, monocytes also express components of the angiotensin system. The angiotensin-converting enzyme (ACE) that turns angiotensin I (Ang I) into vasoactive angiotensin II (Ang II) is expressed in atherosclerotic plaques and colocalizes with monocyte-derived macrophages.[23] ACE is also expressed on circulating monocytes, particularly on those with the $CD14^{++}CD16^{+}$ phenotype.[24] Dialysis patients with high expression of ACE on intermediate monocytes have a dramatically enhanced CV mortality risk.[24]

Expression of ACE on monocytes is strongly upregulated by the uremic milieu.[25] A consequence of this might be that monocytes transmigrate into the subendothelial space of arteries and provide high levels of ACE in the atherosclerotic plaque. The local production of Ang II through ACE is thought to contribute to further leukocyte attraction, inflammatory activation, and plaque growth. In addition, expression of ACE on monocytes alters their functional capacities. In vitro assays show that a higher expression of ACE leads to stronger endothelial adhesion and transmigration of the monocytes. This effect appears to be mediated via locally produced Ang II, because adhesion and transmigration could be inhibited by losartan.[25]

Monocytes also express ACE-2, a peptidase that degrades Ang II to Ang1-7, a vasodilatory peptide. Whereas CKD leads to the overexpression of ACE, the ACE-2 enzyme is downregulated compared with healthy individuals.[26] Experimental overexpression of ACE-2 in a rodent model of atherosclerosis limited the progression of disease. These findings suggest that the uremic milieu alters monocyte function in a strongly proatherogenic way.

Monocytes are closely related to circulating blood dendritic cells. Dendritic cells are mainly found in organs and tissues, where they have strong capabilities in antigen presentation and activation of immune reactions. Their immature precursors circulate in blood in low numbers. There are different subtypes of circulating dendritic cells, but investigators have used different marker sets for their detection. This limits comparison among different studies, so that understanding of dendritic cell quantification and pathophysiology remains limited. There is a relation between elevated numbers of $CD14^{++}CD16^{+}$ monocytes in the blood and the propensity of these cells to differentiate into dendritic cells in cell culture.[27] Other studies[28] found significantly lower numbers of dendritic cells in advanced CKD compared with healthy controls. The finding may be related to CV disease, because studies in patients with coronary heart disease and normal renal function also reported reduced circulating numbers of dendritic cells.

T Lymphocytes

Impaired vaccination responses against viral antigens such as HBV or influenza, as well as reduced skin reaction in the Mantoux test, result from impaired T cell activation. T cells are an important component of the antigen-specific adaptive immune defense. Their activation depends on antigen-presenting cells (APCs) that present foreign antigens with major histocompatibility complex and provide important costimulatory signals. Only T cells with specificity of their T cell receptor toward the particular antigen are activated and proliferate.

Major APCs are dendritic cells and their precursors are monocytes. Early studies showed that proliferative T cell responses are impaired in dialysis patients and this impairment is directly correlated with nonresponses to HBV vaccination. Both replacement of the patient's APCs in in vitro assays with cells from healthy donors and overexpression of costimulatory molecules on the APCs normalize proliferation of T cells, indicating that the major defect leading to reduced T cell activation is in the APC.[29] However, these rather crude assays did not consider T cell subpopulations. Helper T cells express the surface marker CD4 and interact with various other cell types. The $CD4^{+}$ helper T cell is particularly needed for activation of B cells for antigen-specific seroresponses to viral antigens as in HBV vaccination. The $CD8^{+}$ cytotoxic T cells are important for antiviral defense because they are able to lyse infected host cells. In CKD the relation of $CD4^{+}/CD8^{+}$ T cells is reduced.

$CD4^{+}$ helper cells can be further distinguished into cells that mainly support cellular immune reactions (T helper cells Type 1, Th1) and others that are more important for immunoglobulin production by members of the B cell lineage (Th2). These cell types differ in the pattern of cytokines they produce, with interferon-γ being the major cytokine of Th1 and IL-4 the main cytokine of Th2 cells. CKD leads to a marked deviation of T cell differentiation toward the Th1 phenotype.[30] Most likely the major cause is elevated production of IL-12 by monocytes and APCs in the context of their inflammatory activation.[30]

Another T-lymphocyte subpopulation is regulatory T cells (Tregs) that are important for the downregulation of immune responses once the aim of an antiinfectious response is reached. They prevent ongoing inflammation and the development of autoimmunity. The typical Treg cells originate in the thymus and have a distinct pattern of surface molecule expression. In patients with CKD the number of circulating Treg cells is unaltered, but their capacity to downregulate $CD4^{+}$ helper T cell activity is impaired.[31]

B Lymphocytes

Impaired vaccination efficacy in CKD suggests impaired function of immunoglobulin producing B-lymphocytes and plasma cells; thus a major dysfunction of this cell type might be expected. However, CKD patients have normal circulating immunoglobulin levels. Their B cell lymphopenia is modest and probably not very clinically relevant. It is caused by a higher rate of apoptosis of these cells compared with healthy individuals.[32] Lymphopenia appears to result from reduced numbers of the majority of B cell subpopulations (naïve B cells, memory B cells, etc.).[33] Taken together, the alterations of B-lymphocytes in CKD appear to be less pronounced than alterations of other immune cell types. Impaired vaccination responses are caused by altered interaction of APCs, helper T lymphocytes, and the cytokine network in CKD rather than by abnormalities of B lymphocytes.

Granulocytes

Polymorphonuclear granulocytes (neutrophils) are components of the antigen-independent innate immune system. Their main activity is to kill and phagocytose invading pathogens via numerous enzymes that produce bactericidal substances. Among them are defensins, proteolytic enzymes, and enzymes that produce highly active oxygen species such as hypochlorous acid. In CKD patients these nonspecific defense systems are highly activated and the cells spontaneously release more reactive oxygen species.[34] Inflammation, activation of different cell types, antiinfectious defense, and vascular disease are closely interwoven. Thus the elevation of oxygen species H_2O_2 and malondialdehyde has predictive value for CV events and mortality in CKD.[35]

Another important function of granulocytes is phagocytosis, which is also mildly compromised in CKD.[36]

It is difficult to establish whether these alterations can be improved by dialysis. HD inevitably involves marked contact between blood and foreign surfaces. When cellulose-based membranes were still in use, the activation of the complement system by these membranes led to marked depletion of circulating granulocytes within the first 20 minutes of a dialysis session.[37] Newer synthetic membranes lead to minimal complement activation, and the leukocyte drop is much less pronounced. These findings on immune cells relate to CKD. It is important to consider that some primary diseases, in particular diabetes mellitus, further influence immune cell function.

PLATELET DYSFUNCTION AND PLATELET INHIBITORS IN CHRONIC KIDNEY DISEASE

Normal hemostasis begins with platelet adhesion to vascular endothelium and requires a relatively vasoconstricted vessel wall, integrity of platelet glycoproteins (GPs), and a normal quantity of large molecular weight, multimeric von Willebrand factor (vWF) (Figs. 83.3 and 83.4). Main platelet GPs are GPIb, the platelet receptor for vWF, involved in platelet adhesion, and GPIIb/IIIa, the platelet receptor for fibrinogen, involved in platelet aggregation.

Under static conditions, GPIb and vWF have no affinity for each other. However, these molecules develop a specific affinity for each other at high shear stress, resulting in arterial platelet adhesion. Aggregated fibrinogen-platelet mesh acts as a trap for binding and activation of other plasma clotting factors. The exposure of the preceding clotting factors to tissue factors, present on damaged endothelial cells, catalyzes the conversion of prothrombin to thrombin, which converts fibrinogen to fibrin. Subsequent cross-linking of insoluble fibrin results in a stable hemostatic plug.

Hemorrhagic Diathesis and Uremic Platelet Dysfunction

Patients with CKD have a high risk for bleeding. This hemorrhagic diathesis frequently has cutaneous (easy bruising, ecchymoses, or prolonged hemorrhage from needle puncture or postoperative sites) and mucosal (epistaxis; gastrointestinal or gingival bleeding) manifestations. More dramatic—albeit infrequent—manifestations are hemorrhagic pericarditis/hemopericardium, hemorrhagic pleural effusion/hemothorax, and intracranial and retroperitoneal bleeding.[38]

This hemorrhagic diathesis is not reflected in a prolongation of the prothrombin time or the partial thromboplastin time. Similarly, even though platelet counts may be moderately decreased because of platelet consumption outperforming platelet production, severe thrombocytopenia is rarely seen in uremia; the occurrence of very low platelet counts therefore requires a thorough search for alternative causes.[39] Instead, platelet dysfunction is generally considered as the central contributor to the high bleeding risk, and a high number of pathophysiologic alterations have been suggested to contribute, comprising alterations in platelet function and structure, and extrinsic factors (see Table 83.1). Unfortunately, many studies on platelet functions in CKD date back to early days of clinical nephrology, when clinical care and dialysis treatment were less sophisticated, and when less advanced laboratory methods were available for evaluation of hemostasis. For the various pathophysiologic alterations listed in Box 83.1, controversial data have been published.

In the search for uremic toxins inducing platelet dysfunction, a direct pathologic role of urea can be ruled out because no correlation exists between blood urea levels and bleeding time[40] and individuals

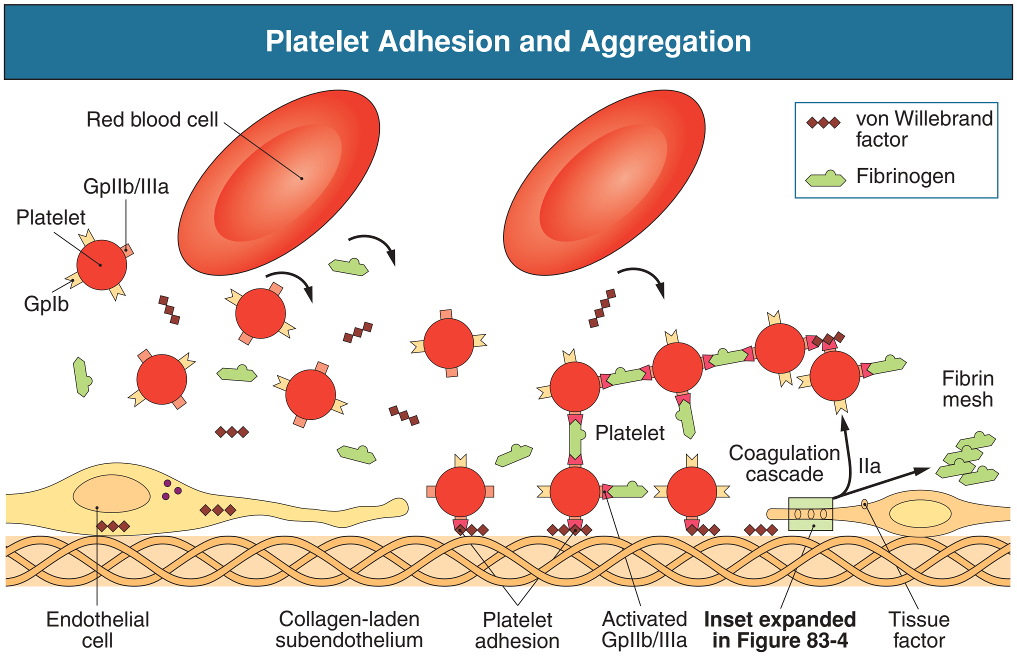

Fig. 83.3 Platelet adhesion and aggregation. Platelets are pushed peripherally toward the vascular wall by red blood cells traversing centrally through the bloodstream. Damage to the vessel wall results in a disruption of the nonthrombogenic endothelial cell lining and exposure of subendothelial structures. Whereas collagen supports initial platelet adhesion (and subsequent aggregation), von Willebrand factor (vWF) deposition on the subendothelium serves as the main anchor for platelet adhesion through platelet GPIb receptor. Postadhesion conformational change in platelet GPIIb/IIIa receptor (fibrinogen or vWF receptor) results in interlinking platelet aggregation.

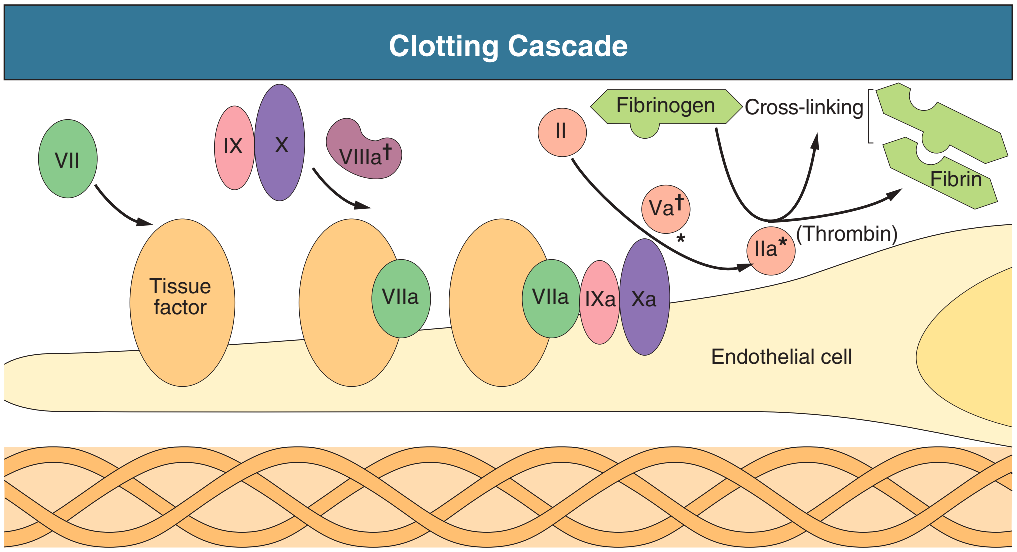

Fig. 83.4 **Clotting cascade.** Expansion of the inset in Fig. 83.3 shows the clotting cascade that takes place at the damaged vessel wall. Exposure of subendothelial tissue factor, present on pericytes and fibroblasts, allows eventual activation of prothrombin (factor II) to thrombin. Thrombin converts fibrinogen to fibrin, activates fibrin cross-linking, stimulates further platelet aggregation, and activates anticoagulant protein C. Naturally occurring anticoagulants antithrombin III, protein C, and protein S help maintain control and counterbalance on coagulation. *Site of anticoagulant effect for antithrombin III. †Site of anticoagulant effect for protein C–protein S complex. (Courtesy James A. Sloand, MD, FACP, FASN, Baxter Healthcare Corporation, Deerfield, Ill.)

BOX 83.1 Proposed Contributors to Platelet Dysfunction in Uremia

Intrinsic Factors That Contribute to Platelet Dysfunction

- Dysfunction of glycoprotein IIb/IIIa
- Abnormal expression of platelet glycoprotein
- Altered release of adenosine diphosphate (ADP) and serotonin from platelet α-granules
- Faulty arachidonic acid and depressed prostaglandin metabolism, decreased platelet thromboxane A2 generation
- Abnormal platelet cytoskeletal assembly with reduced incorporation of actin and diminished association of actin binding proteins (α-actin and tropomyosin) with the cytoskeleton

Extrinsic Factors That Contribute to Platelet Dysfunction

- The action of uremic toxins
- Anemia
- Increased nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) production
- Functional von Willebrand factor abnormalities
- Decreased platelet production
- Abnormal interactions between the platelet and the endothelium of the vessel wall

Modified from Berns JS, Coutre S. Platelet dysfunction in uremia. UpToDate, http://www.annemergmed.com/article/S0196-0644(15)00034-7/pdf; reference 38.

with high serum urea levels but otherwise normal renal function have no bleeding tendency.[41]

Among the different extrinsic factors that contribute to platelet dysfunction, the contribution of anemia has gained particular interest. Physiologically, erythrocytes occupy the center of a vessel, displacing platelets from the axial flow toward the vessel walls. This allows platelets to adhere to injured endothelial cells and initiate the formation of a platelet plug. In anemia, platelets are more dispersed, which impairs their adherence to the endothelium. Moreover, in CKD, red blood cells may affect coagulation by releasing adenosine diphosphate (ADP), by inactivating PGI_2, and by scavenging nitric oxide (NO), which are all central regulators of platelet function.[39]

Treatment of Uremic Platelet Dysfunction

Despite the previously discussed pathophysiologic considerations, few data establish the extent to which initiation of RRT reduces the risk for bleeding in CKD.

In the early decades of HD, the interaction of blood with cellulose-based dialyzer membranes resulted in complement activation and transient thrombocytopenia during the dialysis procedure. When using more biocompatible dialyzer membranes, such complement-induced platelet reduction no longer has clinical relevance. Nonetheless, HD treatment may still affect bleeding disorders; while potentially removing uremic toxins, which affect platelet function, it requires systemic anticoagulation and exposes patients to the potential risk for heparin-induced thrombocytopenia (HIT). Moreover, HD may disrupt the platelet cytoskeleton, induce repeated platelet stress, decrease the percentage of RNA-rich platelets, and reduce the percentage of available reticulated platelets.[42] As RNA-rich and reticulated platelets are more able to be activated, the accumulation of less RNA-rich and less reticulated platelets indicates the presence of less reactive platelets. Although treatment of anemia may improve some parameters of platelet dysfunction,[42] it has not been demonstrated to ameliorate bleeding or risk for bleeding.

In summary, dialysis and anemia treatment will not completely normalize platelet function. Therefore drug treatment should be considered for those patients who have active bleeding or are scheduled to undergo an invasive diagnostic or therapeutic procedure with bleeding risk.

Desmopressin

Desmopressin (1-deamino-8-D-arginine-vasopressin, DDAVP) is a synthetic derivative of the antidiuretic hormone with little vasopressor activity. It acts by stimulating the release of large factor VIII:von Willebrand factor multimers from endothelial cells into the plasma and potentially by increasing the membrane glycoprotein expression of platelets.

At a dose of 0.3 mcg/kg (if given intravenously [in 50 ml of saline over 15 to 30 minutes] or subcutaneously]) or 3 mcg/kg (if given intranasally), desmopressin improves the bleeding time over the subsequent 4 to 8 hours. Typical side effects include water retention, hyponatremia, moderate thrombocytopenia, facial flushing, mild transient headache, nausea, abdominal cramps, and mild tachycardia; thrombotic events are rarely observed.[38]

Although its efficacy on laboratory measures of platelet function is undisputed, its clinical efficacy for preventing or treating bleeding remains unproven. Additionally, depletion of endothelial stores of the factor VIII:von Willebrand factor multimers after a second DDAVP injection may result in tachyphylaxis, which precludes its chronic use.

Cryoprecipitate

In many uremic patients, cryoprecipitate may improve the bleeding time within 1 hour after infusion. This effect is supposed to be mediated by the provision of factor VIII:von Willebrand factor multimers, fibrinogen, and by other factors that enhance platelet aggregation. However, this effect is short-lasting (4 to 24 hours). Moreover, cryoprecipitate may have infectious, hemorrhagic and anaphylactic complications, and not all patients respond to cryoprecipitate.[38,39,42] Thus use of cryoprecipitate should be limited to patients with life-threatening bleeding who are resistant to treatment with desmopressin and blood transfusions.

Tranexamic Acid

As an antifibrinolytic agent, tranexamic acid (TXA) is licensed for treatment of heavy bleeding, as well as before dental interventions in patients with coagulopathies. Its use in CKD has been reported in several (mostly small) cohort studies, which often focused on surrogate markers of hemorrhagic diathesis. Therefore TXA may be considered for life-threatening bleeding events in CKD patients. However, it should be reserved for those in whom other treatments have failed to control bleeding, because renal excretion is the main route of TXA clearance. TXA has an unpredictable pharmacokinetic profile in advanced CKD patients, who are at particular risk for neurologic side effects of TXA (i.e., seizures).[43]

RECOMBINANT ACTIVATED FACTOR VII

Recombinant activated factor VII (rFVIIa) was developed for treatment of hemorrhage in individuals with hemophilia with antibodies inactivating factor VIII or IV. Because of the central role of activated factor VII in coagulation, rFVIIa has been used off label in a variety of other severe bleeding disorders, including some case reports that claimed successful use of rFVIIa for treatment of bleeding in CKD patients.[39] This very limited evidence, together with a substantial risk for thromboembolic events, mandates very prudent use of rFVIIa, which should be considered only in very severe bleeding when other interventions have failed.

ESTROGENS

Estrogens may improve bleeding time in CKD patients in a dose-dependent manner. Their mode of action involves a reduced production of L-arginine, which is a precursor of NO. Thus estrogens may lower elevated NO production in CKD patients and subsequently reduce NO-induced guanylyl cyclase stimulation and cyclic guanosine monophosphate (cGMP) synthesis, which will finally increase thromboxane A and ADP availability. Estrogens may additionally lower hemorrhagic diathesis by affecting production of coagulation factors and their inhibitors.

Estrogens may be given intravenously, orally, or cutaneously. Compared with other approaches, estrogen treatment may affect bleeding tendency for a prolonged time. However, its long-term safety has again not been assessed in prospective studies.

IMPLICATIONS FOR ANTIPLATELET AGENT THERAPY

Uremic platelet dysfunction and the increased bleeding risk also implies that treatment with antiplatelet agents—particularly aspirin, clopidogrel, prasugrel, and ticagrelor—may induce more bleeding events among CKD patients than in the general population. At the same time, CKD patients are at high CV risk and use of aspirin or other antiplatelet agents may reduce their risk for myocardial infarctions and stroke.

A recent KDIGO guideline[8] recommends that "adults with CKD at risk for atherosclerotic events be offered treatment with antiplatelet agents unless there is an increased bleeding risk that needs to be balanced against the possible CV benefits." However, it remains unclear how to identify the patients who may benefit from antiplatelet agents, and risk scores from the general population work poorly among CKD patients.

Antiplatelet agents should not routinely be prescribed to all CKD patients because the increased risk for major bleeding appears to outweigh the CV benefits, at least in CKD patients with low risk for atherosclerotic events.[44] Their use among CKD patients with overt atherosclerotic vascular disease is strongly recommended (see Chapter 81). However, dual-antiplatelet therapy should be limited to the very early period after acute myocardial infarction or after coronary stenting among CKD patients, whose bleeding risk with dual-antiplatelet therapy is much higher than in patients with intact renal function.

CIRCULATING COAGULATION FACTORS

Despite their elevated bleeding risk, patients with advanced CKD also may show features of a hypercoagulable state. Although general measures of the coagulation system—prothrombin time and partial thromboplastin time—are within normal ranges, venous thromboembolism (VTE) occurs more frequently in patients with low GFR and/or high albuminuria than among individuals with intact kidney function. A variety of factors may contribute, which include elevated levels of factor VIII and vWF, and a variety of comorbidities, including immobilization, congestive heart failure, and obesity. Iatrogenic factors may additionally play a part in CKD-associated hypercoagulation, such as drug treatment (erythropoietin, corticosteroids), intravascular interventions, and devices.

THERAPEUTIC INTERVENTION

Components of the coagulation system are targets of many drugs for prevention or treatment of thrombotic disease, including unfractionated and low molecular weight heparin (LMWH), vitamin K antagonists (VKA) and of non–vitamin K antagonist oral anticoagulants (NOAC).

First, unfractionated and LMWH are routinely used during HD for preventing clotting in the extracorporeal circulation. Thus nearly all

HD patients are exposed to potential side effects of heparin, which comprise an increased bleeding risk and some less frequent adverse events, of which the development of HIT is the most serious complication. HIT is a clinical syndrome induced by antibodies that bind to heparin and platelet factor IV complexes on the platelet surface and thereby cause platelet activation. Clinically, HIT often manifests with arterial or venous thrombosis; less frequent complications are venous limb gangrene, adrenal hemorrhagic necrosis, necrotizing skin lesions at heparin injections sites, and acute systemic reactions within a few minutes after exposure to unfractionated heparin or LMWH injections. Of note, many patients have heparin-dependent antibodies without clinically apparent HIT. Therefore, to avoid over-diagnosing HIT, immunologic tests should not be ordered in patients with a low clinical likelihood but focused on patients in whom HIT is suspected clinically (as suggested by the 4T score; Table 83.2). This is of particular importance for HD patients, in whom an incorrect diagnosis may result in the withdrawal of heparin treatment during HD and in the initiation of less established (and more expensive) anticoagulation strategies. In the absence of CKD-specific pathways, the diagnosis of HIT should follow recommendations from the general population. Here, the likelihood of HIT should first be estimated with clinical prediction tools and use of antigen assays for confirmation of HIT antibodies should focus on patients with high and intermediate clinical likelihood (Fig. 83.5). Importantly, these antigen assays for detection of HIT antibodies have a high sensitivity but poor specificity. Wherever available, functional assays (serotonin release assays or heparin-induced platelet activation)

TABLE 83.2 4 Ts Score to Determine the Likelihood of Heparin-Induced Thrombocytopenia (HIT)

	Score = 2	Score = 1	Score = 0
Thrombocytopenia: Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the percent of platelet fall (select only one option)	>50% platelet fall *and* nadir of ≥20 k per uL *and* no surgery within preceding 3 days	>50% platelet fall *but* surgery within preceding 3 days *or* Any combination of platelet fall and nadir that does not fit criteria for score 2 or score 0 (e.g., 30%-50% platelet fall or nadir 10-19)	<30% platelet fall Any platelet fall with nadir <10
Timing (of platelet count fall or thrombosis*) Day 0 = First day of most recent heparin exposure (select only one option)	Platelet fall day 5-10 after start of heparin Platelet fall within 1 day of start of heparin *and* exposure to heparin within past 5-30 days	Consistent with platelet fall days 5-10 but not clear (e.g., missing counts) Platelet fall within 1 day of start of heparin AND exposure to heparin in past 31-100 days Platelet fall after day 10	Platelet fall day 4 or earlier without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae) (select only one option)	Confirmed new thrombosis (venous or arterial) Skin necrosis at injection site Anaphylactoid reaction to intravenous heparin bolus Adrenal hemorrhage	Recurrent venous thrombosis in a patient receiving therapeutic anticoagulants Suspected thrombosis (awaiting confirmation with imaging) Erythematous skin lesions at heparin injection sites	Thrombosis suspected
oTher cause for Thromboycytopenia[†] (select only one option)	No alternative explanation for platelet fall is evident	Possible other cause is evident: Sepsis without proven microbial source Thrombocytopenia associated with initiation of ventilator Other	Probable other cause present: Within 72 h of surgery Confirmed bacteremia/fungemia Chemotherapy or radiation within past 20 days DIC as a result of non-HIT cause Post-transfusion purpura (PTP) Platelet count <20 *and* given a drug implicated in causing D-ITP[‡] (see list) Non-necrotizing skin lesions at LMWH injection site (presumes DTH) Other

See Figure 83.5 for interpretation of score results.

*Timing of clinical sequelae, such as thrombocytopenia, thrombosis, or skin lesions.

[†] Two points if necrotizing heparin-induced skin lesions even if thrombocytopenia not present.

[‡] Drugs implicated in drug-induced immune thrombocytopenia (D-ITP):

Relatively common: Glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban), quinine, quinidine, sulfa antibiotics, carbamazepine, vancomycin.

Less common: Actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins (cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fusidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin, trimethoprim. *NOTE:* This is a partial list.

This table follows the *Antithrombotic Therapy and Prevention of Thrombosis,* 9th ed, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (*Chest.* 2012;141[2 Suppl]:e495S-e530S).

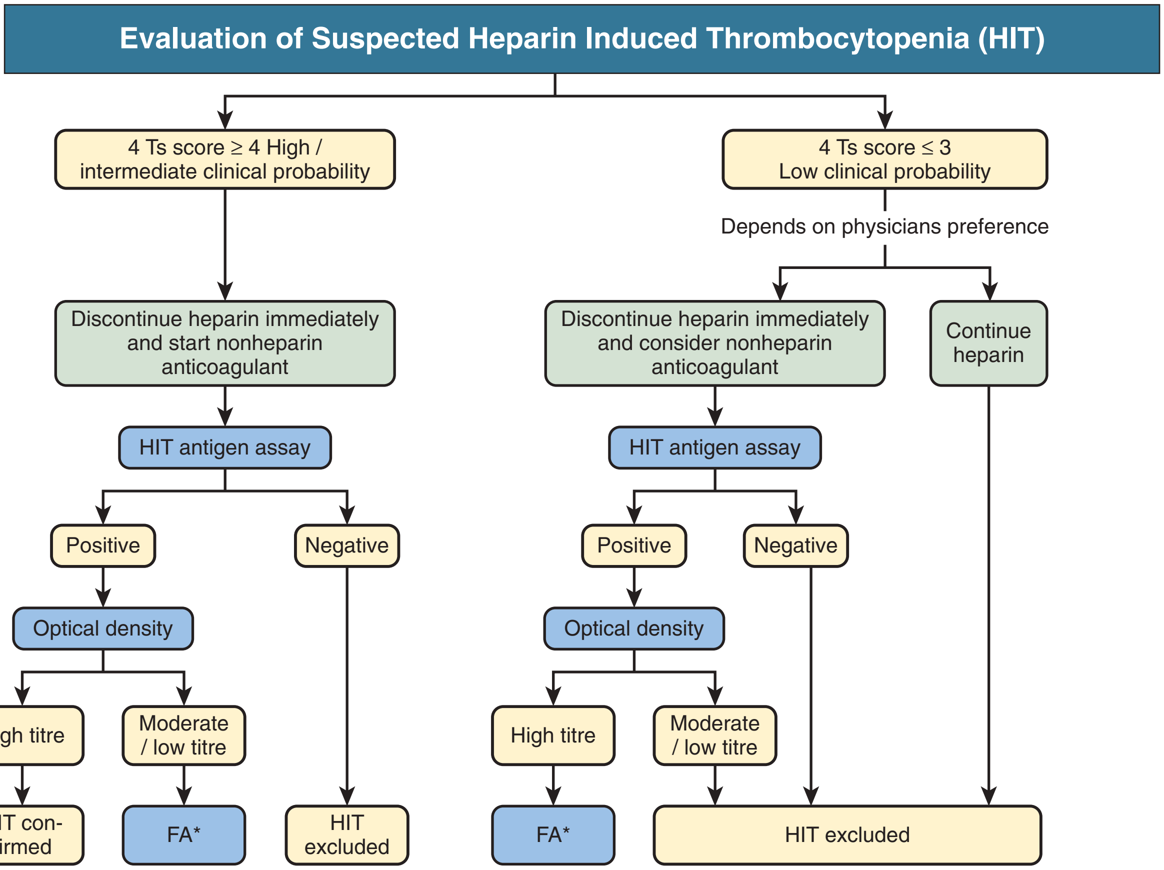
Evaluation of Suspected Heparin Induced Thrombocytopenia (HIT)
4 Ts score ≥ 4 High / intermediate clinical probability
4 Ts score ≤ 3 Low clinical probability
Depends on physicians preference
Discontinue heparin immediately and start nonheparin anticoagulant
Discontinue heparin immediately and consider nonheparin anticoagulant
Continue heparin
HIT antigen assay
HIT antigen assay
Positive
Negative
Positive
Negative
Optical density
Optical density
High titre
Moderate / low titre
High titre
Moderate / low titre
HIT confirmed
FA*
HIT excluded
FA*
HIT excluded

Fig. 83.5 Diagnostic work-up of suspected heparin-induced thrombocytopenia (HIT). Because of the high number of patients with antibodies against heparin without clinical HIT, a diagnostic algorithm is needed to have a high a priori likelihood of HIT before ordering antibody tests. There is no algorithm specific to patients with CKD, and the diagnosis should be made as in patients with normal renal function. *Confirm with functional assay (FA), if available. "4T" refers to a risk score based on four clinical parameters (*t*hrombocytopenia, *t*iming of platelet count fall or thrombosis, *t*hrombosis [or other clinical sequelae], and o*t*her cause for thrombocytopenia; see Table 83.2 for a detailed description).

should be used to confirm positive findings from antigen assays in the majority of patients with suspected HIT.

Once a patient has a high or intermediate clinical probability of HIT, all heparin treatment must be stopped and alternative anticoagulation initiated. The most relevant treatment options are listed in Table 83.3. Of note, no VKA should be initiated at this stage because these agents may reduce activation of anticoagulatory protein C and thus further perpetuate the prothrombotic state.

Additionally, anticoagulants are approved for prevention of thromboembolic stroke in patients with atrial fibrillation, for prevention and treatment of VTE (particularly deep-vein thrombosis and pulmonary embolism), and for prevention of clotting in patients with mechanical heart valves. In the latter case, the need for life-long anticoagulation with VKA is indisputable. Similarly, in patients with proximal deep-vein thrombosis and symptomatic pulmonary embolism, anticoagulation is indicated for a minimum of 3 months. Recommendations on extended anticoagulation are mainly derived from the general population, in whom indefinite anticoagulation with either VKA or NOAC (Table 83.4) may be considered in patients with unprovoked proximal deep-vein thrombosis and symptomatic pulmonary embolism, whereas anticoagulation should be stopped after 3 months in patients with provoked VTE with one or more transient risk factors. In patients with active cancer and VTE, data from the general population suggest indefinite anticoagulation with LMWH. When considering indefinite anticoagulation in patients with advanced CKD, their elevated bleeding risk must be considered.

For patients with advanced CKD, the use of anticoagulants in atrial fibrillation is controversial (see also Chapter 81). In the general population, patients who have one or more risk factors for cerebral stroke or systemic embolization (defined as a CHA_2DS_2-VASc score of ≥1 in men and ≥2 in women) should receive oral anticoagulation. Similarly, use of warfarin (if adjusted to target INR 2.0-3.0) has been shown to reduce stroke risk substantially in patients with CKD 3a/3b.[45] In these patients, NOACs are at least as efficient as VKA for prevention of thromboembolic events, but may cause fewer intracerebral bleeding events. For patients with GFR <30 ml/min/1.73 m^2, few data demonstrate the efficacy (i.e., prevention of thromboembolic events) and safety (i.e., major bleeding events) of either VKA or NOAC because most prospective clinical trials excluded patients with advanced CKD. Moreover, VKA accelerates vascular calcification[46] and possibly also CKD progression, in particular if overdosed.[47] In dialysis patients with atrial fibrillation, retrospective cohort studies yielded conflicting findings on whether oral anticoagulation lowers stroke incidence.[48]

For the time being, patients with atrial fibrillation and at least moderate risk for thromboembolism (defined by CHA_2DS_2-VASc score ≥2 for women, and ≥1 for men) should be offered NOACs if they have

TABLE 83.3 Characteristics of Anticoagulants Used to Treat Patients With Heparin-Induced Thrombocytopenia

Characteristic	Argatroban	Danaparoid	Bivalirudin	Fondaparinux
Target	Thrombin	Factor Xa (predominantly)	Thrombin	Factor Xa
Elimination	Hepatobiliary	Renal	Enzymatic (80%)/renal (20%)	Renal
Approved for patients with HIT*	Treatment/PCI	Treatment	PCI/cardiac surgery	No
Method of administration	IV	IV, SC	IV	SC
Monitoring	aPTT ACT	Anti-Xa level	aPTT ACT or ECT (high doses)	Anti-Xa level
Effect on INR	+++	0	++	0
Immunologic features	None	5% cross-reactivity with HIT Ab†	Potentially cross-reactive with antilepirudin Ab	May cause HIT‡
Antidote available	No	No	No	No
Dialyzable	20 %	Yes	25 %	20 %

*In some countries (check with local health regulatory authorities).

†Clinical significance is uncertain and routine testing for cross-reactivity is not recommended.

‡Case reports only.

Ab, Antibodies; *ACT,* activated clotting time; *aPTT,* activated partial thromboplastin time; *ECT,* ecarin clotting time; *FDA* = U.S. Food and Drug Administration; HIT, heparin-induced thrombocytopenia; *INR,* international normalized ratio; *IV,* intravenous; *PCI,* percutaneous coronary intervention; *SC,* subcutaneous.

This table follows the *Antithrombotic Therapy and Prevention of Thrombosis,* 9th ed, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (*Chest.* 2012;141[2 Suppl]:e495S-e530S).

TABLE 83.4 Absorption and Metabolism of Novel Oral Anticoagulants

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3%-7%	50%	62%	66% without food Almost 100% with food
Prodrug	Yes	No	No	No
Clearance nonrenal/renal, percent of absorbed dose*	20%/80%	73%/27%	50%/50%	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution ~25%)	Minimal (<4% of elimination)	Yes (hepatic elimination ~18%)
Absorption with food	No effect	No effect	6%-22% more; minimal effect on exposure	+39% more
Intake with food recommended?	No	No	No	Mandatory
Absorption with H2B/PPI	–12% to 30% (not clinically relevant)	No effect	No effect	No effect
Dose if Asian ethnicity	+25%	No effect	No effect	No effect
GI tolerability	Dyspepsia 5%-10%	No problem	No problem	No problem
Elimination half-life	12 to 17 h	12 h	10-14 h	5-9 h (young) 11-13 h (elderly)

*For clarity, data are presented as single values, which are the mid-point of ranges as determined in different studies.

H2B, H_2 blocker; *GI,* gastrointestinal; *PPI,* proton pump inhibitor.

This table follows The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation (Eur Heart J 2018 in press).

mild to moderate CKD (CKD 1 to 3b), unless they have prohibitive high risk for bleeding. For CKD 4 and 5 patients with atrial fibrillation, lack of evidence precludes strong recommendations whether to use NOACs, VKA, or no anticoagulation.

Both LMWH and NOACs require dose adjustment in patients with CKD because they undergo renal excretion. As of 2017, only one NOAC (apixaban) has been licensed for use among dialysis patients in the United States, but not yet in Europe. Compared with other NOACs, apixaban is characterized by the least accumulation in CKD, but still requires (like all NOACs) dose adjustment for renal function. Notably, pharmacokinetic studies (and subsequent recommendations on NOAC dosages) used GFR estimated with the Cockcroft-Gault equation. In clinical practice, eGFR is now mostly calculated using the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease–Epidemiology (CKD-EPI) formula. Substituting the latter for the former may cause large dosage errors, particularly when physicians fail to consider that the more recent equations yield estimates standardized for a body surface area of 1.73 m^2, and nonstandardized measures of renal function (as provided by Cockcroft-Gault equation) are suggested for dose adjustment.

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SELF-ASSESSMENT QUESTIONS

1. The following diagnostic finding is reliable (sensitive and specific enough to be useful) in patients with chronic kidney disease (CKD) even in the presence of their typical immune dysfunction:
   A. Fever as a sign of bacteremia
   B. Radiologic infiltration on chest x-ray film for pneumonia
   C. Mendel-Mantoux skin reaction for tuberculosis
   D. Blood culture for bacteremia
   E. C-reactive protein for infection
2. Viral hepatitis is a typical complication of hemodialysis treatment. Which statement describes viral hepatitis in advanced CKD correctly?
   A. Hepatitis B virus (HBV) infection leads to chronic infection in the majority of affected CKD patients.
   B. Acute HBV infection in CKD patients is typically severe, characterized by jaundice and fever.
   C. HBV infection can be easily prevented in CKD patients by vaccination as recommended to the general population.
   D. The clinical course of hepatitis C infection is largely different in CKD patients and those with normal renal function.
   E. Standard hygienic precautions have largely failed to reduce HBV transmission in dialysis centers. Only vaccination succeeded in preventing nosocomial transmission.
3. The hemorrhagic diathesis in CKD patients is typically mirrored by which of the following?
   A. A prolongation of the prothrombin time
   B. A prolongation of the partial thromboplastin time
   C. Severely thrombocytopenia
   D. Hyperchromic anemia
   E. None of these
4. The spectrum of interventions that may allow reducing hemorrhages in advanced CKD does not include which of the following?
   A. Desmopressin
   B. Conjugated estrogens
   C. Tranexamic acid (TXA)
   D. Cryoprecipitates
   E. Clopidogrel

Bone and Mineral Disorders in Chronic Kidney Disease

Kevin J. Martin, Jürgen Floege, Markus Ketteler

DEFINITION

Disturbances of mineral metabolism are common if not ubiquitous in chronic kidney disease (CKD) and lead to serious and debilitating complications unless these abnormalities are addressed and treated. The spectrum of disorders includes abnormal concentrations of serum calcium, phosphate, and magnesium and disorders of parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and vitamin D metabolism. These abnormalities as well as other factors related to the uremic state affect the skeleton and result in the complex disorders of bone known as *renal osteodystrophy;* it is now recommended that this term be used exclusively to define the bone disease associated with CKD. The clinical, biochemical, and imaging abnormalities heretofore identified as correlates of renal osteodystrophy should be defined more broadly as a clinical entity or syndrome called *chronic kidney disease–mineral and bone disorder* (CKD-MBD).[1] The spectrum of skeletal abnormalities seen in renal osteodystrophy includes the following (Fig. 84.1):

- Osteitis fibrosa, a manifestation of hyperparathyroidism characterized by increased osteoclast and osteoblast activity, peritrabecular fibrosis, and increased bone turnover.
- Osteomalacia, a manifestation of defective mineralization of newly formed osteoid most often caused by aluminum deposition; bone turnover is decreased.
- Adynamic bone disease (ABD), a condition characterized by abnormally low bone turnover.
- Osteopenia or osteoporosis.
- Combinations of these abnormalities termed *mixed renal osteodystrophy.*
- Other abnormalities with skeletal manifestations (e.g., chronic acidosis, β_2-microglobulin amyloidosis [Aβ_2M amyloidosis]).

EPIDEMIOLOGY

The prevalence of the various types of renal osteodystrophy in patients with end-stage renal disease (ESRD) is illustrated in Fig. 84.2.[2] In patients on hemodialysis (HD), osteitis fibrosa, and ABD now occur with almost equal frequency. In contrast, in patients on peritoneal dialysis (PD), the adynamic bone lesion predominates. Osteomalacia represents only a small fraction of cases in either group but is more common in certain ethnic groups, particularly Indo-Asians. Skeletal abnormalities associated with CKD start while the estimated glomerular filtration rate (eGFR) is still relatively preserved (~50 ml/min/1.73 m^2).

PATHOGENESIS

Several biochemical and hormonal abnormalities associated with CKD contribute to renal osteodystrophy and can be affected by efforts at prevention and therapy. The major factors may vary as CKD progresses (Fig. 84.3). Similarly, the predominance of one particular pathogenetic mechanism over another may contribute to the heterogeneity of bone disorders. We therefore discuss separately the two major entities—high- and low-turnover osteodystrophy.

OSTEITIS FIBROSA: HYPERPARATHYROIDISM—HIGH-TURNOVER RENAL BONE DISEASE

Elevated levels of PTH in blood, hyperplasia of the parathyroid glands, and elevations in FGF-23 are seen once eGFR declines below approximately about 50 ml/min/1.73 m^2. Whereas the level of free (i.e., non–protein bound) calcium in blood is normally the principal determinant of PTH secretion, several metabolic disturbances associated with CKD also alter the regulation of the secretion of PTH.

Abnormalities of Calcium Metabolism

There are three main body pools of calcium: the bony skeleton (mineral component), the intracellular pool (mostly protein bound), and the extracellular pool (see Chapter 10). The calcium in the extracellular pool is in continuous exchange with that of bone and cells and is altered by diet and excretion. Calcium metabolism depends on the close interaction of two hormonal systems: PTH and vitamin D. Perturbations of both systems occur during the course of CKD, with adverse consequences on the skeleton. Total serum calcium tends to decrease during the course of CKD as a result of phosphate retention and decreased production of 1,25-dihydroxyvitamin D (calcitriol) from the kidney, decreased intestinal calcium absorption, and skeletal resistance to the calcemic action of PTH, but the levels of free calcium remain within the normal range in most patients[3] as a result of compensatory hyperparathyroidism. Because calcium is a major regulator of PTH secretion, persistent hypocalcemia is a powerful stimulus for development of hyperparathyroidism and also contributes to parathyroid growth.

Abnormalities of Phosphate Metabolism

With progressive CKD, phosphate is retained, at least, transiently, by the failing kidney. However, hyperphosphatemia usually does not become evident before CKD stage 4. Until then, compensatory

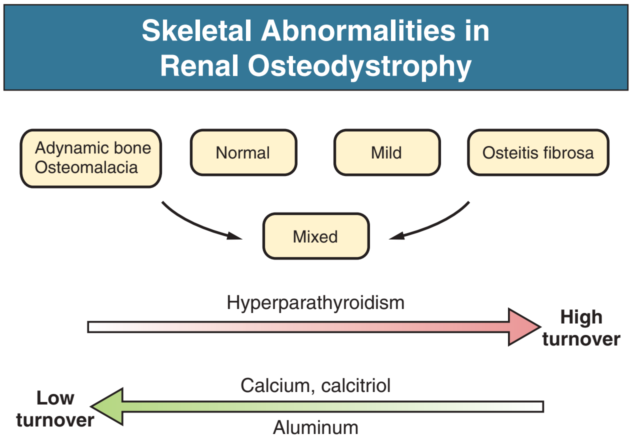
Skeletal Abnormalities in Renal Osteodystrophy

Fig. 84.1 The spectrum of renal osteodystrophy. The range of skeletal abnormalities in renal bone disease encompasses syndromes with both high and low bone turnover.

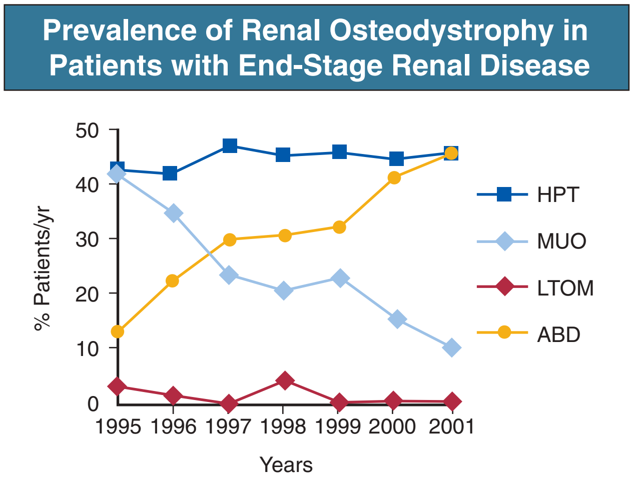
Prevalence of Renal Osteodystrophy in Patients with End-Stage Renal Disease

Fig. 84.2 Prevalence of renal osteodystrophy in patients with end-stage renal disease. *ABD,* Adynamic bone disease; *HPT,* high-turnover renal osteodystrophy; *LTOM,* low-turnover osteomalacia; *MUO,* mixed uremic osteodystrophy. (From reference 32.)

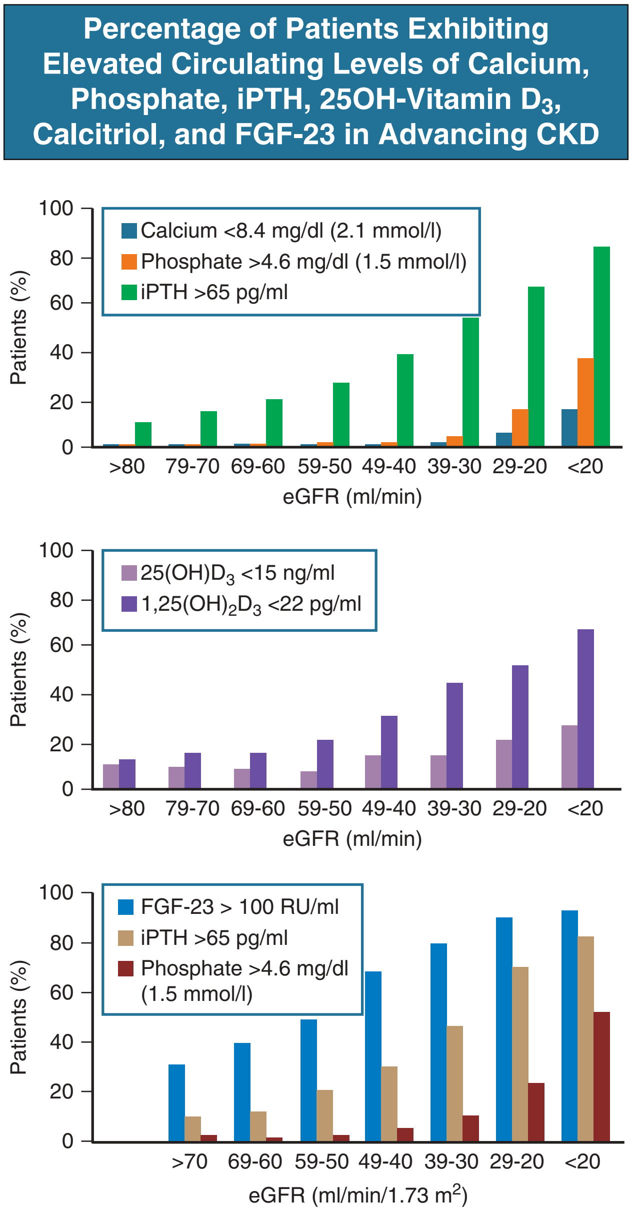
Percentage of Patients Exhibiting Elevated Circulating Levels of Calcium, Phosphate, iPTH, 25OH-Vitamin D_3, Calcitriol, and FGF-23 in Advancing CKD

Fig. 84.3 Percentage of patients exhibiting elevated circulating levels of calcium, phosphate, intact parathyroid hormone (iPTH), 25OH-vitamin D_3, calcitriol, and fibroblast growth factor-23 (FGF-23) in advancing chronic kidney disease (CKD). Particularly in early CKD stages there is wide variability at the individual level, and some patients, for example, may exhibit increased FGF-23 and normal iPTH, whereas others may have elevated iPTH levels with normal FGF-23 or elevations of both. (Data from references 54 and 55.)

hyperparathyroidism and increases in circulating FGF-23 result in increased phosphaturia, maintaining serum phosphate levels in the normal range.[4]

One mechanism by which phosphate retention may lead to hyperparathyroidism is by a decrease in serum free calcium, which in turn stimulates the secretion of PTH (Fig. 84.4). Thus a new steady state is achieved in which serum phosphate is restored to normal at the expense of a sustained high level of PTH. This cycle is repeated as renal function declines until sustained and severe hyperparathyroidism is present. Second, phosphate retention leads to decreased production of calcitriol by the kidney, either directly or by increasing the levels of FGF-23 (which decreases the activity of 1α-hydroxylase). The decrease in calcitriol allows increases in PTH gene transcription by direct action and also decreases intestinal calcium absorption, leading to hypocalcemia, which in turn stimulates PTH secretion. Third, hyperphosphatemia is associated with resistance to the actions of calcitriol in the parathyroid glands, which also favors development of hyperparathyroidism and induces resistance to the actions of PTH in bone. Finally, phosphate per se appears to affect PTH secretion independently of changes in serum calcium or serum calcitriol.[5,6] Phosphate may have an effect on parathyroid growth independent of serum calcium.[7,8] Regardless of the mechanism by which phosphate retention causes hyperparathyroidism, experimental studies suggest that restriction of dietary phosphate in proportion to the decrease in GFR can prevent development of hyperparathyroidism. Current evidence suggests that FGF-23 also acts directly on the parathyroid gland and has inhibitory effects on PTH secretion and parathyroid growth.[9,10] This suggests that the main effects of FGF-23 on the pathogenesis of hyperparathyroidism are indirect as a result of the potent effect of FGF-23 to decrease calcitriol production. These various actions may explain, at least in part, the association between higher levels of FGF-23 and adverse clinical outcomes.[11]

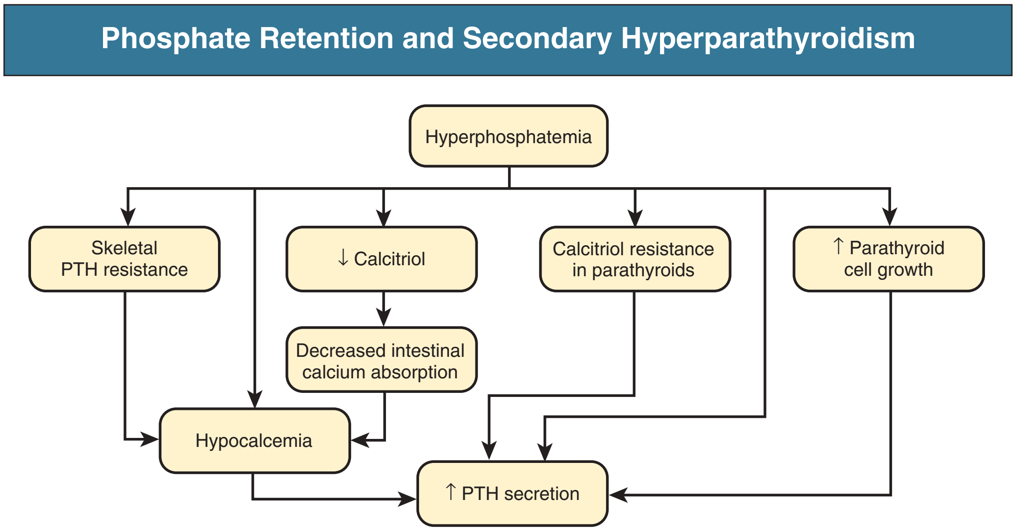
Phosphate Retention and Secondary Hyperparathyroidism
Hyperphosphatemia
Skeletal PTH resistance
↓ Calcitriol
Calcitriol resistance in parathyroids
↑ Parathyroid cell growth
Decreased intestinal calcium absorption
Hypocalcemia
↑ PTH secretion

Fig. 84.4 Role of phosphate retention in the pathogenesis of secondary hyperparathyroidism. Hyperphosphatemia stimulates parathyroid hormone *(PTH)* secretion indirectly by inducing hypocalcemia, skeletal resistance to PTH, low levels of calcitriol, and calcitriol resistance. Hyperphosphatemia also has direct effects on the parathyroid gland to increase PTH secretion and parathyroid cell growth. *eGFR,* Estimated glomerular filtration rate.

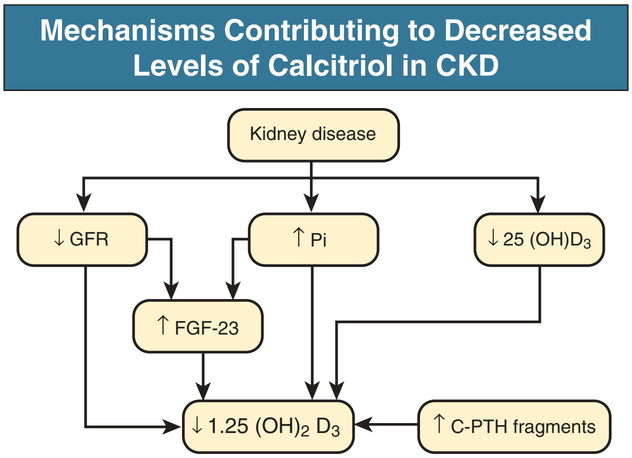
Mechanisms Contributing to Decreased Levels of Calcitriol in CKD
Kidney disease
↓ GFR
↑ Pi
↓ 25 (OH)D3
↑ FGF-23
↓ 1.25 (OH)2 D3
↑ C-PTH fragments

Fig. 84.5 Mechanisms contributing to decreased levels of calcitriol in chronic kidney disease (CKD). *C-PTH,* Carboxyl-terminal parathyroid hormone; *FGF-23,* fibroblast growth factor-23; *GFR,* glomerular filtration rate; *Pi,* inorganic phosphate.

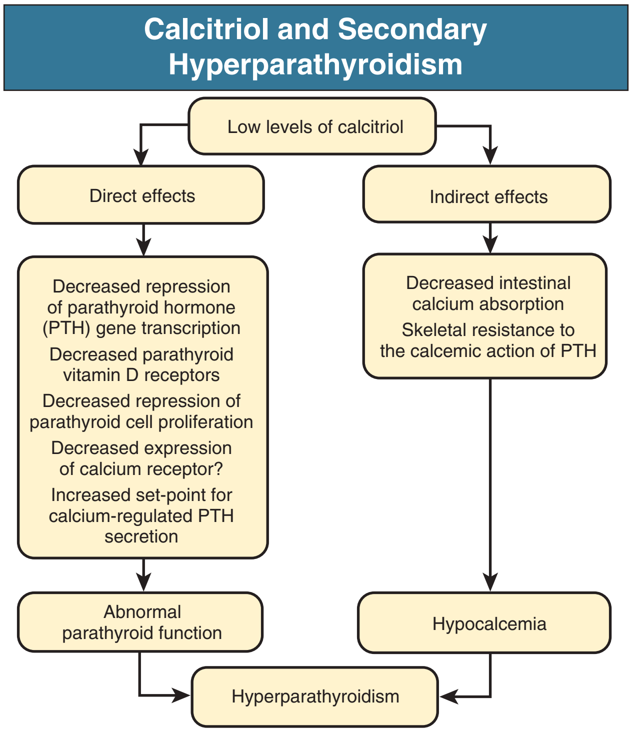
Calcitriol and Secondary Hyperparathyroidism
Low levels of calcitriol
Direct effects
Indirect effects
Decreased repression of parathyroid hormone (PTH) gene transcription
Decreased parathyroid vitamin D receptors
Decreased repression of parathyroid cell proliferation
Decreased expression of calcium receptor?
Increased set-point for calcium-regulated PTH secretion
Decreased intestinal calcium absorption
Skeletal resistance to the calcemic action of PTH
Abnormal parathyroid function
Hypocalcemia
Hyperparathyroidism

Fig. 84.6 Role of low levels of calcitriol in the pathogenesis of secondary hyperparathyroidism.

Abnormalities of Vitamin D Metabolism

The conversion of 25-hydroxyvitamin D to its active metabolite 1,25-dihydroxyvitamin D occurs mainly in the kidney by the enzyme 1α-hydroxylase. Extrarenal production of calcitriol also occurs and contributes to the circulating levels of calcitriol. Renal calcitriol production progressively declines in parallel with eGFR as a result of several mechanisms (Fig. 84.5).

Calcitriol production is compromised in CKD by a reduction in 25-hydroxyvitamin D levels[12] and the decrease in GFR, which further limits the delivery of 25-hydroxyvitamin D to the site of the 1α-hydroxylase in the proximal tubule. Phosphate retention either directly or by inducing an increase in FGF-23 also decreases the activity of 1α-hydroxylase. Finally, circulating PTH fragments may directly decrease calcitriol production. The resultant decreased levels of calcitriol contribute to the pathogenesis of hyperparathyroidism by several direct and indirect mechanisms as described earlier (Fig. 84.6). Low levels of calcitriol directly release the gene for PTH from suppression by the vitamin D receptor and allow increased PTH secretion. In many tissues, vitamin D regulates its own receptor by positive feedback; in CKD the vitamin D receptor content is decreased in parathyroid tissue. Administration of calcitriol has been shown to increase the vitamin D receptor content in the parathyroid glands coincident with the suppression of PTH secretion. Studies in vitro have shown that calcitriol is a negative growth

BOX 84.1 Parathyroid Abnormalities in Chronic Kidney Disease

- Parathyroid gland hyperplasia: diffuse, nodular
- Decreased expression of vitamin D receptors
- Decreased expression of calcium receptors
- Increased set-point of calcium-regulated parathyroid hormone secretion

regulator of parathyroid cells, and therefore calcitriol deficiency in patients with CKD may facilitate parathyroid cell proliferation. Other direct consequences of low levels of calcitriol contributing to the pathogenesis of secondary hyperparathyroidism include an increase in the parathyroid set-point for calcium-regulated PTH secretion and possibly a decrease in the expression of calcium receptors.

Low levels of calcitriol also may promote the development of hyperparathyroidism indirectly. First, decreased calcitriol production as renal function decreases can lead to progressive reductions in intestinal absorption of calcium, leading to hypocalcemia and stimulation of PTH release. Second, low levels of calcitriol have been implicated in skeletal resistance to the calcemic actions of PTH, which may contribute to the development of hyperparathyroidism.

Abnormalities of Parathyroid Gland Function

CKD is associated with intrinsic abnormalities in parathyroid gland function, in addition to those caused by hypocalcemia, low levels of calcitriol, and skeletal resistance to the actions of PTH (Box 84.1).

Parathyroid hyperplasia is an early finding in CKD. In experimental models, hyperplasia begins within a few days after the induction of CKD and can be prevented by dietary phosphate restriction or by the use of calcimimetic agents.[8,13] Resected parathyroid glands from patients with severe hyperparathyroidism have nodular areas throughout the gland, which represent monoclonal expansions of parathyroid cells. Within these nodules, there is decreased expression of vitamin D receptors as well as of calcium receptors. The decreased expression of calcium receptors renders efforts to therapeutically affect these enlarged hyperplastic glands difficult.

The parathyroid calcium receptor is centrally involved in the regulation of PTH secretion by calcium.[14] Its expression and synthesis are decreased in the parathyroid glands from hyperparathyroid patients, leading to altered calcium-regulated PTH secretion. Increased concentrations of calcium are required in vitro to suppress PTH release from the parathyroid cells of uremic patients compared with those of normal controls. Thus the set-point for the concentration of calcium required to decrease PTH release by 50% appears to be increased.

Abnormal Skeletal Response to Parathyroid Hormone

In patients with CKD, there is an impaired response of serum calcium to the administration of PTH and a delay in the recovery from induced hypocalcemia in the presence of larger increments in PTH levels. Thus in CKD the skeleton is relatively resistant to the calcemic actions of PTH. The resultant decrease in serum calcium levels stimulates PTH secretion and contributes to the pathogenesis of secondary hyperparathyroidism. Factors involved in the skeletal resistance to PTH in CKD include decreased levels of calcitriol, downregulation of the PTH receptor, and phosphate retention. In addition, circulating fragments of PTH, truncated at the *N*-terminus, which still react in the older, second-generation two-site PTH assays, have been suggested to oppose the calcemic actions of PTH, possibly acting at a presumed receptor for the C-terminal region of PTH.[15,16]

Clinical Manifestations of High-Turnover Renal Osteodystrophy

Clinical manifestations of hyperparathyroidism are usually nonspecific and often preceded by biochemical or imaging abnormalities. Nonspecific aches and pains are common, occur in the lower back, hips, and legs, and are aggravated by weight bearing. Acute, localized bone pain can occur and may be suggestive of acute arthritis. Pain around joints may be caused by acute periarthritis, which is associated with periarticular deposition of calcium phosphate crystals, especially in patients with marked hyperphosphatemia. The symptoms may be confused clinically with gout or pseudogout and often respond to nonsteroidal antiinflammatory drugs (NSAIDs). The gradual onset of muscle weakness is also common in patients with ESRD. Many factors are probably involved in its pathogenesis, including hyperparathyroidism and abnormalities of vitamin D. β_2-Microglobulin amyloidosis (Aβ_2M) (see later discussion) should be considered in the differential diagnosis in very-long-term dialysis patients.

Bone abnormalities may occur in patients with severe hyperparathyroidism, particularly in children, and are manifested on x-ray films by subperiosteal erosions, resorption of terminal digits. In adults, deformities arise as a result of fractures, sometimes induced by brown tumors (see later discussion); the axial skeleton is most commonly affected. This can lead to kyphoscoliosis or chest wall deformities. Slipped epiphysis may occur in children, and frank rachitic features are occasionally evident. Growth retardation is also common in children, and although some improvement has been shown with calcitriol, this has not been the universal finding.

Extraskeletal calcifications are frequently encountered in patients with advanced CKD and are aggravated by persistent elevation of the calcium-phosphate product. Most commonly, vascular calcifications are seen, but calcifications may occur in other sites, such as the lung, myocardium, and periarticular areas (Fig. 84.7).

In the skin, hyperparathyroidism can manifest as pruritus (see Chapter 87). Rarely, it can also underlie the development of calciphylaxis, or calcific uremic arteriolopathy (see Chapter 87, Figs. 87.6 and 87.7).

Diagnosis and Differential Diagnosis

In addition to the clinical manifestations of renal osteodystrophy, a variety of biochemical and radiographic techniques are helpful to establish the specific diagnosis and serve as a guide for the initiation and adjustment of therapy. Although bone biopsy is not widely used in clinical practice, it remains the gold standard for the diagnosis of renal osteodystrophy.

Serum Biochemistry

The levels of free calcium and phosphate in serum are usually normal in patients with mild to moderate CKD. Normally in stage 4 CKD the levels of serum calcium tend to fall and hyperphosphatemia manifests. Hypercalcemia may result from the administration of large doses of calcium-containing antacids or vitamin D metabolites or from severe hyperparathyroid bone disease. It is important to identify the cause of hypercalcemia in patients with CKD (see Chapter 10) because the management will vary greatly according to the cause. Also, the levels of serum calcium and phosphate, when used alone, are not useful in predicting the specific type of bone disease.

Parathyroid Hormone

Measurements of PTH are important for diagnostic purposes and therapeutic guidance in the management of renal osteodystrophy. With renal impairment, there is accumulation of circulating PTH fragments, which complicates the interpretation of PTH assays, including the two-site

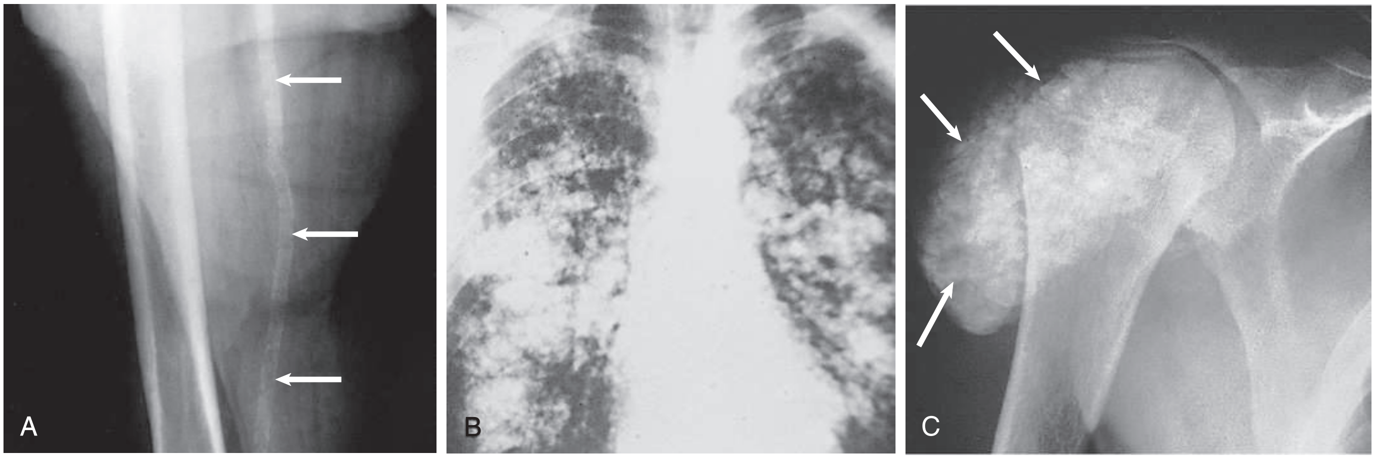

Fig. 84.7 **Extraskeletal calcification in chronic renal failure.** (A) Arterial calcification *(arrows).* (B) Pulmonary calcification. (C) Periarticular calcification *(arrows).*

immunometric assays, which were thought to measure "intact" PTH (iPTH). Refinements in PTH assays have demonstrated that these iPTH assays also measure some large fragments of PTH, which are truncated at the *N*-terminus. More specific assays for so-called "biointact" PTH (PTH 1-84) have been developed that exclude these fragments from measurement, but their clinical usefulness continues to be defined.[17-19] The presence of oxidized PTH, which is biologically inactive, in patients with ESRD may further complicate PTH measurements.[20] Standardization needs to be improved among different PTH assays from various laboratories and various manufacturers of assay reagents. With existing iPTH assays (upper limit of the reference range, ~60 pg/ml), only values at the extremes are useful in the noninvasive diagnosis of renal osteodystrophy. In dialysis patients, iPTH levels above approximately 600 pg/ml are characteristic of patients with osteitis fibrosa. The threshold values for earlier stages of CKD are not well defined. It is well accepted, however, that there is an element of skeletal resistance to PTH in patients with CKD; therefore supranormal levels of PTH appear to be required to maintain normal bone turnover. Serial measurements of PTH are useful in the initial evaluation of patients with renal osteodystrophy and are essential during the management of these disorders to assess response to therapy and to avoid overtreatment and undertreatment because either can have detrimental effects on bone histology. There are marked differences among commercial PTH assay results so that precise recommendations of desired ranges cannot reliably be provided and results obtained in different laboratories cannot be easily compared.[21]

Vitamin D Metabolites

The levels of calcitriol in patients with CKD are not helpful in differentiating the histologic lesions of renal osteodystrophy. Measurements of calcitriol are not used routinely for diagnostic purposes unless extrarenal production of this metabolite is suspected, as in granulomatous disorders (see Chapter 10).

Vitamin D deficiency in CKD rarely results in osteomalacia in the United States and Europe but may contribute to hyperparathyroidism. In patients with CKD and marked proteinuria, there is loss of vitamin D–binding protein in the urine, which may result in decreased levels of 25-hydroxyvitamin D. Vitamin D deficiency may be encountered in patients with limited sun exposure, in those with intestinal malabsorption or malnutrition, and in susceptible racial groups, particularly South Asians. Assessment of vitamin D nutrition is by measurement of serum 25-hydroxyvitamin D_3.

Markers of Bone Formation and Bone Resorption

Levels of circulating alkaline phosphatase offer an approximate index of osteoblast activity in patients with CKD. High levels are commonly present in hyperparathyroid bone disease. The discriminatory power of alkaline phosphatase measurements is enhanced by measurement of bone-specific alkaline phosphatase (BAP) isoenzyme, especially in conjunction with PTH values. Serial measurements of alkaline phosphatase may be useful in assessing the progression of bone disease. Osteocalcin is another marker of osteoblastic activity, but it is not superior to alkaline phosphatase. Tartrate-resistant acid phosphatase and collagen degradation products are both markers of osteoclastic activity but are considered investigational at present.

Radiology of the Skeleton

Routine x-ray examination of the skeleton is relatively insensitive for the diagnosis of renal osteodystrophy, and x-ray films can appear virtually normal in patients with severe histologic evidence of renal osteodystrophy. However, subperiosteal erosions are often present in severe secondary hyperparathyroidism, detected in the hands (Fig. 84.8), clavicles, and pelvis. Skull x-ray films may show focal radiolucencies and a ground-glass appearance, known as *pepper pot* skull. Osteosclerosis of the vertebrae is responsible for the "rugger-jersey" appearance of the spine (Fig. 84.9). Very rarely, brown tumors, focal collections of giant cells and typical of severe hyperparathyroidism, are seen as well-demarcated radiolucent zones in long bones, clavicles, and digits (Fig. 84.10). They may be confused with osteolytic metastases. Looser zones or pseudofractures are characteristic of osteomalacia. Routine skeletal x-ray films are not indicated unless there are symptoms.

Measurements of Bone Density

Dual-energy x-ray absorptiometry (DEXA) is widely used to assess bone density. Although DEXA does not identify the nature of the underlying osteodystrophy or distinguish this from osteoporosis, it does allow prediction of fracture risk in patients with CKD. Vascular and soft tissue calcifications may contribute to errors in bone density measurements.

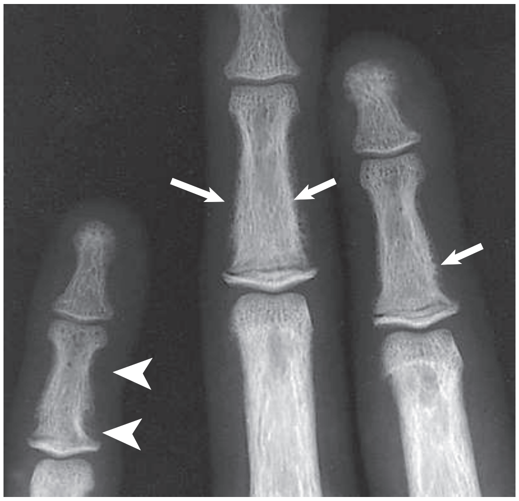

Fig. 84.8 **Subperiosteal erosions in hyperparathyroidism.** Severe subperiosteal erosions as a manifestation of hyperparathyroidism *(arrows)*. The extensive scalloped appearance of the middle phalanx on the left *(arrowheads)* represents a small brown tumor.

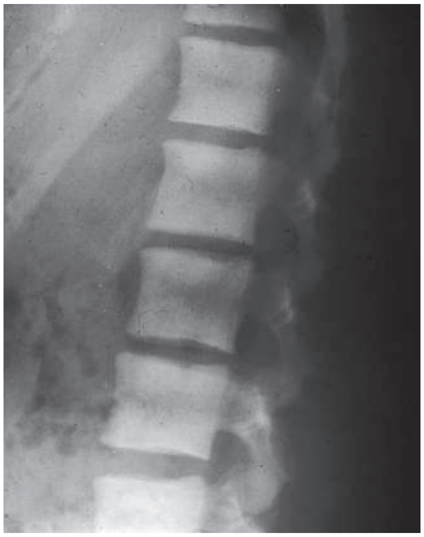

Fig. 84.9 **"Rugger-jersey spine" in hyperparathyroidism.** Vertebral bodies show the increased density of the ground plates and central radiolucency, which gives the striped appearance of a rugger jersey.

Bone Biopsy

Biopsy of bone and the microscopic analysis of undercalcified sections after double tetracycline labeling provide a definitive and quantitative diagnosis of renal osteodystrophy.[22] To standardize reports on bone histology, the Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Epidemiology Collaboration (CKD-MBD) work group proposed the TMV classification, an assessment of turnover (T), mineralization (M), and bone volume (V).[1] Bone mineralization is assessed by the administration of two different tetracyclines spaced apart (e.g., tetracycline 500 mg three times daily for 2 days, followed by a 10-day interval, then demeclocycline 300 mg three times daily for 3 days) and biopsy 4 days later; the quantitation of bone mineralization rate is achieved by measuring the distance between the two fluorescent tetracycline bands.

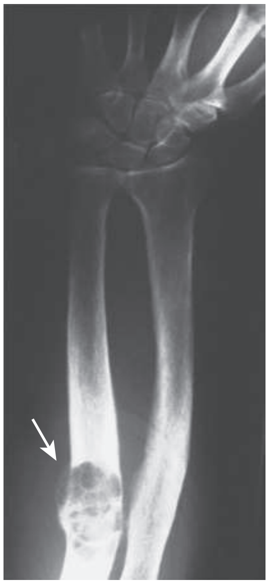

Fig. 84.10 **Brown tumor *(arrow)* in a hemodialysis patient with severe hyperparathyroidism.** The tumor can easily be confused with a lytic bone metastasis.

Although noninvasive testing is useful to distinguish low or normal from high bone turnover, there is considerable overlap, and therefore biopsy might be required for definitive diagnosis when biochemistry is not conclusive (e.g., PTH in recommended range but bone alkaline phosphatase elevated, hypercalcemia with PTH only modestly elevated, or bone pain).

Osteitis fibrosa (hyperparathyroid bone disease) is characterized by increased bone turnover, increased number and activity of osteoblasts and osteoclasts, and variable amounts of peritrabecular fibrosis (Fig. 84.11A). Osteoid may be increased but usually has a woven pattern distinct from the normal lamellar appearance. Osteomalacia is characterized by increased osteoid seam width, increase in the trabecular surface covered with osteoid, and decreased bone mineralization as assessed by tetracycline labeling (see Fig. 84.11B). The presence of aluminum can be detected on the mineralization front by specific staining (see Fig. 84.11C). Aluminum-related bone disease is defined by aluminum staining exceeding 15% of the trabecular surface and a bone formation rate of less than 220 mm^2/day. Features of osteitis fibrosa may occur together with features of osteomalacia; the combination is termed *mixed renal osteodystrophy.*

Treatment of High-Turnover Bone Disease

Prevention is the primary goal in management of renal osteodystrophy. Therapy for hyperparathyroidism ideally should be initiated in CKD stage 3 so parathyroid gland hyperplasia can be prevented. Because renal osteodystrophy is usually asymptomatic early in the course of CKD, attention often is not paid to secondary hyperparathyroidism. By the time CKD is advanced, patients may have already developed significant skeletal abnormalities or nodular parathyroid hyperplasia, and more aggressive therapy is required to prevent the long-term consequences of renal osteodystrophy. The successful approach to the prevention and management of this disorder involves the integration of a variety of measures directed toward the suppression of PTH secretion and prevention of parathyroid hyperplasia.

Prevention of Hypocalcemia

Hypocalcemia, if present, should be corrected because it is a potent stimulus for PTH secretion. In patients with hypoalbuminemia, ionized

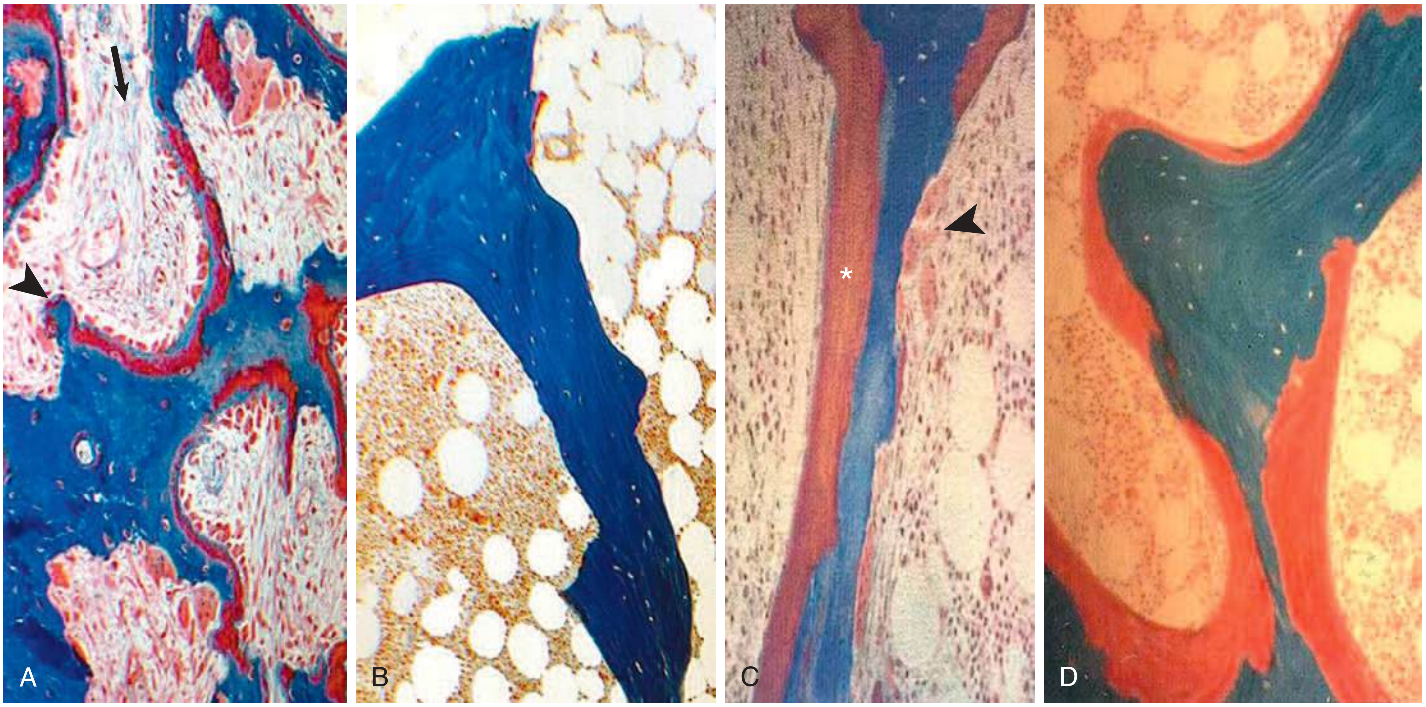

Fig. 84.11 **Bone histology in renal osteodystrophy.** (A) Osteitis fibrosa: Characteristic manifestations of severe hyperparathyroidism with increased osteoclast and osteoblast activity and peritrabecular fibrosis (stained blue; *arrow*). (B) Adynamic bone disease: There is no cellular activity along the bone surface and no osteoid visible. (C) *(arrowhead)* Mixed renal osteodystrophy: There is evidence of active osteoclasts on one bone surface *(arrowhead)* and evidence of thickened osteoid (stained red; *asterisk*) indicating a mineralization defect on the other. (D) Osteomalacia: Marked excess of unmineralized osteoid *(stained red)* surrounding the mineralized bone *(stained blue).*

calcium should be measured. The initial approach to therapy for hypocalcemia in patients with mild to moderate CKD is the administration of calcium supplements such as calcium carbonate, taken between meals with increasing doses as required. Assessment of vitamin D status should be undertaken by measurement of 25-hydroxyvitamin D, and this should be corrected if it is below 30 ng/ml. The determination of 1,25-dihydroxyvitamin D levels is not helpful in this respect, given its 8-hour half-life. Assessment of efficacy of therapy is by follow-up determinations of serum calcium and PTH. Adjunctive therapy with active vitamin D sterols should be considered if hyperparathyroidism or hypocalcemia persists. In patients with ESRD, active vitamin D sterols are often required. In dialysis patients, the goal is to achieve levels of iPTH that are approximately two to nine times above the upper limit of the assay used.[23] Also, iPTH trends over time should be closely monitored. In CKD stages 3 to 5, progressive rises in iPTH above the normal range should be abrogated by correction of hypocalcemia, vitamin D deficiency, and hyperphosphatemia. The latter should be corrected before the correction of hypocalcemia.

Control of Phosphate

Control of phosphate is the cornerstone of effective management of secondary hyperparathyroidism. In mild to moderate CKD, a normal serum phosphate concentration does not necessarily indicate normal parathyroid status, and except for the late stages of CKD, normophosphatemia may be maintained at the expense of elevated serum PTH and FGF-23. Therefore efforts to control phosphate, including dietary phosphate restriction and the use of phosphate binders, should not be delayed until frank hyperphosphatemia develops.

Dietary Phosphate Restriction

In experimental animals with mild CKD, dietary phosphate restriction can prevent excessive PTH synthesis and secretion, as well as parathyroid cell proliferation, independently of changes in serum calcium and calcitriol concentrations. Accordingly, restriction of dietary phosphate intake might be considered in patients with CKD stage 2 or 3. The input of a dietician is essential. Protein restriction and avoidance of dairy products (especially processed foods containing high amounts of added phosphate) are the mainstays of the regimen. Phosphate-protein restriction increases the serum levels of calcitriol in patients with mild to moderate CKD. However, restriction of phosphate by severe dietary protein restriction below 0.8 g/kg/day may lead to protein-calorie malnutrition.

Phosphate Binders

Whereas dietary phosphate restriction is usually sufficient in early CKD, the control of phosphate becomes more difficult as renal function deteriorates. It then becomes necessary to also use agents that bind ingested phosphate in the intestinal lumen to limit its absorption. Compounds used for this purpose include calcium-containing antacids, magnesium salts, aluminum hydroxide, and non–calcium-containing, non–aluminum-containing phosphate binders (Fig. 84.12). Most phosphate binders, especially in advanced CKD, have to be given in large numbers (often accounting for 50% of the daily pill burden) and consequently patient adherence with the medication is a major problem.

Aluminum-containing antacids are effective phosphate binders, but in patients with CKD, their long-term use can no longer be recommended because of the risk for aluminum toxicity. Ingestion of

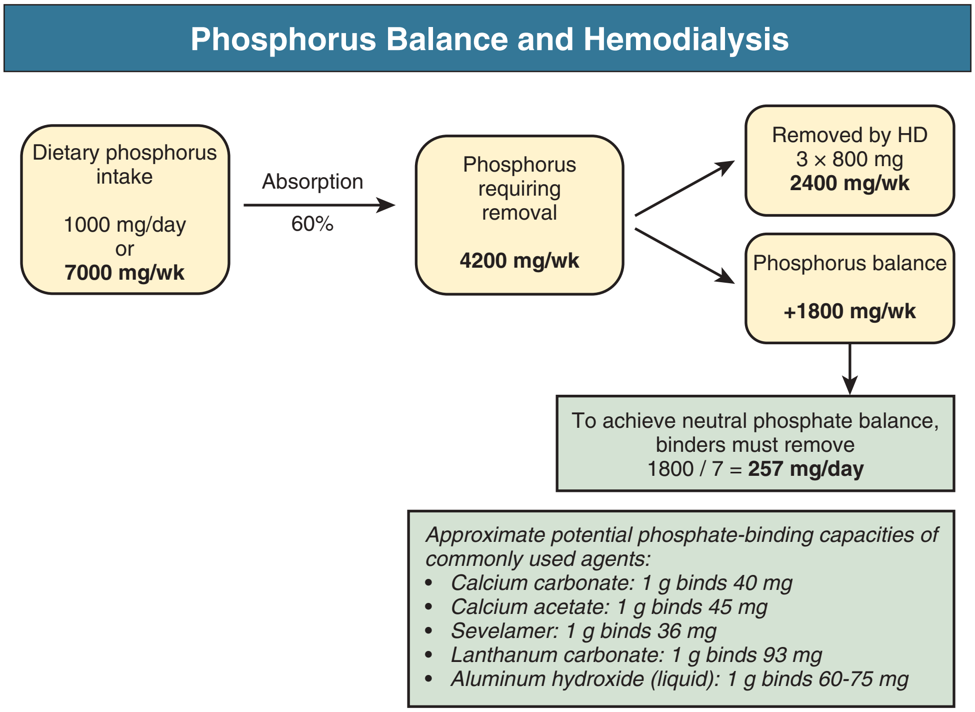
Phosphorus Balance and Hemodialysis
Dietary phosphorus intake
1000 mg/day
or
7000 mg/wk
Absorption
60%
Phosphorus requiring removal
4200 mg/wk
Removed by HD
3 × 800 mg
2400 mg/wk
Phosphorus balance
+1800 mg/wk
To achieve neutral phosphate balance, binders must remove
1800 / 7 = 257 mg/day
Approximate potential phosphate-binding capacities of commonly used agents:
• Calcium carbonate: 1 g binds 40 mg
• Calcium acetate: 1 g binds 45 mg
• Sevelamer: 1 g binds 36 mg
• Lanthanum carbonate: 1 g binds 93 mg
• Aluminum hydroxide (liquid): 1 g binds 60-75 mg

Fig. 84.12 Phosphate balance and phosphate binders used in hemodialysis patients.

aluminum-containing antacids together with foods containing citric acid (e.g., fruit juices and foods with sodium, calcium, or potassium citrate) may significantly increase aluminum absorption and therefore should be avoided.

Calcium carbonate or calcium acetate taken with meals effectively binds phosphates and limits their absorption. They are effective phosphate binders in 60% to 70% of patients on HD. The doses required to prevent hyperphosphatemia may vary according to patient compliance with dietary phosphate restriction as well as the CKD stage. Hypercalcemia and calcium loading are the major potentially serious side effects. Current recommendations are to limit the ingestion of elementary calcium to 1500 mg/day. Consideration of overall calcium balance may be important with the use of calcium-containing phosphate binders.

Magnesium salts are effective phosphate binders for patients who become hypercalcemic with calcium-containing phosphate binders, but they should be administered with caution in CKD patients not on dialysis because hypermagnesemia may have serious adverse effects. In patients on dialysis, magnesium carbonate (elemental magnesium 200 to 500 mg/day) has been used successfully, with prevention of hypermagnesemia through a reduction in dialysate magnesium concentration. The use of magnesium carbonate also allows reduction of the dose of calcium carbonate required by about half, but its use is frequently complicated by diarrhea.

Nonabsorbable, calcium-free polymers, such as sevelamer hydrochloride in a dose range of 2.4 to 4.8 g/day, provide effective phosphate control. Agents such as sevelamer may offer great advantage over calcium-containing phosphate binders in terms of limiting the calcium load, although they are significantly more expensive. Studies have suggested that the use of sevelamer is associated with decreased progression of vascular calcification.[24] Sevelamer hydrochloride has largely been replaced by sevelamer carbonate, which has similar properties. Sevelamer may be combined with both calcium- and magnesium-containing phosphate binders if necessary. Lanthanum carbonate also is an effective phosphate binder. No significant toxicity has been observed, although some lanthanum appears to accumulate in bone, liver, and gastric mucosa. Newly approved iron-containing phosphate binders include ferric citrate and sucroferric oxyhydroxide. Ferric citrate allows significant oral iron uptake and therapy necessitates monitoring of iron stores, whereas iron uptake from sucroferric oxyhydroxide is low.[24]

Use of Vitamin D Metabolites

Calcitriol and other 1α-hydroxylated vitamin D sterols, such as 1α-hydroxyvitamin D_3 (alfacalcidol), 1α-hydroxyvitamin D_2 (doxercalciferol), and 19-nor-1α,25-dihydroxyvitamin D_2 (paricalcitol), are effective in the control of secondary hyperparathyroidism. Calcitriol lowers PTH levels and improves bone histologic status. In patients with very high levels of PTH and markedly enlarged glands with severe nodular hyperplasia, the effectiveness of vitamin D metabolites may be limited because the levels of vitamin D receptor are low in such tissue. Accordingly, it would appear rational to initiate treatment of secondary hyperparathyroidism with vitamin D metabolites early in CKD when the parathyroid glands are more sensitive to such therapy and thereby prevent the progression to a refractory stage. A beneficial effect of vitamin D metabolite therapy in treatment of secondary hyperparathyroidism in patients with mild to moderate CKD has been shown, but the concern with initiation of vitamin D therapy at this stage of CKD is acceleration of the progression of renal disease should hypercalcemia occur. Because of the effect of calcitriol to increase intestinal phosphate absorption, hyperphosphatemia and elevations in calcium-phosphate product may predispose patients to the development of metastatic calcification; however, it appears that doses of 1α-hydroxyvitamin D_3 or calcitriol up to 0.5 mcg/day are not commonly associated with hypercalcemia, hyperphosphatemia, or worsening renal impairment. Another concern with the use of vitamin D metabolites before dialysis is that oversuppression of hyperparathyroidism may increase the risk for adynamic bone. Accordingly, vitamin D therapy should be monitored carefully and should not be instituted without documentation of hyperparathyroidism, correction of 25-hydroxyvitamin D deficiency, and prior control of serum phosphate.

In patients with ESRD, indications for therapy with vitamin D metabolites are better defined; however, hypercalcemia and aggravation of hyperphosphatemia are frequent complications of therapy. Vitamin D metabolites are increasingly used as oral or intravenous pulses given intermittently (e.g., three times weekly) rather than as continuous oral therapy. Analogues of calcitriol that have less calcemic activity than the parent compound and yet retain the ability to suppress PTH release in vivo have been developed. Such analogues of vitamin D studied in patients with ESRD are 22-oxacalcitriol, 1α-hydroxyvitamin D_2, and 19-nor-1α,25-dihydroxyvitamin D_2 (paricalcitol). Direct comparisons between these compounds are not available. It is likely that a wider therapeutic window may be offered by these analogues. Several but not all studies have suggested there may be a survival advantage associated with active vitamin D administration in patients with CKD as well as with ESRD.[25,26]

Role of Calcimimetics

An additional approach to the treatment of hyperparathyroidism in ESRD is the use of a calcimimetic agent, such as cinacalcet, which targets the calcium-sensing receptor and increases its sensitivity to calcium. In dialysis patients, cinacalcet results in a significant fall in PTH levels and can facilitate the control of hyperparathyroidism. The addition of cinacalcet to standard therapy in patients with iPTH serum levels exceeding 300 pg/ml while receiving standard therapy allowed significantly more dialysis patients to achieve guideline targets for calcium, phosphate, and iPTH.[27] Cinacalcet is especially useful in patients with marginal or frank hypercalcemia or with hyperphosphatemia and can be used in conjunction with other therapies. Central side effects include hypocalcemia and nausea and vomiting; the latter can be somewhat improved by administering cinacalcet at night. Cinacalcet may attenuate progression of cardiovascular (CV) calcification.[28] A large randomized controlled trial (RCT)—Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE)—to examine the effect of cinacalcet therapy on CV events and survival in HD patients with secondary hyperparathyroidism was nondefinitive because of, at least in part, significant migration from the control arm to commercial cinacalcet and an age difference between the two arms, whereby the cinacalcet patients were older on average and thus at higher CV risk.[29] In that trial, however, cinacalcet significantly reduced rates of parathyroidectomies and of calciphylaxis.[29] In CKD patients not on dialysis, the use of calcimimetics is accompanied by significant phosphate retention and is currently not recommended. The potent, parental peptide-based calcimimetic etelcalcetide was recently licensed in dialysis patients. Although the parenteral administration offers improved patient adherence, gastrointestinal adverse events were similar to those with cinacalcet.[30]

Role of Parathyroidectomy

Although the strategies discussed previously are effective for the control of hyperparathyroidism in many patients, there are occasions when these steps fail or are contraindicated and surgery should be considered (Box 84.2). Parathyroidectomy is indicated for patients with severe hyperparathyroidism that cannot be controlled medically. Severe hyperphosphatemia in these patients precludes the use of vitamin D metabolites because of the risk for metastatic calcification. Some control of iPTH levels may be obtained with calcimimetics, but even these compounds may fail in severe hyperparathyroidism because of downregulated calcium-sensing receptors in the parathyroid glands. Some patients with severe hyperparathyroidism may become hypercalcemic. It is important to be certain that hypercalcemia represents severe hyperparathyroidism and is not caused by adynamic bone or other disease. In some cases, a bone biopsy may be required for a definite diagnosis. For hypercalcemia to occur because of hyperparathyroidism in CKD, the levels of iPTH generally exceed 1000 pg/ml and BAP is usually elevated. Surgical parathyroidectomy might be considered in patients with very severe hyperparathyroidism who may receive a renal transplant in the near future, particularly if they are female and have significant osteopenia. Parathyroidectomy in these patients can help avoid post-transplantation hypercalcemia and hypophosphatemia (caused by PTH-induced phosphaturia), as well as osteopenia. By avoiding hypercalcemia, this may lead to improved graft function and possibly to less intragraft calcification. Parathyroidectomy might be considered in patients with severe hyperparathyroidism who have evidence of metastatic calcification. The development of calciphylaxis is an urgent indication for parathyroidectomy if PTH levels are elevated (see Chapter 87). Before parathyroidectomy, consideration should be given to the possibility of coexisting aluminum accumulation, with deferoxamine testing and bone biopsy performed if necessary, because this might predispose to osteomalacia after parathyroidectomy.

BOX 84.2 Indications for Parathyroidectomy

- Severe hyperparathyroidism
  - With persistent hyperphosphatemia
  - Unresponsive to calcitriol and calcium
  - With hypercalcemia
  - With intolerance or unresponsiveness to calcimimetics
  - In renal transplantation candidate
  - With evidence of metastatic calcification
- Calciphylaxis with evidence of hyperparathyroidism
- Severe pruritus, only if additional evidence of hyperparathyroidism

The most commonly used surgical procedures are subtotal removal of the parathyroid glands and total removal of the parathyroid glands with reimplantation of parathyroid tissue in the forearm. Recurrence of hyperparathyroidism occurs in about 10% of patients. Total parathyroidectomy alone is less commonly performed; although this is an appropriate procedure for patients remaining on dialysis, hypoparathyroidism after renal transplantation may lead to marked hypercalciuria with nephrocalcinosis and progressive renal failure. This may become less of an issue now that recombinant PTH has become available. Total parathyroidectomy with forearm implantation (our preference) or subtotal parathyroidectomy in the neck, marking remaining tissue with clips, may be performed. Unregulated tumor-like growth of parathyroid tissue implants has been described and may be related to the monoclonal nature of the nodular hyperplasia of severe hyperparathyroidism.

Recurrence of hyperparathyroidism may respond to further medical therapy, but more surgery to remove the forearm implant or further neck exploration to search for additional glands is often necessary and may be guided by parathyroid imaging.

Synthesis of Therapeutic Strategies

The general recommendations for the prevention and therapy of renal osteodystrophy are summarized in Fig. 84.13, in which therapeutic maneuvers are stratified according to the degree of CKD.

Therapy should be initiated if possible in stage 2 or 3 CKD (GFR, 30 to 90 ml/min), and dietary phosphate intake may be restricted once patients enter CKD stage 3. Levels of iPTH should be measured; if elevated above the normal range, the levels of 25-hydroxyvitamin D should be measured and corrected if less than 30 ng/ml. If hyperparathyroidism persists, phosphate binders may be considered. As CKD progresses within stage 3, dietary phosphate restriction should be continued or intensified, and the doses of phosphate binders should be

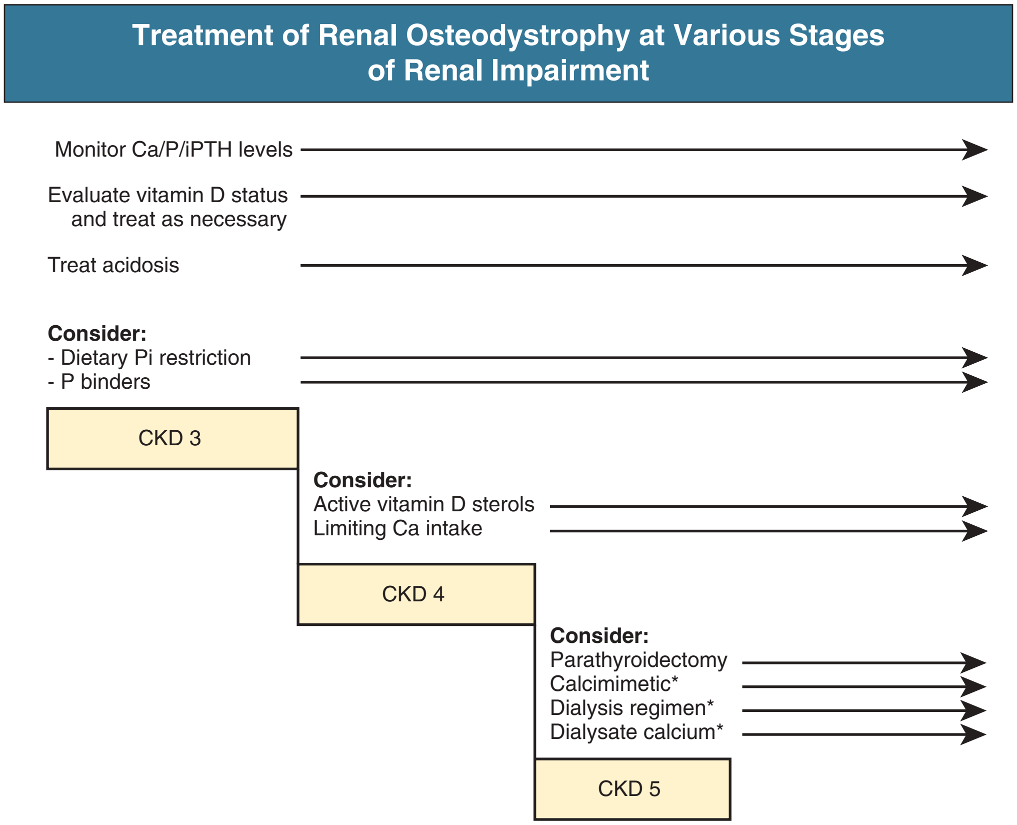

Fig. 84.13 Treatment of renal osteodystrophy at various stages of renal impairment. *Consider in CDK5D (i.e., dialysis dependent) only. *Ca,* Calcium; *CKD,* chronic kidney disease; *iPTH,* intact parathyroid hormone; *P,* phosphate; *Pi,* inorganic phosphate. (Modified from reference 56.)

adjusted based on serial measurements of iPTH, with careful attention to avoid hypercalcemia or excessive calcium load. Acidosis, if present, should be treated with oral sodium bicarbonate because persistent acidosis has deleterious effects on the skeleton. The additional sodium load may require further salt restriction or increases in diuretics. Aluminum-based phosphate binders should be avoided. If hyperparathyroidism (iPTH more than two to three times above the upper normal range of the assay) persists despite these measures, consideration should be given to the addition of calcitriol (0.25 to 0.5 mcg/day), vitamin D analogues, or vitamin D prohormones to the regimen. This therapy should be monitored carefully to avoid hypercalcemia and acceleration of progression of CKD.

In CKD stages 4 and 5, the preceding therapies may need to be intensified and larger amounts of phosphate binders may be required to avoid hyperphosphatemia. The use of aluminum-containing phosphate binders is particularly undesirable at this stage in view of the increased risk for aluminum accumulation with worsening renal function. In patients on dialysis, calcitriol therapy can be intensified, with attention to the serum levels of calcium and phosphate and monitoring of iPTH levels. In CKD stage 5, iPTH levels should be maintained approximately two to nine times above the upper limit of the assay used to maintain normal bone turnover.[23] Calcitriol may be administered orally either daily or intermittently (pulse therapy) or administered intravenously to patients on HD. During therapy with calcitriol, it is imperative to ensure serum phosphate remains controlled and elevations of serum calcium do not occur to prevent metastatic calcification. Vitamin D analogues, which are less calcemic and phosphatemic than calcitriol and yet retain the ability to suppress the levels of PTH, may be useful. Cinacalcet provides additional effective control of hyperparathyroidism in patients with ESRD and may be used alone or in combination with the other strategies if iPTH levels do not fall into the target range. Parathyroidectomy should be considered in selected circumstances. Bone biopsy may be indicated in selected patients, particularly if aluminum overload is suspected. Aluminum overload may require chelation therapy with deferoxamine in selected circumstances, especially if it is symptomatic, but in most patients the prevention of further aluminum exposure is sufficient to allow a gradual reduction in the serum levels of aluminum. During therapy with potent vitamin D metabolites, attention should be given to the dialysate calcium concentrations because high concentrations may aggravate hypercalcemia. However, the increasingly frequent use of lower dialysate calcium levels, such as 1.25 mmol/l, requires careful monitoring of the patient to ensure compliance with calcium-containing phosphate binders and vitamin D metabolites to avoid progressive negative calcium balance. Dialysate calcium should remain within the range of 1.25 to 1.75 mmol/l and, when possible, should be individually prescribed.

LOW-TURNOVER RENAL BONE DISEASE

ABD describes the morphologic consequences of low-turnover osteopathy in CKD. As CKD progresses, hyperparathyroidism initially develops as an adaptive response to counteract the increasing skeletal PTH resistance and phosphate overload. ABD mainly results from too rigorous suppression of this adaptive response. ABD is increasingly important in CKD-MBD because of the high percentage of affected individuals (>40% in CKD stage 5) and because of its association with CV calcification and mortality.[31,32] Furthermore, fracture incidence is estimated to be twice as high in individuals with low than in those with high bone turnover. ABD prevalence is markedly increasing in bone biopsy registries of dialysis patients, which may relate to the increasing

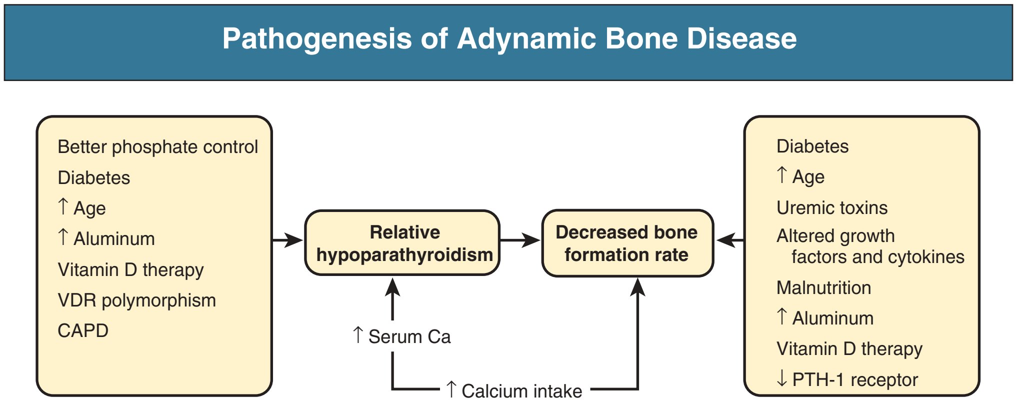

Fig. 84.14 Pathogenesis of adynamic bone disease. *Ca,* Calcium; *CAPD,* continuous ambulatory peritoneal dialysis; *PTH,* parathyroid hormone; *VDR,* vitamin D receptor. (Modified reference 57.)

prevalence of its key risk factors—advanced age and diabetes mellitus. PD also represents a risk factor, possibly because of an often continuous exposure to high dialysate calcium as opposed to the cyclic exposure associated with HD.

Pathogenesis of Adynamic Bone Disease

Given that the bone develops a relative resistance of the PTH-1 receptor to its ligand PTH as CKD progresses, PTH levels above the normal range are required to maintain adequate bone turnover. Unfortunately, there are no definite ranges of elevated PTH levels that can reliably differentiate an adaptive response (normal bone turnover) from a maladaptive response (increased bone turnover) because PTH resistance individually varies and because it depends on the stage of CKD. Accordingly, ABD is a consequence of inadequately low PTH levels, which cause suppression or cessation of both osteoblast and osteoclast activities, resulting in a reduced bone formation rate and low bone mass. Iatrogenic oversuppression of PTH in CKD mainly results from high-dose active vitamin D metabolite treatment, from calcium loading (high doses of calcium-containing phosphate binders, high dialysate calcium concentration), or after parathyroidectomy. The effects of calcimimetic treatment on bone turnover have been prospectively evaluated in HD patients, and patients in this cohort had significant high-turnover osteopathy at baseline (average iPTH >1200 pg/ml). Therapy with cinacalcet decreased elevated bone formation rate and improved bone histologic status.[33] ABD occurred only if iPTH was suppressed below the KDIGO target range of two to nine times the upper reference range of the assay. Finally, diabetes, uremic toxins, malnutrition, and potentially, C-terminal PTH fragments may be additional factors favoring a state of low bone turnover (Fig. 84.14).

Diagnosis and Differential Diagnosis

Serum Biochemistry

Low iPTH levels (<100 to 150 pg/ml) are almost always indicative of low bone turnover in CKD stage 5D. However, histologically proven ABD may occur in many dialysis patients with iPTH levels of up to 300 pg/ml and, in exceptions, of up to 600 pg/ml.[34,35] Therefore PTH levels alone are not a sensitive biomarker of ABD. Serum levels or activities of alkaline phosphatase or bone alkaline phosphatase are usually normal or low; downward trends may indicate the development of ABD. Serum calcium and phosphate can be normal or elevated, dependent on the choices of cotreatment (phosphate binders, vitamin D metabolites) and nutritional status. Particularly in instances of calcium and phosphate loading, hypercalcemia and hyperphosphatemia may be pronounced because adynamic bone is unable to buffer calcium and phosphate loads by osseous deposition (Fig. 84.15).

In CKD stages 3 and 4, there are uncertainties about the diagnosis of ABD and its clinical consequences. It is unclear which PTH levels are required to maintain adequate bone turnover in these stages. It seems reasonable to correct vitamin D deficiency, hyperphosphatemia, and hypocalcemia when PTH levels start to rise, but beyond that, no firm recommendations can be given.

Bone Biopsy

The gold standard for diagnosis of ABD is bone biopsy. According to the TMV classification (see earlier discussion),[1] ABD is characterized by low turnover, normal (or high secondary) mineralization, and low bone (osteoid) volume. The individual indication to perform bone biopsy should be considered in symptomatic patients based on inconsistencies of biochemical parameters associated with unexplained fractures, bone pain, progressive extraosseous calcifications, or hypercalcemia. The KDIGO initiative recently investigated more than 492 bone biopsy samples and concomitant serum samples to identify biomarker patterns that may allow noninvasive assessment of bone turnover status. ABD was quite strongly associated with low-normal to low BAP levels. In general, PTH and BAP could distinguish low from non-low and high from non-high bone formation rate.[36] However, there is considerable heterogeneity between the extremes. Aluminum toxicity is a relevant differential diagnosis versus ABD. Thus, if the patient's history suggests significant aluminum exposure, aluminum bone deposition should be excluded by measurement of serum aluminum and specific staining of a bone biopsy specimen.

Radiology and Measurements of Bone Density

There are no typical features of ABD in conventional bone radiographs or DEXA. In the latter, bone density may be low, normal, or high, depending on the primary or secondary mineralization state, but it never reflects the actual turnover and is therefore not a helpful diagnostic test (Fig. 84.16). A very high CV calcification burden on conventional radiographs may raise the suspicion of a low bone turnover state if accompanying biochemical parameters are compatible with this diagnosis. Biopsy-proven ABD is associated with the highest magnitude of vascular calcification in dialysis patients.[31]

Treatment of Adynamic Bone Disease

The key therapeutic approaches in the treatment of ABD are to avoid PTH overexpression and restore adequate PTH levels, without triggering the progressive development of secondary hyperparathyroidism. Such a stepwise treatment approach may include avoidance of calcimimetics, reduction or withdrawal of active vitamin D metabolites, reduction or withdrawal of calcium-containing phosphate binders, and reduction of the dialysate calcium concentration (usually to 1.25 mmol/l). Indeed, a recent RCT found a histologic improvement of low bone turnover when the dialysate calcium concentrations were decreased from 1.5 or 1.75 mmol/l to 1.25 mmol/l.[37] Any aluminum should be withdrawn. After these interventions, biochemical parameters (PTH, calcium, phosphate, perhaps alkaline phosphatase, and especially BAP) should be monitored more frequently than usual.

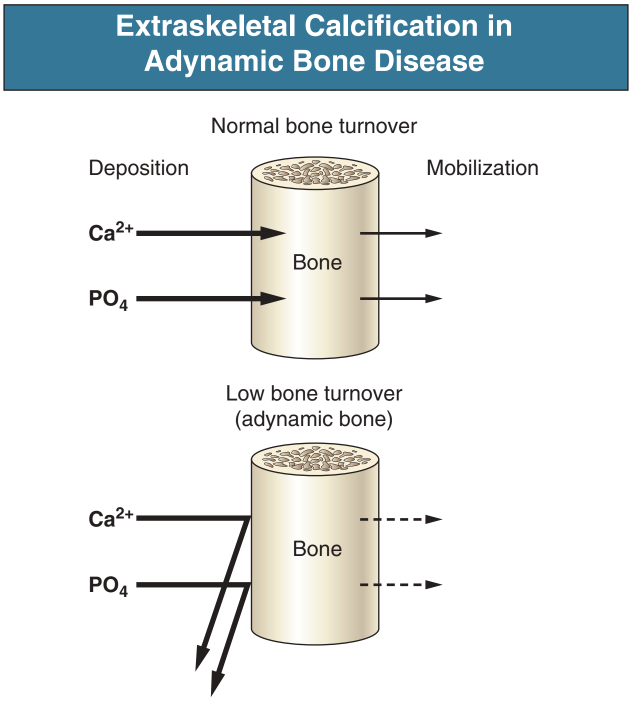
Extraskeletal Calcification in Adynamic Bone Disease
Normal bone turnover
Deposition
Mobilization
Ca^{2+}
PO_4
Bone
Low bone turnover (adynamic bone)
Ca^{2+}
PO_4
Bone

Fig. 84.15 **Bone turnover in adynamic bone disease.** Reduced bone turnover leads to increased extraskeletal calcification. *Ca^{2+}*, Calcium ion; *PO_4*, phosphate.

Studies comparing calcium-containing with non–calcium-containing phosphate binders in dialysis patients[35,38] found that the administration of calcium-containing phosphate binders was associated with a higher proportion of individuals who developed ABD. This development was associated with a fall in serum PTH because of the higher calcium load. In an observational study, high-dose calcium-containing phosphate binder intake was associated with both low bone turnover and increased aortic calcification.[39]

Other therapeutic approaches to ABD have not been systematically studied. They include optimized diabetes control, a change from PD to HD to facilitate a more flexible dialysate calcium prescription, the administration of recombinant PTH (e.g., for patients after total parathyroidectomy), and calcilytics (agents that antagonize the calcium receptor and thus increase endogenous PTH).[40] At present, many patients with ABD remain refractory to treatment.

OSTEOPOROSIS IN CHRONIC KIDNEY DISEASE

Whereas abnormal bone is common and fracture risk is increased in CKD patients, the relative contribution of classic osteoporosis (as defined by World Health Organization [WHO] criteria) to the CKD-MBD complex is not well defined. Data from studies of antiosteoporosis agents are mostly available for patients in CKD stages 1 to 3, and subjects with features of CKD-MBD were largely excluded. Nevertheless, postmenopausal women and elderly men are highly prevalent in late-stage CKD populations, and it is thus likely that classic osteoporosis also contributes to their bone disease.

Pathogenesis of Osteoporosis in Chronic Kidney Disease

Osteoporosis may be associated with low, normal, or high bone turnover and is characterized by thin and disconnected trabeculae and loss of the plate-like bone structure. Many patients with CKD have abnormal

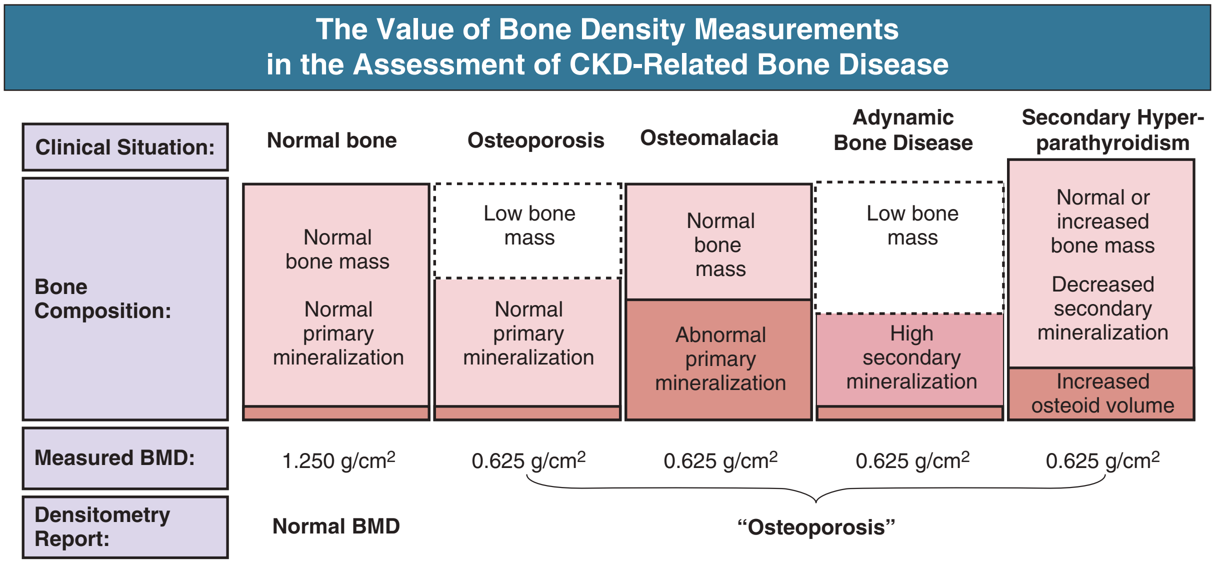
The Value of Bone Density Measurements in the Assessment of CKD-Related Bone Disease
Clinical Situation:
Normal bone
Osteoporosis
Osteomalacia
Adynamic Bone Disease
Secondary Hyper-parathyroidism
Bone Composition:
Normal bone mass
Normal primary mineralization
Low bone mass
Normal primary mineralization
Normal bone mass
Abnormal primary mineralization
Low bone mass
High secondary mineralization
Normal or increased bone mass
Decreased secondary mineralization
Increased osteoid volume
Measured BMD:
1.250 g/cm²
0.625 g/cm²
0.625 g/cm²
0.625 g/cm²
0.625 g/cm²
Densitometry Report:
Normal BMD
"Osteoporosis"

Fig. 84.16 **The value of bone density measurements in the assessment of chronic kidney disease (CKD)–related bone disease.** *Pink boxes* indicate mineralized bone; *red boxes* indicate osteoid. *BMD,* Bone mineral density. (Courtesy Prof. M. H. Lafage-Proust, St. Etienne, France.)

mineralization and increased osteoid, which is quite atypical for osteoporosis. Typical pathogenetic factors of osteoporosis, including hypoestrogenemia, immobilization, and corticosteroid use, are frequent in CKD patients, although some postmenopausal women with late-stage CKD may have relatively normal estrogen levels. However, the sum of CKD-MBD–related biochemical disturbances probably represents the decisive factors as to which bone phenotype predominates. Secondary hyperparathyroidism, relative hypoparathyroidism (as in ABD), and 25-hydroxyvitamin D, as well as 1,25-dihydroxyvitamin D deficiencies, may dominate and "overrule" the bone phenotype of osteoporosis even if classic risk factors are present.

Diagnosis and Differential Diagnosis

In patients with advanced CKD, bone turnover biomarkers and measurements of bone mineral density by DEXA are of no value (see Fig. 84.16) in the differential diagnosis of classic osteoporosis versus other CKD-MBD–related bone disease. Assays for biomarkers, such as β-CrossLaps (C-terminal cross-linked, CTX; marker of bone collagen degradation), procollagen type I *N*-terminal propeptide (PINP; marker of bone collagen synthesis), and tartrate-resistant alkaline phosphatase 5b (TRAP5b; marker of osteoclast activity) are insufficiently validated in CKD patients, and low bone mineral density can be found in CKD-MBD–induced high-turnover bone disease, ABD, and osteomalacia (see Fig. 84.16). However, there is recent evidence that bone mineral density (as measured by DEXA) does predict fracture risk in CKD patients to an extent similar to that in the general population, so this method may become useful in monitoring therapeutic drug effects or risk assessments. Still, DEXA remains unable to distinguish osteoporosis from CKD-MBD–associated bone phenotypes. Peripheral quantitative tomography (pQCT) of the radius may be a superior methodology for assessment of CKD patients in the future but awaits validation in sufficiently large patient cohorts.[41] The only reliable methodology to diagnose osteoporosis and discriminate it from other bone manifestations in CKD patients is bone biopsy. In a large bone biopsy study, including 1429 samples from dialysis patients, osteoporosis was diagnosed in 52% of individuals and 49% of them also had ABD.[42] These proportions may be quite different in patients in earlier CKD stages, but there are no systematic data available on such cohorts.

Treatment of Osteoporosis in Chronic Kidney Disease

Post hoc analyses of large prospective treatment studies using antiosteoporotic medications indicate that it is safe and efficacious to treat postmenopausal women in stages CKD 1 to 3 if they have a high risk for fractures (according to WHO criteria) and no features of CKD-MBD.[43-46] In such populations, bisphosphonates, denosumab, raloxifene, and teriparatide appear to be feasible therapeutic options. The former three drugs antagonize high bone turnover with an antiresorptive mode of action; teriparatide exerts bone anabolic effects (PTH analogue). With bisphosphonates, there may be concerns of an extended oversuppression of osteoclasts, but only in patients with advanced CKD. A recent subanalysis of patients in CKD stages 2 to 4 from the Following Rehabilitation, Economics and Everyday-Dialysis Outcomes Measurements (FREEDOM) trial demonstrated a significantly reduced fracture risk with denosumab treatment versus placebo, independent of the stage of CKD.[47] In contrast, for patients in CKD stages 3 to 5 with features of CKD-MBD, no data are available on the safety and efficacy of any of these antiosteoporotic medications. In CKD patients with ABD, bisphosphonates and denosumab may aggravate osteoclast paralysis. In CKD patients with secondary hyperparathyroidism, these antiresorptive agents may upregulate PTH secretion. Patients with advanced CKD (stages 4 and 5) may develop particularly severe hypocalcemia when treated with denosumab; coadministration of vitamin D analogues may be required to blunt this effect. However, given the growing evidence that antiresorptive therapies may be effective at least in patients with CKD stages 3 and 4, and the lack of definite evidence that these drugs induce ABD in this population, it may not be necessary to perform a bone biopsy before treatment initiation, if a clinical response is otherwise suspected.

β_2-MICROGLOBULIN–DERIVED AMYLOID

β_2-Microglobulin–derived (Aβ_2M) amyloidosis, also termed *dialysis-associated amyloidosis,* exclusively affects patients with stage 5 CKD. It is a systemic amyloidosis. Clinical manifestations are largely confined to the musculoskeletal system. In recent years the disease has become notably infrequent. Aβ_2M amyloidosis in CKD stage 5 should not be confused with a rare hereditary systemic amyloidosis derived from the Asp76Asn variant of β_2-microglobulin, which manifests in the absence of CKD.

Pathogenesis

Fibrils of Aβ_2M amyloid are derived from the circulating precursor protein β_2-microglobulin, the nonvariable light chain of the human leukocyte antigen (HLA) class I complex. The pathogenesis appears to involve three events:

1. Pronounced renal retention of β_2-microglobulin (11.8 kDa), leading to plasma levels that can be elevated up to 60-fold in dialysis patients[48]; however, even massive overproduction of β_2-microglobulin in mice was not sufficient to induce amyloid deposits and thus further steps must be important.[49]
2. Modifications of the β_2-microglobulin molecule that render it more amyloidogenic, such as limited proteolysis or the formation of different sugar-protein cross-links.[50]
3. Local factors that contribute to and determine the spatial localization of the amyloidosis.

Epidemiology

Histologic studies from the 1990s observed amyloid deposits in 100% of dialysis patients treated for more than 13 years.[51] Most amyloid deposits never cause clinical problems. The main risk factors for Aβ_2M amyloid deposition are age at onset of renal replacement therapy (RRT) and the duration of (nontransplant) RRT.[48-50] Aβ_2M amyloid–related symptoms presently are largely confined to patients who have been dialyzed for more than 15 years.

Clinical Manifestations and Diagnosis

Aβ_2M amyloidosis mainly manifests at osteoarticular sites, particularly synovial membranes; visceral manifestations are rare.[48-50] Carpal tunnel syndrome occurs and symptoms typically worsen at night and during HD. It is often bilateral and usually requires surgery. Osteoarthropathy of peripheral joints, resulting from amyloid deposition in periarticular bone and the synovial capsule (Fig. 84.17), is characterized by recurrent or persistent arthralgias, stiffness of large and medium-sized joints, and swelling of capsules and adjacent tendons. Recurrent joint effusions and synovitis, often in the shoulders and knees, may occur. The clinical presentation may vary from frank, acute arthritis to slow, progressive destruction of the affected joints. Destructive spondyloarthropathy (Fig. 84.18) resulting from Aβ_2M amyloidosis can manifest as asymptomatic deposits, radiculopathy, stiffness, "mechanical ache," and, finally, medullary compression with resulting paraplegia or cauda equina syndrome. Other manifestations include camptodactyly (a flexion deformity resulting in bent fingers that cannot completely extend or straighten) resulting from amyloid deposits along the flexor tendons of the hands (Fig. 84.19).

Patients undergoing dialysis also can have subcutaneous tumorous deposits of Aβ_2M amyloid; however, diffuse infiltration of the subcutaneous fat or skin has not been observed.

Case reports of clinically relevant organ manifestations are usually in patients treated with HD for more than 15 years and have described heart failure, odynophagia (painful swallowing), intestinal perforation of both small and large bowel, gastrointestinal bleeding and pseudoobstruction, gastric dilation, paralytic ileus, persistent diarrhea, macroglossia or functional tongue disturbances (abnormal taste, mobility, articulation), ureteral stenosis, and renal calculi.

Diagnosis

Serum levels of β_2M do not distinguish between patients with amyloidosis and those without. Ultrasound can detect synovial Aβ_2M amyloidosis as thickening of the joint capsules of the hip and knee, biceps tendons, and rotator cuffs, as well as the presence of echogenic structures between muscle groups and joint effusions.[48-50] On radiologic examination, affected joints may present with single or multiple juxtaarticular, "cystic" (i.e., amyloid-filled) bone radiolucencies (Fig. 84.20; see also Fig. 84.17). Such bone defects are prone to pathologic fractures. Diagnostic criteria for Aβ_2M amyloid–induced cystic bone radiolucencies have been published.[52] They include (1) diameter of lesions more than 5 mm in wrists and more than 10 mm in shoulders and hips, (2) normal joint space adjacent to the bone defect, (3) exclusion of small subchondral cysts in the immediate weight-bearing area of the joint and of defects of the "synovial inclusion" type, (4) increase of defect diameter of more than 30% per year, and (5) presence of defects in at least two joints. Scintigraphy, using either radiolabeled serum amyloid P component or β_2-microglobulin,[53] offers more specific detection of amyloid deposits but is not widely available. The definitive diagnosis of Aβ_2M amyloidosis relies on histologic findings. Fat aspiration and rectal biopsy are not helpful in Aβ_2M amyloidosis, but diagnostic material can be obtained from synovial membranes, synovial fluid, or bone lesions.[48]

Treatment and Prevention

Therapy for established Aβ_2M amyloidosis is symptomatic. NSAIDs and physical and surgical measures, such as carpal tunnel

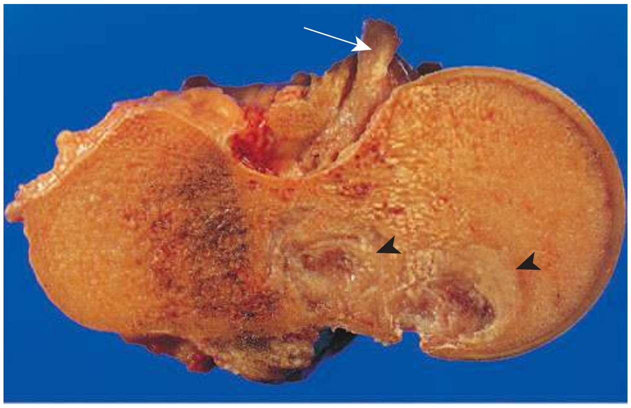

Fig. 84.17 Aβ_2M amyloid deposition in the femoral head. Postmortem specimen from a long-term hemodialysis patient. Two large lesions *(arrowheads),* partly filled with grayish amyloid and partly cystic, are noted in the femoral head. Also note the marked thickening of the synovial capsule from amyloid deposition *(arrow).*

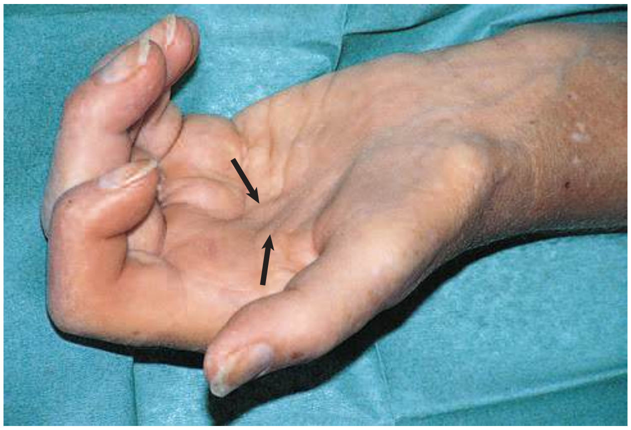

Fig. 84.19 Hand involvement in Aβ_2M amyloidosis. Hand of a long-term hemodialysis patient showing maximal extension. Note the prominence of shrunken flexor tendons *(arrows).* This is also known as the *guitar string* sign.

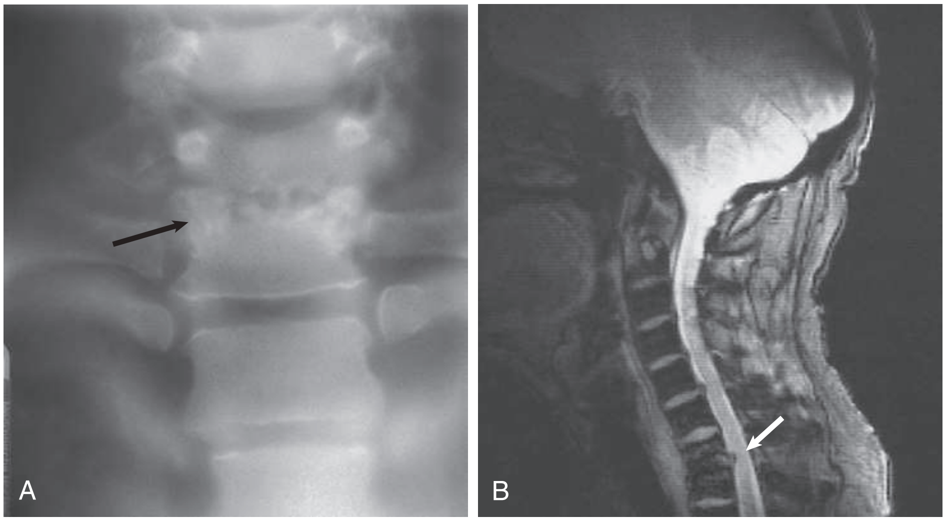

Fig. 84.18 Aβ_2M amyloidosis–associated spondyloarthropathy. (A) Destruction of an intervertebral disk *(arrow)* in the neck vertebrae of a long-term hemodialysis patient. (B) Magnetic resonance image of the same patient as in A. Note destruction of the intervertebral space and protrusion of material into the spinal canal *(arrow).*

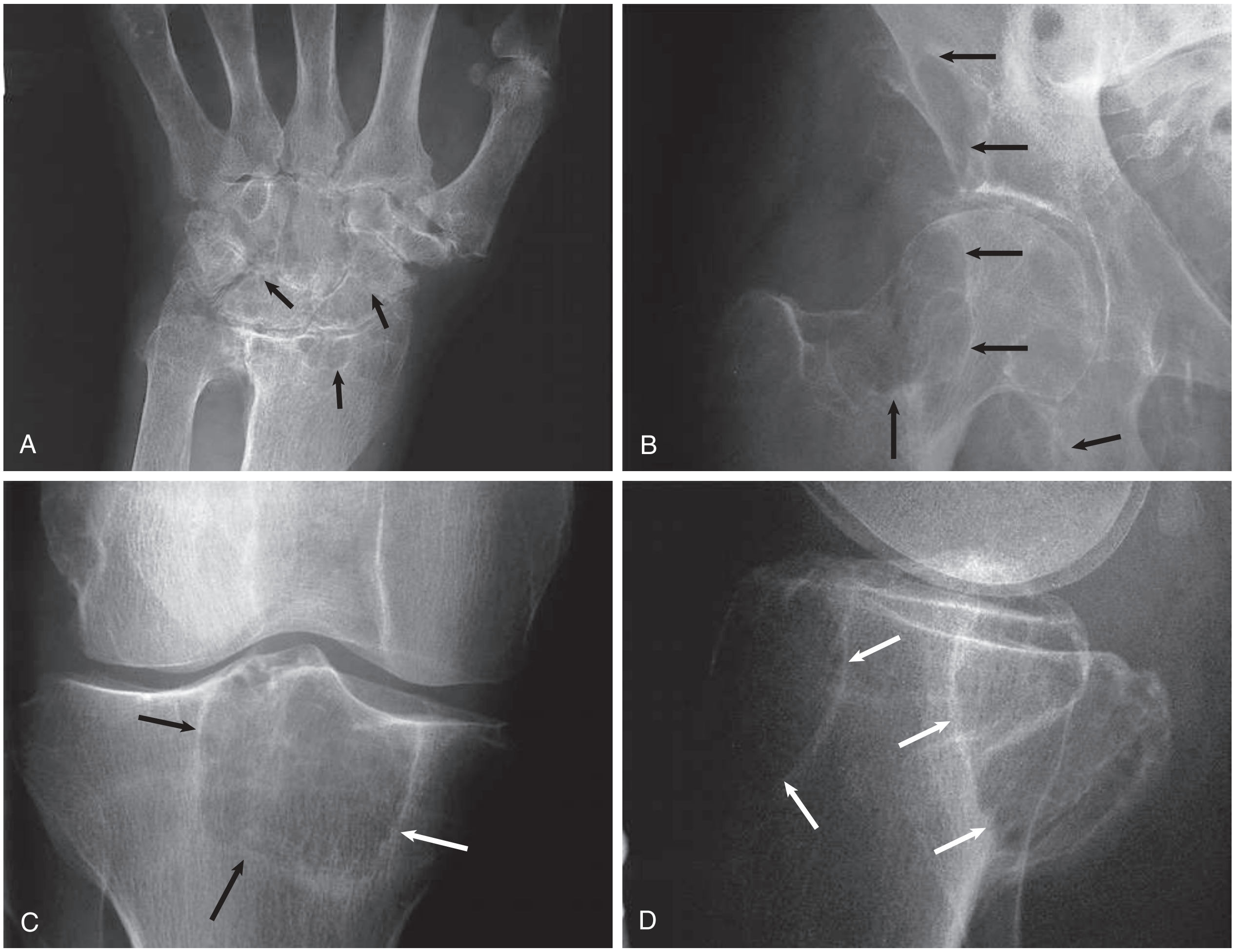

Fig. 84.20 Peripheral bone cystic radiolucencies in Aβ_2M amyloidosis. Radiographic findings in a long-term hemodialysis patient. (A) Multiple cystic lesions *(arrows)* are present in the hand bones. (B) Large cysts *(arrows)* in the neck of the femur and adjacent pelvic bones. (C and D) Anterior and lateral views of the head of the tibia with two very large, cystic lesions *(arrows)* resulting in posterior bulging of the tibial plateau.

decompression, endoscopic coracoacromial ligament release, and bone stabilization in areas of cystic destruction, are all used.[48] Although some dialysis modalities allow significant removal of β_2M, there is at present no convincing evidence that this is of therapeutic value in established Aβ_2M amyloidosis. Renal transplantation is the preferred treatment because it leads to rapid symptomatic improvement and halts further progress of the disease, but whether this can actually lead to regression of established Aβ_2M amyloid deposits is a subject of controversy.

A number of strategies exist for prevention of the clinical manifestations of Aβ_2M amyloidosis.[48] The risk for carpal tunnel syndrome is reduced by 40% to 50% in patients treated with high-flux hemo(dia)filtration and minimal in patients receiving online hemodiafiltration. A dramatic reduction in the prevalence of carpal tunnel syndrome occurred in patients dialyzed with ultrapure dialysate. In another study, an 80% reduction of amyloid signs in a chronic HD population appeared to relate to dialysate factors such as microbiologic purity and the use of bicarbonate buffer. Finally, in uncontrolled studies a β_2M adsorption column was reported to decrease Aβ_2M amyloid–associated symptoms, but the effect on bone lesions was not significant.

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SELF-ASSESSMENT QUESTIONS

1. A 56-year-old White woman with end-stage renal disease (ESRD) secondary to presumed hypertensive nephrosclerosis has been on maintenance hemodialysis (HD) for 3.5 years. She reports to dialysis treatments regularly and is being adequately dialyzed. Laboratory data over the past few months reveal that intact parathyroid hormone (PTH) levels have ranged from 360 to 545 pg/ml, serum calcium 9.5 to 10.5 mg/dl (2.4 to 2.6 mmol/l), and phosphorus 5.5 to 7.0 mg/dl (1.83 to 2.33 mmol/l). She has been treated with increasing doses of paricalcitol, dietary phosphate restriction, and calcium carbonate as a phosphate binder. A few days ago, she was seen by her internist regarding vague symptoms that included abdominal pain. At that time, blood tests showed serum phosphorus 7.6 mg/dl (2.5 mmol/l) and calcium 10.1 mg/dl (2.5 mmol/l). The rest of the metabolic profile was within normal limits. A kidney, ureter, and bladder (KUB) film of the abdomen showed calcification of the abdominal aorta. What is the most appropriate next step in the management of this patient's chronic kidney disease–mineral and bone disorder (CKD-MBD)?
   A. Increase the dose of paricalcitol
   B. Increase the dose of calcium carbonate to improve phosphate control
   C. Stop calcium carbonate and add a non–calcium-containing phosphate binder
   D. Refer for parathyroidectomy
   E. Decrease dialysate calcium
2. A 75-year-old White man on HD because of diabetic nephropathy exhibits rapid progression of vascular calcification. His total serum calcium fluctuates around the upper limit of normal, with occasional episodes of mild hypercalcemia. Serum phosphorus is around 7 mg/dl (2.3 mmol/l) despite various changes of his phosphate binder medication. The latest intact PTH level is 105 pg/ml (previous levels ranged from 90 to 180 pg/ml). Current medication includes fluvastatin, calcium acetate, low-dose aspirin, a β-blocker, and insulin. What is the most appropriate next step in the management of this patient's CKD-MBD?
   A. Continue the described therapy.
   B. Increase the dose of calcium acetate to improve phosphate control.
   C. Repeat dietary counseling.
   D. Add low-dose calcitriol (e.g., 0.25 mcg/day).
   E. Replace calcium acetate with a calcium-free phosphate binder.
3. A 68-year-old White woman with an estimated glomerular filtration rate (eGFR) of 25 ml/min as a result of presumed hypertensive nephrosclerosis presents for a regular checkup. She has no specific complaints. Medication consists of an angiotensin-converting enzyme (ACE) inhibitor, a loop diuretic, a β-blocker, and low-dose aspirin. Current laboratory values include intact PTH level 90 pg/ml (reference range: <60), serum calcium 8.1 mg/dl (2.0 mmol/l) and phosphorus 5.7 mg/dl (1.8 mmol/l), 25(OH)-vitamin D_3 17 μg/l (target range 30 to 100). What step in the management of this patient's CKD-MBD is *not* appropriate?
   A. Educate the patient about phosphate content in food.
   B. Initiate therapy with a phosphate binder.
   C. Initiate substitution of 20,000 IU vitamin D_3 every second week.
   D. Educate the patient about food additives.
   E. Initiate therapy with a low dose of a calcimimetic.

85

Neurologic Complications of Chronic Kidney Disease

Julian L. Seifter, Martin A. Samuels

Disorders of the nervous system may coexist with renal disease in patients with systemic disorders (e.g., hypertensive encephalopathy, thrombotic microangiopathies, atheroembolic and atherosclerotic disease, vasculitides) and fluid and electrolyte abnormalities. Neurologic complications accompany acute kidney injury (AKI) in the intensive care setting and in outpatients with chronic kidney disease (CKD). Furthermore, patients with CKD are at increased risk for toxin- and pharmacologic agent–induced neurotoxicity. This chapter focuses on the direct neurologic consequences of CKD.

UREMIC ENCEPHALOPATHY

The syndrome of uremic encephalopathy (UE) involves a spectrum of brain abnormalities that may clinically range from nearly imperceptible changes to coma.

Pathogenesis

The brain in CKD has decreased metabolic activity and oxygen consumption.[1,2] As long as the underlying renal disease has not affected cerebral hemodynamics and responsiveness to carbon dioxide, these functions appear intact, but subtle disturbances have been detected after dialysis.

Many theories support the role of uremic toxins that accumulate in CKD. The balance of excitatory and inhibitory neurotransmitters may be disrupted by organic substances,[3] in particular guanidino compounds, which are increased in cerebrospinal fluid.[4,5] These compounds antagonize γ-aminobutyric acid ($GABA_A$) receptors and at the same time have agonistic effects on *N*-methyl-D-aspartate glutamate receptors, leading to enhanced cortical excitability. Asymmetric dimethylarginine,[6] which is increased in CKD, inhibits endothelial nitric oxide synthase, and levels correlate with cerebrovascular complications in uremia. Disturbances in monoamine metabolism include a depletion of norepinephrine and suppression of central opamine, which has been linked to the impairment of motor activity in uremic rats. Myo-inositol, carnitine, indoxyl sulfate, and polyamine content, as well as disrupted solute transport and permeability, have been implicated in the neuronal dysfunction of uremia. Metabolites of drugs such as cimetidine and acyclovir are increased in uremia because of inhibition of organic anion transporter 3 (OAT3) and may result in neurotoxic syndromes.[7] Levels of opiates and in particular metabolites of meperidine increase in plasma because of decreased excretion through renal cation secretory transport, with subsequent neurotoxicity.[8]

Secondary hyperparathyroidism also may play a role in UE[9,10] because brain calcium is increased in CKD and calcium transporters within neurons are sensitive to parathyroid hormone. Increased cellular calcium may play a role in neuroexcitation.

Appetite regulation is abnormal in uremia (see Chapter 86). A high rate of tryptophan entry across the blood-brain barrier may increase the synthesis of serotonin, a major appetite inhibitor.[11] High levels of cholecystokinin, a powerful anorectic, and low levels of neuropeptide Y, an appetite stimulant, have been observed. Cachexia may result from anorexia, acidosis, and inflammation. Inflammatory cytokines such as leptin, tumor necrosis factor-α, and interleukin-1 may signal anorexigenic neuropeptides such as proopiomelanocortin and α-melanocyte–stimulating hormone in the arcuate nucleus of the hypothalamus.

Clinical Manifestations

Whereas 20% of patients with AKI in an intensive care unit setting developed neurologic impairment,[12] the syndrome in CKD is more subtle, not correlating closely to the level of renal function.[13] Cross-sectional studies in hemodialysis (HD) patients found cognitive impairment in 30%, with about 10% exhibiting severe impairment. Neurocognitive deficits may have special implications for CKD in early childhood, adversely affecting development of the brain.[14]

UE can manifest as complex mental changes or motor disturbances (Box 85.1). The full-blown syndrome is a risk factor for morbidity and mortality.[1,2] Mental findings include emotional changes, depression, disturbing and disabling cognitive and memory deficits, and, in the most severe form, a generalized disorder characterized by delirium, psychosis, seizures, coma, and ultimately death. Severe motor symptoms or signs are rare. Depression, anxiety, and even suicide are important underdiagnosed and undertreated aspects of uremia and may be related to metabolic or poor nutritional state and fear of dialysis or death. Other known causes of depression should always be sought.

Stable UE manifests with fine action tremor, asterixis, and hyperreflexia. Asterixis is characterized by intermittent loss of muscle tone in antigravity muscles. It is distinguished from tremor by the fact that it is not an oscillation but rather an intermittent loss of tone. Myoclonus is also seen in patients with UE. It is similar in timing to asterixis (10 to 100 ms) but is caused by activation of antigravity muscles. For this reason, some consider asterixis to be a form of negative myoclonus. The distinction between asterixis and myoclonus is less important than once thought because both or either may be present in many metabolic encephalopathies and some structural brain diseases as well. Asterixis and myoclonus may be elicited with the hands outstretched but may be more sensitively assessed by looking at the protruded tongue or the index finger raised with the hand resting on a firm surface. Asterixis and myoclonus may be seen in patients with renal impairment who have received various drugs (e.g., metoclopramide, phenothiazines, antiepileptic drugs including gabapentin, and opioids, especially meperidine). With increased use of opiates it is imperative for the treating physician to understand the life-threatening complications of drugs in

BOX 85.1 Clinical Manifestations of Uremic Encephalopathy

Early Encephalopathy

Mental Changes

- Mood swings
- Impaired concentration, loss of recent memory
- Insomnia, fatigue, apathy

Motor Changes

- Hyperreflexia
- Tremor, asterixis
- Dysarthria, altered gait, clumsiness, unsteadiness

Late Encephalopathy

Mental Changes

- Altered cognition and perception
- Illusions, visual hallucinations, agitation, delirium
- Stupor, coma

Motor Changes

- Myoclonus, tetany
- Hemiparesis
- Seizures

TABLE 85.1 Opioid Use in End-Stage Renal Disease

Drug	Active Metabolites	Comments
Codeine	Morphine	Active metabolites accumulate in patients with renal failure; should avoid in dialysis.
Hydrocodone	Hydromorphone	
Meperidine	Normeperidine	
Morphine	Morphine-3-glucuronide Morphine-6-glucuronide	Active metabolites accumulate in patients with renal failure; can cause myoclonus and respiratory depression; mostly replaced by hydromorphone.
Hydromorphone	Hydromorphone-3-glucuronide	Mostly metabolized in liver. Active metabolites removed by dialysis, but small amounts accumulate in patients with renal failure.
Oxycodone	Oxymorphone Noroxycodone	
Fentanyl	No active metabolites	Metabolized in liver; not removed by dialysis
Methadone		Fecal excretion; not removed by dialysis

this class for the patient with CKD before and after initiation of dialysis[8] (Table 85.1). Metabolic acidosis may produce an indistinguishable encephalopathy, as can aluminum toxicity. Therefore a careful search for other causes is required before features potentially consistent with UE are attributed to advanced uremia requiring renal replacement therapy (RRT).

Advanced UE is usually characterized by a reduced level of consciousness, anorexia, asterixis, myoclonus, and upper motor neuron signs that result in disturbances of gait and speech.

Diagnosis and Differential Diagnosis

Severe UE is unlikely to occur in patients with CKD who are followed closely before initiation of RRT (see Chapter 90). UE is more likely to occur in the patient who initially presents with kidney failure or a dialysis patient after missing many treatments. The blood urea nitrogen concentration most commonly exceeds 200 mg/dl. Hypertension is often present, and the manifestation may be mistaken for hypertensive encephalopathy. The diagnosis of UE is based on clinical findings and their improvement after adequate therapy (see next section). If the patient develops more insidious signs of cognitive impairment while undergoing dialysis, inadequate dialysis treatment must be distinguished from dialysis-associated dementia, Alzheimer disease, or other cause of chronic impairment. Lumbar puncture, electroencephalography, and imaging procedures largely serve to exclude other causes in patients in whom the clinical diagnosis is doubtful. In UE the cerebrospinal fluid is often abnormal, sometimes demonstrating a modest pleocytosis (usually <25 cells/mm^3) and increased protein (usually <100 mg/dl). The electroencephalogram is usually abnormal but nonspecific. Generalized slowing in the theta and delta wave ranges is found.[15] Brain imaging usually shows cerebral atrophy and enlargement of the ventricles (Fig. 85.1).

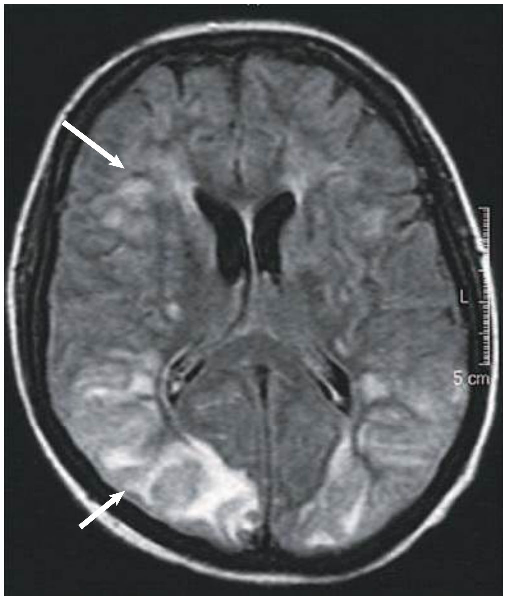

Fig. 85.1 Magnetic resonance imaging (MRI) findings in uremic encephalopathy. Axial T2-weighted MRI (fluid-attenuated inversion recovery) scan from a 40-year-old woman. The extensive hyperintense lesion involves the cortical and subcortical areas of both occipital lobes and, in a more focal distribution, the basal ganglia and the frontal white matter *(arrows)*. The volume of the affected brain parenchyma is increased. Reversibility of the MRI changes was noted 2 weeks after the initiation of regular dialysis. (Courtesy A. Thron, Aachen, Germany.)

The differential diagnosis of UE is shown in Table 85.2. Seizure activity may be secondary to UE, hypertensive encephalopathy, cerebral embolism, cerebral venous thrombosis, or electrolyte and acid-base abnormalities. Tetany can develop when treatment involves alkalinization of an acidemic patient with renal disease and hypocalcemia. Severe electrolyte abnormalities, including hypocalcemia, hypomagnesemia, hyponatremia and hypophosphatemia, may manifest with delirium.

Treatment

Most nephrologists consider advanced cognitive or memory impairment an indication for initiation of RRT. Most of the manifestations of central nervous system (CNS) involvement are reversible with dialysis within days or weeks, but mild signs of UE may persist. Patients who do not manifest severe signs of encephalopathy often notice improvement in

TABLE 85.2 **Differential Diagnosis of Uremic Encephalopathy**

Differential Diagnosis	Comment
Hemodynamic or Vascular Encephalopathy	
Systemic inflammatory response syndrome (SIRS)	Observed in septic patients.
Systemic vasculitis	Vasculitis or lupus with cerebral involvement.
Cerebral atheroembolic disease	Follows recent aortic or cardiac angiography; associated with peripheral manifestations, including lower extremity cyanosis, livedo reticularis, and eosinophilia.
Drug-Induced Neurotoxicity	
Analgesics	Meperidine, codeine, morphine, gabapentin.
Antibiotics	High-dose penicillins (may cause seizures), acyclovir, ethambutol (optic nerve damage), erythromycin and aminoglycosides (may cause ototoxicity), nitrofurantoin and isoniazid (peripheral neuropathy).
Psychotropics	Lithium, haloperidol, clonazepam, diazepam, chlorpromazine.
Immunosuppressants	Cyclosporine, tacrolimus.
Chemotherapeutics	Cisplatinum, ifosfamide.
Others	High doses of loop diuretics (ototoxic), ephedrine, methyldopa, aluminum metoclopramide (myoclonus, dystonia).
Subdural Hematoma	
Posterior reversible encephalopathy syndrome (PRES)	Observed particularly after renal transplantation as a result of reversible, abnormal permeability of the blood-brain barrier. Often manifests with headache followed by mental depression, visual loss, and seizures in the context of volume expansion, acute hypertension, and often treatment with corticosteroids or calcineurin inhibitors. Lesions in the parietal, temporal, and occipital lobes may be seen on imaging studies.

cognitive function once they start RRT. Some may describe this as a "fog lifting." In dialyzed patients with persistent or recurrent symptoms, increasing the delivered dialysis dose may improve clinical findings. Successful renal transplantation usually results in resolution of the UE syndrome within days.

Correction of anemia with recombinant erythropoietin in the dialysis patient to a target hemoglobin level (see Chapter 82) may be associated with improved cognitive function and decreased slowing on the electroencephalogram.[16] Too rapid overcorrection of anemia may be associated with seizures. Treatment of psychosis in kidney disease must consider the pharmacokinetics of the specific agent. For example, risperidone may be useful, but dose reduction is necessary because of prolonged half-life in CKD.

PERIPHERAL NEUROPATHY

Patients with CKD are susceptible to both polyneuropathies and mononeuropathies. The pathophysiologic process of polyneuropathy involves axonal degeneration in a length-dependent fashion. Primary demyelinating neuropathies are rare in the context of CKD except when the renal disease is the result of an illness that also causes demyelination (e.g., multiple myeloma). Mononeuropathies in CKD may be caused by nerve entrapment with compression of metabolically weakened nerves, particularly in wheelchair-bound or bed-bound patients. Mononeuritis multiplex should raise the possibility of vasculitic neuropathy, especially when systemic vasculitis (e.g., antineutrophil cytoplasmic antibody–positive small-vessel vasculitis or polyarteritis nodosa) is causing the CKD. Functional sparing of small-diameter axons in uremia is suggested by relatively intact thermal thresholds (hot and cold thermal threshold testing is a surrogate for pain threshold). The modestly slowed nerve conduction velocities in the polyneuropathies of uremia may be related to the reversible inhibition of the sodium-potassium adenosine triphosphatase by a uremic toxin. According to the middle molecule hypothesis, accumulated toxins in the range of 300 to 12,000 d, including peptide hormones and polyamines, may lead to progression of neuropathy in HD patients.[4,9,10] Lower limb motor axons in uremic patients are depolarized before but not after dialysis, consistent with a role of hyperkalemia in the development of altered nerve excitability.[17] Elevated magnesium levels will also slow nerve conduction velocity. In vitro, extracellular acidosis contributes to decreased sodium conductance in large sensory neurons. Very slow nerve conduction velocities (i.e., less than half normal) suggest a demyelinating neuropathy, a finding that should lead the physician to seek a specific cause (e.g., a paraprotein).

Uremic neuropathy may progress rapidly in advanced CKD.[1,17,18] Characteristic symptoms and signs are sensory loss, pain, paresthesias, and insensitivity to temperature, particularly cold. These findings can advance to include motor findings, such as foot drop. Phrenic neuropathy may cause dyspnea because of poor diaphragmatic movement, whereas hiccups are more likely a result of the CNS effects of uremia. The distal lower extremities are usually affected first because axonal polyneuropathies are length dependent. Decrease in vibratory sensation and position sense and Romberg sign (i.e., greater instability of stance with eyes closed than with eyes open) are common signs. Muscle stretch reflexes are reduced or absent. In the patient with diabetes who is on dialysis and has progressive neuropathy, it is important to establish adequacy of dialysis as well as glucose control. Uremic polyneuropathy is aggravated by malnutrition, inadequately controlled hypertension, certain comorbid conditions (e.g., diabetes mellitus, alcohol abuse, atherosclerotic vascular disease), and medications (e.g., nitrofurantoin, isoniazid, hydralazine).

The diagnosis of uremic polyneuropathy can usually be made from clinical findings. Nerve conduction velocity is modestly reduced, and needle electromyography shows evidence of chronic denervation and sometimes reinnervation. If electromyography and nerve conduction tests are performed, they should not be done in an extremity bearing an arteriovenous fistula because vascular access surgery may cause local nerve injury, which can complicate the interpretation of these studies.[17]

Lead polyneuropathy should be considered, particularly when there is a known exposure history. Lead accumulates in the dialysis patient but could also be the cause of CKD. A lower motor neuron syndrome caused by lead toxicity may be mistaken for amyotrophic lateral sclerosis. A bone lead scan using K-line x-ray fluorescence spectroscopy of the tibia is a promising new noninvasive test that may become useful. Serum lead values and red cell protoporphyrin levels may be normal if exposure is remote. There may be associated depression, the so-called "saturnine temperament," so named because the ancients believed that Saturn was made of lead and was associated with a melancholy disposition. Gout, hypertension, renal glycosuria, and microcytic anemia also may be caused by lead toxicity.

Other conditions in the differential diagnosis of mixed polyneuropathy include other heavy metals (e.g., arsenic, mercury), nutritional deficiencies (e.g., pyridoxine, thiamine, niacin), HIV-related neuropathy, amyloid, vasculitis, sarcoid, lupus, and a paraneoplastic syndrome.

Progressive polyneuropathy may be an indication for initiation of dialysis or renal transplantation. Symptoms usually will not deteriorate further or may even show a slow improvement thereafter. If polyneuropathic symptoms worsen in a dialysis patient, the dialysis dose should be increased. Physical therapy is an important component of the management. Patients experiencing neuropathic pain may be treated with tricyclic antidepressants (e.g., amitriptyline 10 to 25 mg, increasing to 75 to 150 mg at bedtime) or antiepileptic drugs (e.g., carbamazepine 200 to 400 mg initially, increasing to 1200 mg maximally; phenytoin 100 to 200 mg initially, maximally 600 mg).[1,2] Gabapentin is an antiepileptic drug that is sometimes used to treat neuropathy but may result in oversedation and myoclonus in CKD because of marked prolongation of the drug's half-life. When gabapentin is used, it should be monitored closely at reduced doses. Deficiencies of cobalamin (vitamin B_{12}), folate, and pyridoxine may be reflected in an elevated serum homocysteine level. Methylmalonic acid may be elevated in vitamin B_{12} deficiency, and it is critical to promptly diagnose this deficiency because irreversible changes to the nervous system may develop within months. Loss of balance and position sense may be mistaken for neuropathy in pernicious anemia. Vitamin B_{12} deficiency and folate deficiency manifest with a megaloblastic or macrocytic anemia. If folate is given to a patient deficient in vitamin B_{12}, the acute posterior column findings of subacute combined degeneration of the spinal cord may develop as the low store of vitamin B_{12} is used to correct the anemia. Thiamine deficiency, often associated with malnutrition, can aggravate neuropathy, but whether replacement of any of these vitamins is effective in preventing or curing polyneuropathy in uremic patients is not well established. Thiamine deficiency is the cause of Wernicke encephalopathy in dialysis or malnourished patients. This syndrome is suspected when the triad of mental change (often amnesia), ataxia, and oculomotor disturbances (most often abducens palsies with gaze-evoked nystagmus) is seen in any patient whose diet is deficient in B vitamins. When amnesia is combined with a polyneuropathy, the term *Korsakoff psychosis* applies. In malnourished patients, the cause of Korsakoff psychosis is usually multiple subclinical attacks of Wernicke encephalopathy, hence the term *Wernicke-Korsakoff disease.*

Specific mononeuropathic syndromes include ulnar nerve entrapment, associated with uremic tumoral calcinosis and subsequent ischemia, and carpal tunnel syndrome, for example, caused by β_2-microglobulin–derived amyloidosis (see Chapter 84) or by an arteriovenous fistula.[1,18] These syndromes may be treated with antiinflammatory agents, anticonvulsants, and surgical decompression. It is important to ensure adequacy of dialytic treatment.

Pruritus in the uremic patient may be severe and is not primarily a skin disorder (see also Chapter 87). Rather, it may represent a form of sensory neuropathy. This symptom usually improves with RRT. Antihistamines, with their sedating effect, are not always effective. Gabapentin and carbamazepine block the afferent pathway in uremic neuropathic itch. Gabapentin and pregabalin inhibit calcitonin gene–related peptide from primary afferent neurons by inhibiting GABA and opioid receptor antagonists (naloxone and naltrexone) and may antagonize transmission of itch. Antidepressants also have been successful, possibly by interfering with reuptake of serotonin and norepinephrine to reduce pruritus perception.[19]

AUTONOMIC NEUROPATHY

Autonomic neuropathy is also very common in patients with advanced CKD, probably because diabetes is a common cause of CKD. Hyperglycemia may be more difficult to control in CKD because glucose filtration is decreased. Amyloidosis, a less common cause of CKD, is associated with autonomic neuropathy. A typical manifestation is orthostatic hypotension, which is most severe in patients with diabetes mellitus or amyloidosis as a cause of CKD. Some dopaminergic drugs used in Parkinson disease or parkinsonism itself may cause orthostasis. Some patients have evidence of peripheral neuropathy and may manifest hyporeninemic hypoaldosteronism with hyperkalemia and renal tubular acidosis. The low blood pressure (BP) may preclude antiproteinuric treatment with angiotensin antagonists in the predialysis patient and may complicate fluid removal during dialysis. Patients on peritoneal dialysis (PD) may be particularly affected. CKD patients were thought to have decreased baroreceptor function, but normal baroreceptor responses to graded decrements in mean arterial BP have been described.[20] Instead, CKD patients have sympathetic hyperactivity, which contributes to hypertension, more rapid progression to renal failure in the predialysis patient, and greater cardiovascular (CV) risk. Accordingly, α- and β-adrenergic blockade has been advocated in CKD.[20] Autonomic neuropathy is caused by axonal disease and thus is length dependent. For that reason, the longest autonomic nerve, the vagus, is usually the first affected, resulting in the loss of the normal sinus arrhythmia, significant reductions of day-night BP variation, and possibly sudden cardiac death related to the loss of the balance between the sympathetic and parasympathetic limbs of the autonomic nervous system. Reports of gastrointestinal problems include gastroparesis, particularly problematic for the diabetic patient. In the predialysis patient, nausea and early satiety associated with gastroparesis may be confused with uremia. Several medical regimens have been used for the uremic patient with gastroparesis; they include erythromycin, which can activate the gastric motilin receptor. Levodopa-carbidopa, as a dopamine agonist, may be effective, as may metoclopramide 10 mg before sleep or domperidone 10 to 20 mg. Nocturnal diarrhea is another consequence of vagal neuropathy. Erectile dysfunction and incontinence (urinary more commonly than fecal) also may be related to autonomic neuropathy.

CRANIAL NEUROPATHIES

Cranial nerve involvement is most often vestibulocochlear. Hearing loss needs to be distinguished from drug-induced ototoxicity or the neurosensory deafness of hereditary nephropathy.[1,2] Bilateral vestibular failure leads to inability to stand or to walk normally without vertigo or nystagmus. It is often related to the use of aminoglycoside antibiotics in the patient with CKD, unless the dose is properly adjusted. *N*-Acetylcysteine given with aminoglycosides may reduce the risk for cochlear toxicity. Sulfa-based loop diuretics, often used at high doses in patients with CKD, may cause vestibular or cochlear damage. Decreased olfactory function, especially a reduced ability to discriminate among and identify odors, and dysgeusia are commonly seen in patients with CKD.

SLEEP DISORDERS

Many HD and PD patients exhibit obstructive sleep apnea that is independent of obesity.[21] The associated sleep deprivation contributes to fatigue and cognitive impairment and increases the risk for CV complications.[21] Both obstructive and central sleep apnea are seen in patients with CKD. Obstructive sleep apnea is a condition in which blockage of the upper airway can interfere with nocturnal breathing. Nighttime oxygen and continuous positive airway pressure (CPAP) may help. Treatment of obstructive sleep apnea is effective, including use of CPAP (as in nonuremic individuals) and conversion to nocturnal HD.[21] Central sleep apnea, often accompanied by heart failure, causes prolonged apneic episodes and may respond to oxygen. Initiation of dialysis may be helpful.

Daytime sleepiness is common and underdiagnosed in patients with CKD and contributes not only to worsened hypertension and increased CV risk but also to social dysfunction. Whether obstructive sleep apnea and its associated excessive daytime sleepiness is an independent risk factor for the progression of renal failure is not yet settled. It is assessed by a multiple sleep latency test, that is, the duration of time from "lights out" to the onset of sleep. If it is less than 5 minutes, it is consistent with sleep deprivation. There was also a reduced proportion of rapid eye movement sleep. An increased arousal frequency is related to periodic limb movements during sleep and the presence of sleep apnea.

Sleep-wake complaints are common in patients on dialysis, with an incidence of up to 80%. Contributors include peripheral neuropathy, pain, and pruritus.

RESTLESS LEGS SYNDROME (EKBOM SYNDROME)

Restless legs syndrome (RLS), described by K. A. Ekbom in 1944,[22] is frequent in CKD, particularly in women. It may result from a decrease in dopaminergic modulation of intracortical excitability, with reduced supraspinal inhibition and increased spinal cord excitability. RLS is characterized by unpleasant "creeping" sensations in the extremities and a compulsive need to move the limbs, usually the legs.[23-25] The movement is worsened by periods of rest or inactivity and is relieved by walking or stretching. Symptoms are worse at night and may lead to insomnia and consequent daytime sleepiness and reduced quality of life. Nocturnal muscle cramps are common in CKD and should be distinguished from RLS. The Ekbom syndrome consists of restless legs plus other obsessive-compulsive–like disorders including various pica behaviors, such as pagophagia (ice eating), geophagia (clay eating), and amylophagia (starch eating).

Periodic limb movement disorder is characterized by episodes of involuntary repetitive extension of the big toe and dorsiflexion of the ankle, as well as flexion of the knee and hip.[24,25] This disorder is more likely to occur in those with RLS.

Iron deficiency or iron transport into the CNS plays a central role in RLS. Iron is a cofactor for the enzyme tyrosine hydroxylase, the rate-limiting step in the biosynthesis of dopamine, possibly explaining the link between iron deficiency and dopamine deficiency in RLS. Overt iron deficiency is easily diagnosed and should be treated.[24,25] In patients with normal red blood cell indices and serum iron and total iron-binding capacity, serum ferritin should be tested. Transferrin saturation ratio may be an even more sensitive indicator of iron deficiency. Although not clinically indicated for RLS, analysis of spinal fluid ferritin may reveal a subtle CNS iron-deficiency syndrome. RLS often persists after initiation of dialysis but may improve after transplantation and has been linked to abnormalities in calcium and phosphorus metabolism as well as to anemia. Iron replacement should be initiated if there is any indication of iron deficiency Intravenous iron may be required (see Chapter 82). Dopaminergic treatment is often helpful, usually starting with the dopamine receptor agonists pramipexole and ropinirole. Levodopa combined with decarboxylase inhibitors (e.g., carbidopa-levodopa) may be used as well as gabapentin, opioids, and benzodiazepines.[23-25] As mentioned, gabapentin should be used cautiously because of toxicity with accumulation, the symptoms of which are sedation, cognitive slowing, and various movement disorders, including tremor, ataxia, and asterixis (see previous discussion). Older dopamine receptor agonists, such as bromocriptine and pergolide, are rarely used now for RLS.

NEUROLOGIC SYNDROMES ASSOCIATED WITH RENAL REPLACEMENT THERAPY

RRT is associated with an increased incidence of subdural hematoma and intracranial hemorrhage, presumably connected to hypertension and anticoagulation with HD as well as Wernicke encephalopathy (see earlier discussion).[1,2] A syndrome of muscle weakness has been attributed to L-carnitine depletion from dialysis, leading to decreased mitochondrial fatty acid usage.

Dialysis disequilibrium syndrome is a rare complication of rapid metabolic changes occurring with HD, usually affecting patients in whom HD is being initiated (see Chapter 95).[26] It is most common in patients with severe uremia of long duration and with severe hypertension. Characterized by acute onset of headache, nausea, vomiting, disorientation, a state of confusion, and seizures, it is a diagnosis of exclusion. It usually results from acute changes in osmolality during HD, in which the rapid decrease in urea in the extracellular fluid favors water movement into brain cells, resulting in cerebral edema. Alternatively, other intracellular osmolytes within brain cells may draw water from the extracellular fluid. The syndrome normally reverses spontaneously after a period of regular HD. If no improvement is seen after a month of HD, one should investigate for other possible causes of the clinical syndrome by imaging the brain, obtaining an electroencephalogram, and examining the spinal fluid. Dialysis disequilibrium syndrome may be prevented by decreasing HD length to 2 to 3 hours, dialyzing daily, and reducing HD efficacy during the first sessions.

Dialysis encephalopathy (formerly called *dialysis dementia*) is probably a multifactorial syndrome occurring in sporadic-endemic and epidemic types. In particular, in the epidemic type, aluminum-based phosphate binders and exposure to a dialysate containing more than 20 mcg of aluminum per liter are considered to be major causes.[27,28] Aluminum transferred to the nervous system by transferrin results in a characteristic clinical condition with prominent stuttering that usually worsens toward the end of a dialysis session and encephalopathy, initially responding well to intravenous benzodiazepines but then becoming unresponsive, leading to severe encephalopathy and death. With the almost universal preparation of dialysate water by reverse osmosis and the marked reduction in aluminum-containing phosphate binder use, aluminum-induced encephalopathy has virtually disappeared. If it is present, aluminum toxicity is treated with deferoxamine (see Chapter 84). Renal transplantation is an effective treatment for dialysis dementia.

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SELF-ASSESSMENT QUESTIONS

1. A 50-year-old man with chronic hypertension, chronic kidney disease (CKD), and estimated glomerular filtration rate (eGFR) of 8 ml/min/1.73 m^2 who is not yet on dialysis presents with confusion, lethargy, and myoclonus. Which of the following factors may contribute to the neurologic changes?
   - **A.** Use of gabapentin for neuropathic pain
   - **B.** Poorly controlled secondary hyperparathyroidism
   - **C.** Poorly controlled anemia with iron deficiency
   - **D.** Poor dietary protein intake resulting in decreased blood urea level
   - **E.** A and D
   - **F.** All of the above
2. A 25-year-old woman has hypertension, seizures, and encephalopathy, believed to be caused by uremia. Her blood pressure is 200/120 mm Hg. Her blood chemistries reveal Na 120 mEq/l, K 4 mEq/l, Cl 80 mEq/l, and HCO_3^- 15 mEq/l. The anion gap is 25 mEq/l, glucose 70 mg/dl, and blood urea nitrogen (BUN) 200 mg/dl. Which of the following is the *best* answer?
   - **A.** Hypotonic hyponatremia may contribute to the altered neurologic picture.
   - **B.** The seizures may be from severe hypertension.
   - **C.** This presentation is characteristic of uremic encephalopathy.
   - **D.** The BUN should be decreased to normal promptly with dialysis.
   - **E.** Both A and D are incorrect.
   - **F.** A, B, and C are correct.
3. Findings associated with restless legs syndrome include all of the following *except:*
   - **A.** Obsessive-compulsive behavior
   - **B.** Amylophagia (starch craving)
   - **C.** Iron overload and deposition in the basal ganglia
   - **D.** Response to dopaminergic medication
   - **E.** Commonly, improvement during daytime hours and with exercise

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Gastroenterology and Nutrition in Chronic Kidney Disease

Gemma Bircher, Graham Woodrow

GASTROINTESTINAL PROBLEMS IN CHRONIC KIDNEY DISEASE

Gastrointestinal (GI) symptoms and disease are common in patients with chronic kidney disease (CKD), including those receiving renal replacement therapy (RRT) (Table 86.1). Anorexia, nausea, and vomiting arising from uremic toxicity may indicate the need to start dialysis or be a manifestation of inadequate dialysis clearances. GI disturbances contribute to development of malnutrition and wasting, which are common complications of advanced CKD and carry an adverse prognosis for survival. Some GI conditions are a result of uremia or the effects of RRT or medications. Other GI symptoms are manifestations of conditions also responsible for the renal disease.

GASTROINTESTINAL DISEASE IN CHRONIC KIDNEY DISEASE

Oral Disease in Chronic Kidney Disease

Glossitis can result from deficiency of iron, vitamin B_{12}, other B vitamins, or folic acid. Halitosis is a feature of uremia, and reduced taste sensation or abnormal taste can impair dietary intake. Gingival hyperplasia is a frequent complication of treatment with calcium channel blockers or cyclosporine. Oral candidiasis occurs in patients receiving immunosuppressive drugs, including corticosteroids, those receiving antibiotics, and those with diabetes or who are malnourished. If extensive, particularly with esophageal involvement, candidiasis may lead to dysphagia and should particularly be suspected where there is associated retrosternal pain in patients with risk factors, who also may have oropharyngeal thrush. Treatment requires systemic antifungal therapy such as azoles, echinocandins, or amphotericin B (Fig. 86.1).

Gastroesophageal Reflux Disease and Esophagitis

Gastroesophageal reflux leading to heartburn or mucosal changes arising from reflux of caustic gastric contents into the esophagus occurs more frequently in patients with CKD because of GI tract dysmotility or delayed gastric emptying and may be more prevalent with peritoneal dialysis (PD) because of increased intraabdominal pressure. It is more common in patients with scleroderma with reduced esophageal peristalsis. Esophagitis also results from the irritant effects of drugs, including slow-release potassium preparations, tetracyclines, iron, aspirin, nonsteroidal antiinflammatory drugs, and bisphosphonates. Typical features appear on endoscopy but may be absent in symptomatic patients. Other investigations include 24-hour ambulatory esophageal pH monitoring and demonstration of reflux on barium swallow examination. It is important to consider cardiac ischemia as an alternative cause of atypical symptoms in CKD. Management includes weight loss in obese patients; avoiding bedtime snacks, fatty foods, cigarettes, and alcohol; and raising the head of the patient's bed. Proton pump inhibitors (PPIs) are the most effective medical treatment, and maintenance therapy may be required. Other drugs include histamine H_2-receptor antagonists and antacid preparations. Sucralfate should be avoided in advanced CKD because of the risk for aluminum accumulation.

Peptic Ulcer Disease, Gastritis, and Duodenitis

Despite effective acid-reducing drug therapies and improvement in dialysis therapy, peptic ulcer disease remains more common in CKD than in the general population, with highest incidence in dialysis patients.[1] It is an important cause of GI hemorrhage in CKD.[2] Peptic ulcers in patients with CKD are more likely to occur in multiple locations than are ulcers in the general population and are more often postbulbar, but pain is less frequent.[3]

Gastritis and duodenitis are common in patients with CKD. Hypergastrinemia occurs with CKD but is not important in causation of gastritis, duodenitis, or peptic ulcers. Despite high urea concentrations in patients with CKD, incidence of *Helicobacter pylori* infection is not increased.[4] Where *H. pylori* infection is present, eradication of this (with combined antibiotic and PPI treatment) reduces risk for bleeding in CKD, with greater benefit in earlier initiation of treatment.[5] The presence of *H. pylori* infection in PD has been suggested as a possible cause of anorexia, inflammation, and malnutrition.[6]

Dyspepsia without other warning features (weight loss, vomiting, hemorrhage) may be managed by testing for *H. pylori* with a breath test or stool antigen test and an empiric course of acid-suppressing therapy. Persistent symptoms of new onset in patients older than 55 years warrant upper GI endoscopy to exclude malignant disease. The frequent coexistence of other symptoms in CKD, such as nausea, vomiting, and weight loss, may lead to more frequent need for endoscopy. Management includes use of PPIs or histamine H_2-receptor antagonists. There is a risk for excess calcium and magnesium absorption with some antacids in CKD, and aluminum- or bismuth-containing preparations should be avoided because these metals can accumulate in patients with markedly reduced estimated glomerular filtration rate (GFR).

Delayed Gastric Emptying and Gastroparesis

Gastric emptying is impaired in uremia (especially in PD patients)[7,8] and also in some conditions leading to renal disease, particularly diabetes and amyloidosis. This results in reduced appetite, early satiety, nausea, vomiting, and malnutrition.[7] Mechanisms in uremia may include autonomic neuropathy and retained GI peptides. The diagnosis is confirmed by scintigraphic measurement of gastric emptying and may be suspected

TABLE 86.1 Important Causes of Common Gastrointestinal Symptoms in Patients With Chronic Kidney Disease

Clinical Feature	Important Causes in CKD
Anorexia	Uremic toxicity Inadequate dialysis clearances Delayed gastric emptying
Nausea and vomiting	Uremic toxicity Delayed gastric emptying/gastroparesis Gastritis, duodenitis Peptic ulcer disease Drugs
Constipation	Drugs, including opioid analgesia GI pseudoobstruction Diverticular disease
Diarrhea	Diabetic enteropathy Dialysis-related amyloidosis Diverticular disease *Clostridium difficile* infection
GI hemorrhage	Gastritis, duodenitis Esophagitis Peptic ulcer disease Angiodysplasia Intestinal ischemia Dialysis-related amyloidosis Vasculitis
Acute abdominal pain	Gastritis, duodenitis Complications of peptic ulcer disease Acute pancreatitis Intestinal ischemia Diverticulitis GI pseudoobstruction Colonic perforation from fecal impaction Complications of peritoneal dialysis (peritonitis, dialysis catheter malposition, dialysate infusion or drain pain) Complications of autosomal dominant polycystic kidney disease Retroperitoneal hemorrhage

CKD, Chronic kidney disease; *GI,* gastrointestinal.

when endoscopy demonstrates residual gastric contents despite fasting. Endoscopy is important to exclude gastric outlet obstruction. Reversible causes should be addressed, including optimization of diabetic control (gastroparesis may be an indication for continuous subcutaneous insulin infusion treatment in type 1 diabetes), correction of electrolyte abnormalities, and discontinuation of drugs that impair gastric emptying (e.g., those with anticholinergic and opioid effects). Treatment involves prokinetic drug therapy, including metoclopramide, domperidone, and erythromycin. Prokinetic drugs improve nutritional state in patients with delayed gastric emptying.[9] However, concerns about neurologic side effects with metoclopramide and cardiac arrhythmias with domperidone (in countries where it is available) restrict their longer term use. Dietary measures, with frequent smaller low-fat meals and avoiding nondigestible solids, and antiemetic agents are often ineffective. Nutritional support through nasoenteric or jejunostomy feeding tubes may be required.

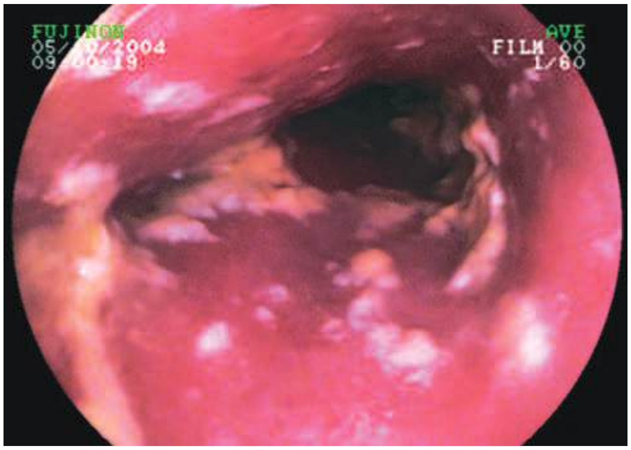

Fig. 86.1 Endoscopic appearance of esophageal candidiasis. (Courtesy Dr. B. Rembacken, Leeds, United Kingdom.)

Large Bowel Disorders

The incidence of diverticular disease is similar in CKD patients to that in the general population, except in patients with autosomal dominant polycystic kidney disease (ADPKD), in whom its incidence is increased.[10] It manifests as acute diverticulitis or colonic perforation and is associated with PD peritonitis caused by enteric organisms. There is a greater risk in CKD for diverticular bleeding (because of uremic bleeding tendency) and perforation in patients receiving high-dose corticosteroids.

Constipation is common in CKD because of dietary restrictions, restricted fluid intake, and electrolyte abnormalities, including hypercalcemia. In PD, constipation results in impaired dialysate drainage and catheter malposition. Severe constipation is a risk factor for large bowel perforation. Management includes stool-softening agents, stimulant laxatives, and fiber preparations. Drugs predisposing to constipation include calcium-based phosphate binders, sevelamer, oral iron, opioid analgesics, and calcium resonium. Some other phosphate binders such as iron-containing agents may conversely cause looser stools and thus may be useful in this situation.

Gastrointestinal Pseudoobstruction

Pseudoobstruction manifests with acute or more chronic features of abdominal pain, vomiting, constipation, or diarrhea. It arises from disordered gut motility and is more common in dysmotility states, including diabetes, amyloidosis, and scleroderma. Drugs that reduce bowel motility (especially narcotics) and electrolyte disturbances (e.g., hypokalemia) predispose to pseudoobstruction, which may be acutely precipitated by surgery, constipation, and retroperitoneal hemorrhage. Investigations include plain abdominal radiography, computed tomographic scanning, and bowel contrast studies. Management includes nutritional support (which may require parenteral feeding) and prokinetic agents. Nasogastric tube insertion and aspiration may be needed for symptomatic control. Complications include intestinal perforation[11] and bacterial overgrowth.

Vascular Disease of the Gastrointestinal Tract

Intestinal ischemia is an important cause of an acute abdomen in older CKD patients. Some cases result from nonocclusive mesenteric ischemia (where there is no critical vascular occlusion)[12] and may be precipitated by excessive intradialytic fluid removal. Predisposing factors include hypotension, cardiac failure, hypoxia, increased plasma viscosity, and constipation (which increases intraluminal pressure, impairing vascular perfusion). Presentation is with abdominal pain, diarrhea, or lower GI

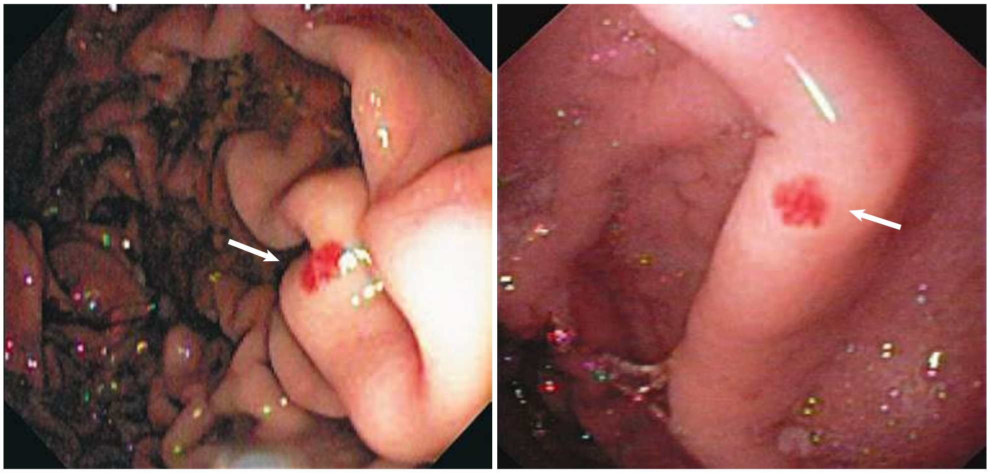

Fig. 86.2 Two examples of gastric angiodysplasia *(arrows)* in a dialysis patient. (Courtesy Drs. R. Winograd and C. Trautwein, Aachen, Germany.)

bleeding. Abdominal examination can be misleadingly benign at presentation, but often peripheral neutrophil leukocytosis and progressive lactic acidosis are present. Milder cases may settle with hemodynamic resuscitation. Patients with more severe features of peritonitis and intestinal infarction require laparotomy and have a high mortality rate.

GASTROINTESTINAL HEMORRHAGE

GI hemorrhage is more common in CKD compared with the general population, and the risk for mortality when bleeding occurs is also higher in CKD patients than those with normal kidney function. Causes of hemorrhage include a greater incidence of lesions such as peptic ulcers, gastritis and duodenitis,[13] angiodysplasia, and, more rarely, systemic vasculitis (Fig. 86.2). Nonulcer, nonvariceal bleeding is more common in CKD and particularly in hemodialysis (HD) patients.[14] Uremic hemostatic defects and anticoagulation during HD also are important. GI endoscopy is the major diagnostic investigation and allows therapeutic procedures. Investigations for when the cause remains unclear include angiography, small bowel enteroscopy or capsule study, and radiolabeled red cell scanning.

Resuscitation requires careful monitoring in CKD. Adequate fluid replacement to maintain renal perfusion in patients with residual renal function is crucial, and monitoring for hyperkalemia (if blood transfusions are given) and fluid overload is also important. Correction of coagulation defects in CKD includes optimization of dialysis clearance, correction of anemia, and use of desmopressin or cryoprecipitate. Drugs that increase bleeding risk should be discontinued when possible. HD (if required) should be performed without heparin. Specific treatment is directed at the cause of hemorrhage.

Clostridium difficile Infection

Clostridium difficile is a major cause of nosocomial diarrheal illness. Clinical manifestations vary from mild diarrhea to severe pseudomembranous colitis (Fig. 86.3). Patients with CKD are at risk for more frequent or severe infection, slower treatment response, more frequent relapse and have a higher risk for death,[15,16] especially with end-stage renal disease (ESRD). Reasons include the older age of CKD patients, frequent use of acid-suppressing drugs, and antibiotics. Diagnosis is made by identifying *C. difficile* toxin in diarrheal stools. In severe cases, there are radiologic appearances of acute colitis with mucosal edema, but these are not specific for *C. difficile.* A pseudomembrane may be visualized on sigmoidoscopy, but diarrhea can occur in its absence. The precipitating antibiotic should be stopped or switched to one less likely to promote *C. difficile* infection. Treatment depends on disease severity with oral metronidazole or oral vancomycin usually being first-line antibiotic therapy. Fidaxomicin is a newer agent that may be used for severe or recurrent infection and results in less frequent relapse.[15] Intravenous immunoglobulin (Ig) has been used for refractory cases,[17] and fecal transfer has been successfully used in severe or recurrent infections. Fluid and electrolyte replacement are important, and drugs that reduce diarrhea or impair gut motility must be avoided because they may precipitate toxic megacolon. Colectomy may be required in life-threatening disease. *C. difficile* infection is a major problem in the hospital setting, including renal units. Preventive measures are essential, including hand washing, cleanliness of physical environment, and isolation of

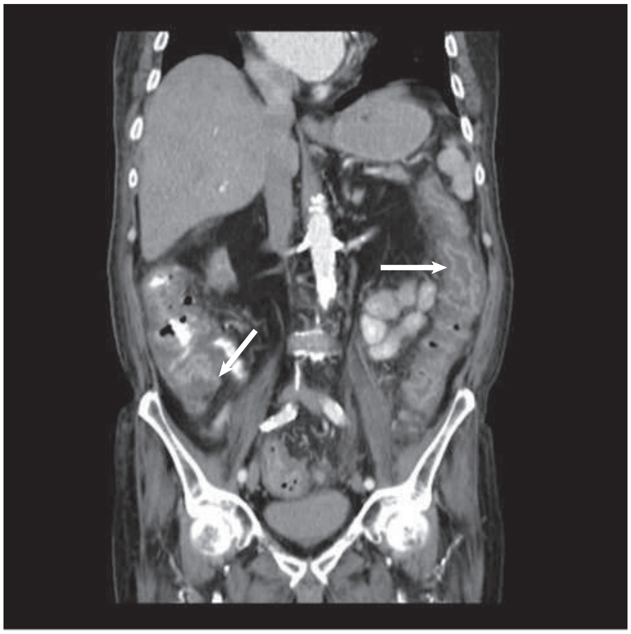

Fig. 86.3 Computed tomographic appearance of *Clostridium difficile* colitis in a hemodialysis patient, demonstrating pancolitis with markedly edematous haustra *(arrows)* after treatment with broad-spectrum antibiotics. (Courtesy Dr. M. Weston, Leeds, United Kingdom.)

affected inpatients with barrier nursing. Antibiotic policies should minimize use of broad-spectrum antibiotics, which induce *C. difficile* infection.

Acute Pancreatitis

Acute pancreatitis may be more common in CKD, especially in PD patients.[18] Most cases are secondary to biliary tract disease or alcohol use or are idiopathic. Rarer causes in CKD patients are hypercalcemia, vasculitis, and drugs, including corticosteroids, azathioprine, angiotensin-converting enzyme (ACE) inhibitors, and diuretics. Serum amylase is the usual diagnostic measure, although levels are elevated up to threefold in renal failure and lowered in PD patients receiving icodextrin dialysate (because of competitive inhibition of icodextrin metabolites with the amylase assay). Serum lipase is an alternative diagnostic marker (although it is also elevated in uremia). Thus pancreatic enzyme levels may be less reliable in CKD, but values more than three times the normal range are strongly suggestive of acute pancreatitis in end-stage renal failure patients. Amylase and lipase concentrations may be measured in dialysate in PD patients with suspected pancreatitis. Radiology, including ultrasound, computed tomography, and magnetic resonance imaging, is useful to confirm the diagnosis and detect underlying biliary disease and complications, including pancreatic necrosis and pseudocyst formation. In PD patients with acute pancreatitis, dialysate may be bloody, cloudy from increased leukocytes, or cola-colored.

Acute Abdomen

Some causes of acute abdominal pain occur more commonly in or are specific to CKD patients. A high index of suspicion for ischemic bowel is important because of the frequency of vascular disease in CKD. Pain may result from complications of polycystic kidney disease. Retroperitoneal hemorrhage can arise from anticoagulation, including during HD. In PD, abdominal pain arises from peritonitis, infusion pain (as a result of dialysate acidity), drain pain with automated PD, catheter malposition, constipation, or encapsulating peritoneal sclerosis. Other surgical conditions need to be distinguished from dialysis-specific causes. Although air uncommonly enters the peritoneal cavity during PD, in the setting of acute abdominal symptoms, free gas present on radiologic imaging of the abdomen suggests visceral perforation.

COMBINED GASTROINTESTINAL AND RENAL DISEASES

A number of conditions have both renal and GI manifestations (Table 86.2).

Diabetes

Diabetes is commonly complicated by disordered gut motility. Gastroparesis should be distinguished from uremic upper GI symptoms. Diarrhea caused by diabetic enteropathy is also common, typically is nocturnal, and usually is neurogenic in origin. Treatment usually consists of antimotility agents. Bacterial overgrowth is uncommon and is diagnosed by the hydrogen breath test. GI symptoms may be exacerbated by drug treatments for diabetes, including metformin, glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, and α-glucosidase inhibitors. Gastroparesis results in difficulties with glycemic control, fluid and electrolyte imbalance, drug malabsorption, and malnutrition. The speed of colonic transport is decreased in diabetes, which may result in constipation.

Systemic Vasculitis

GI manifestations of vasculitis include intestinal ischemia or infarction, hemorrhage, and perforation with peritonitis. Abnormal liver function test results arise from hepatitis, and cholecystitis and pancreatitis have been described. Serositis with abdominal pain is a feature of systemic lupus erythematosus. Abdominal pain, vomiting, and GI hemorrhage are typical of Henoch-Schönlein purpura.

Systemic Amyloidosis

Primary AL amyloidosis may result in both renal and GI involvement. Conversely, inflammatory bowel disease is an important cause of secondary AA amyloidosis, which may result in renal involvement. Thus, in a patient with renal amyloidosis who has GI symptoms, it is important to characterize the type of amyloid and the underlying cause of GI disturbance.

Autosomal Dominant Polycystic Kidney Disease

Abdominal hernias are more common in ADPKD[19] and are a particular problem in PD patients. Colonic diverticular disease occurs more

TABLE 86.2 Gastrointestinal-Renal Syndromes Conditions Typically Resulting in Both Renal and Gastrointestinal Disease

Disorder	Renal Involvement	GI Involvement
Diabetes	Proteinuria, CKD	Gastroparesis, diabetic enteropathy, constipation
Systemic vasculitis	Proliferative glomerulonephritis, CKD	Intestinal ischemia, GI hemorrhage, bowel perforation, hepatobiliary involvement, acute pancreatitis
Systemic amyloidosis	Nephrotic syndrome, CKD	Diarrhea, malabsorption, splenic rupture
Autosomal dominant polycystic kidney disease	CKD, cyst hemorrhage, and infection	Abdominal pain (from renal or hepatic cysts), diverticular disease, hernia
Inflammatory bowel disease	AA amyloidosis, drug-induced interstitial nephritis, IgA nephropathy, oxalate renal calculi (with terminal ileal Crohn disease)	Abdominal pain, diarrhea, GI hemorrhage, malabsorption
Scleroderma	CKD, acute scleroderma, renal crisis	Dysphagia, constipation, malabsorption, and bacterial overgrowth
Fabry disease	Hematuria, proteinuria CKD	Abdominal pain, episodes of diarrhea, or constipation
Celiac disease	IgA nephropathy	Malabsorption, iron-deficiency anemia
IgG4-related tubulointerstitial nephritis	Tubulointerstitial nephritis	Autoimmune pancreatitis

CKD, Chronic kidney disease; *GI,* gastrointestinal; *IgA,* immunoglobulin A.

frequently. The enlarged kidneys can result in abdominal pain, hemorrhage, abdominal fullness, and anorexia. Hepatic cysts and occasionally massive hepatomegaly may cause chronic abdominal pain and fullness. Common bile duct dilation, of uncertain significance, occurs more frequently in ADPKD.

Inflammatory Bowel Disease

Inflammatory bowel disease may be complicated by AA amyloidosis and IgA nephropathy. Drug therapy, such as aminosalicylates, can lead to renal disease, including chronic interstitial nephritis. Terminal ileal disease in Crohn disease can cause hyperoxaluria and oxalate renal calculi.

Celiac Disease

Celiac disease occurs with increased frequency in association with other autoimmune conditions, such as diabetes mellitus. There is also a reported association with IgA nephropathy.[20]

DRUGS AND GASTROINTESTINAL DISEASE IN CHRONIC KIDNEY DISEASE

Drugs commonly used in CKD can lead to GI complications (Table 86.3). Phosphate-binding drugs commonly result in abdominal symptoms. Nausea and vomiting are important complications of calcimimetics. Other drugs important in CKD that may cause GI problems include statins, ACE inhibitors, iron supplements, sodium bicarbonate, bisphosphonates, and metformin. Acid-suppressing drugs including PPIs and H_2-receptor blockers are commonly prescribed in CKD. They are often inappropriately continued for long periods[21] and increase the risk for *C. difficile* infection, interstitial nephritis, and CKD (see Chapter 60). PPIs can result in nausea, vomiting, abdominal pain, diarrhea, and constipation. By reducing gastric acidity, they also may reduce the effectiveness of calcium carbonate prescribed as a phosphate binder (which is only soluble in an acid environment).

TABLE 86.3 **Gastrointestinal Side Effects of Drugs Commonly Used in Patients With Chronic Kidney Disease**

Drug	GI Side Effects
Calcium-based phosphate binders	Constipation, abdominal discomfort
Sevelamer	Constipation, dyspepsia, bowel obstruction (very rare)
Lanthanum carbonate	Dyspepsia, nausea, diarrhea
Cinacalcet	Anorexia, nausea, vomiting
Statins	Abdominal discomfort, diarrhea, constipation
ACE inhibitors	Nausea, constipation, diarrhea, acute pancreatitis
Iron supplements	Nausea, epigastric pain, constipation, diarrhea
Bisphosphonates	Esophagitis, esophageal ulcers and strictures
Polystyrene sulfonate (calcium resonium, Kayexalate)	Severe constipation, colonic necrosis
Calcium channel blockers	Constipation, intestinal pseudoobstruction
Metformin	Anorexia, nausea, vomiting, diarrhea
Proton pump inhibitors	Nausea, vomiting, abdominal pain, constipation, diarrhea
Glucagon-like peptide-1 agonists	Anorexia, nausea, vomiting, diarrhea, risk for acute pancreatitis
Dipeptidyl peptidase-4 inhibitors	Nausea, diarrhea, risk for acute pancreatitis
Mycophenolate mofetil	Diarrhea, abdominal pain, vomiting
Azathioprine	Dyspepsia, acute pancreatitis, hepatitis

ACE, Angiotensin-converting enzyme; *GI,* gastrointestinal.

SPECIFIC GASTROINTESTINAL COMPLICATIONS OF RENAL REPLACEMENT THERAPY

Idiopathic Dialysis-Related Ascites

Idiopathic ascites occurs in HD patients and may be caused by suboptimal dialysis clearances. Diagnosis is by exclusion of other causes of ascites. Aspirated fluid usually has an elevated protein content. Management includes fluid and sodium intake restriction and ultrafiltration by dialysis. Small-solute clearance must be optimized, and paracentesis may be required for symptom control. The condition may resolve after renal transplantation, and switching to PD can be tried.

Peritoneal Dialysis–Related Gastrointestinal Conditions

Complications relating to PD may affect the abdomen, including infectious peritonitis, pain on dialysate infusion and drainage, and encapsulating peritoneal sclerosis (see Chapter 97). Hemoperitoneum in PD is typically related to the menstrual cycle, occurring during menstruation or ovulation, or may be self-limited, probably resulting from minor peritoneal membrane trauma from the PD catheter (Fig. 86.4). Rarely, underlying pathologic causes are present, including encapsulating peritoneal sclerosis, malignant disease, pancreatitis, hepatobiliary disease, and hemorrhage from polycystic kidneys.

Dialysis-Related Amyloidosis

Amyloidosis caused by deposition of β_2-microglobulin in very rare patients on very-long-term dialysis can result in GI hemorrhage, diarrhea, pseudoobstruction, ischemia, and perforation (see Chapter 84).

Transplantation and Gastrointestinal Disturbance

A variety of GI problems occur after renal transplantation (see Chapters 105 and 106). Gastritis or duodenitis results from corticosteroid therapy,

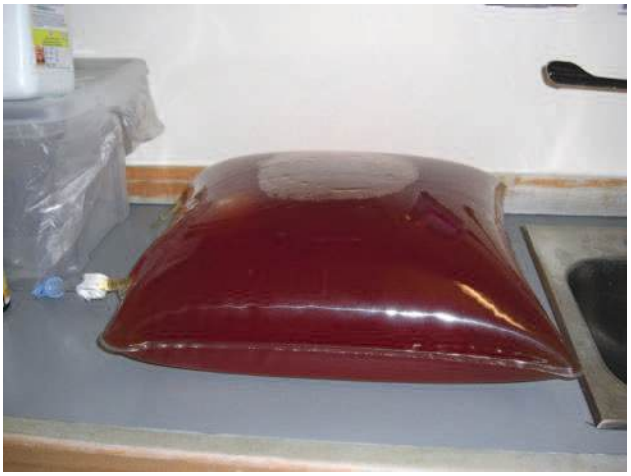

Fig. 86.4 Hemoperitoneum. Blood-stained peritoneal dialysate from a peritoneal dialysis patient who has developed acute pancreatitis.

and peptic ulcers occur most commonly in the initial year after transplantation.[22] Mycophenolate mofetil commonly leads to diarrhea, abdominal pain, or vomiting. Infectious complications of the GI tract include oral and esophageal candidiasis, cytomegalovirus disease, and diarrhea from *C. difficile* infection. Post-transplantation lymphoproliferative disease may involve the GI tract.

Nutrition in Chronic Kidney Disease

Nutrition plays an important role in the management of hypertension, obesity, hyperlipidemia, and diabetes, all of which affect CKD progression. As the GFR deteriorates, retention of nitrogenous metabolites, decreased ability to regulate levels of electrolytes and water, and certain vitamin deficiencies can be affected by dietary changes. In addition, protein-energy depletion is commonly observed and predicts a poor outcome.

Malnutrition: Protein-Energy Wasting

Patients with CKD, particularly more advanced stages, frequently exhibit a progressive loss of muscle and fat mass that may not be related to a reduced intake alone.

Because *malnutrition* refers to an intake that is inadequate for the needs of the individual, it can be misleading to use this blanket term when reduced intake is not necessarily the sole cause of wasting. Protein-energy wasting (PEW) is defined as a state of nutritional and metabolic derangements in patients with CKD that may negatively affect nutritional status and lean body mass, leading to frailty.[23] Inflammation often coexists, and nutrition intervention in isolation may not successfully reverse the loss of skeletal muscle and fat mass.

The prevalence of PEW in dialysis patients ranges from 10% to 70%, depending on the choice of nutritional marker and the population studied.[24,25] There is also diminished nutritional status before initiation of dialysis, which strongly predicts mortality on dialysis. Several factors contribute to the high incidence of PEW:

- Inadequate protein and calorie intake. There is a spontaneous reduction in nutrient intake that parallels the decrease in GFR and is largely driven by CKD-associated anorexia.[26] This anorexia is caused by impaired taste acuity and diminished olfactory function, medications, autonomic gastroparesis, psychological and socioeconomic factors, and inadequate dialysis.
- Frailty, poverty, advanced age, and multiple acute or chronic comorbidities also may contribute to suboptimal intake.
- Inappropriate dietary restrictions may be recommended, which is particularly relevant for patients with ESRD.[27,28]
- Protein and amino acid losses occur during dialysis treatment. These may increase significantly during episodes of PD peritonitis.
- Metabolic acidosis and periods of acute or chronic illnesses may induce protein catabolism. This is mediated in large part through the ubiquitin-proteasome pathway of protein degradation.[29]
- Protein catabolic effects that can further compromise patients early after transplantation include large doses of corticosteroids, the stress response to surgery, and delayed graft function.
- Chronic inflammation may contribute to both an increase in nutritional needs and anorexia. Alterations in intestinal microbiota and increased permeability of the intestinal barrier may play a pivotal role in the pathogenesis of inflammation (see Chapter 81).[30]
- Endocrine disorders, such as insulin resistance (associated with increased muscle breakdown), vitamin D deficiency and increased parathyroid hormone concentrations have long been considered contributors to PEW, although the data remain inconclusive regarding the exact mechanisms involved. There is some evidence of an association between fibroblast growth factor-23 (a phosphate regulating hormone) and inflammation in CKD.[31]

Obesity Paradox in Chronic Kidney Disease

Although there is a high prevalence of PEW in patients with CKD associated with poorer outcomes, paradoxically a higher body mass index (BMI) is associated with better survival. This is termed *reverse epidemiology* (see Chapter 81).

Assessment of Nutritional Status

The measurement of nutritional status does not lend itself to one simple test, and a panel of measures is required. Table 86.4 summarizes some of the methods used for assessment of nutritional status.

Estimation of Intake

Diet history, recall, and food diaries are the mainstays for estimation of dietary intake. In addition, a gradual decrease in blood urea nitrogen and reduced phosphate and potassium levels may indicate a decrease in protein intake in dialysis-dependent patients, and low serum cholesterol level may indicate a poor calorie intake.

The excretion or removal of urea is easily measured and is often used to estimate adequacy of dialysis. The protein equivalent of total nitrogen appearance (PNA) can be estimated on HD from interdialytic changes in urea nitrogen concentration in serum and the urea nitrogen content of urine and dialysate. nPNA is the term for PNA related to body weight. On the basis of the assumption that nitrogen excretion equals nitrogen intake in steady state, nPNA has been used to approximate

TABLE 86.4 Assessment of Nutritional Status

Area	Assessments
Physical Examination	
Assessment of dietary intake	Diet history, food diaries, appetite assessment questionnaires
Anthropometric measurements	Body weight, height, body mass index Percentage weight change Skinfold thickness Midarm muscle circumference
Body composition	Bioelectrical impedance Dual-energy x-ray absorptiometry (DEXA) Near-infrared reactance Neutron activation Total body potassium
Biochemical determinations	Serum electrolytes Serum proteins PNA, PCR Serum cholesterol Creatinine index*
Nutritional scoring systems	Subjective global assessment, malnutrition inflammation score (MIS) Geriatric nutritional risk index (GNRI)
Immunologic assays	Blood lymphocytes Delayed cutaneous hypersensitivity tests
Functional tests	Grip strength

*The creatinine index is measured as the sum of creatinine removed from the body (measured from the creatinine removed in dialysate, ultrafiltrate, and/or urine), any increase in the body creatinine pool, and the creatinine degradation rate. See also www.kidney.org/professionals/kdoqi/pdf/KDOQI2000NutritionGL.pdf.

PCR, Protein catabolic rate (mathematically identical to PNA); *PNA,* protein equivalent of total nitrogen appearance.

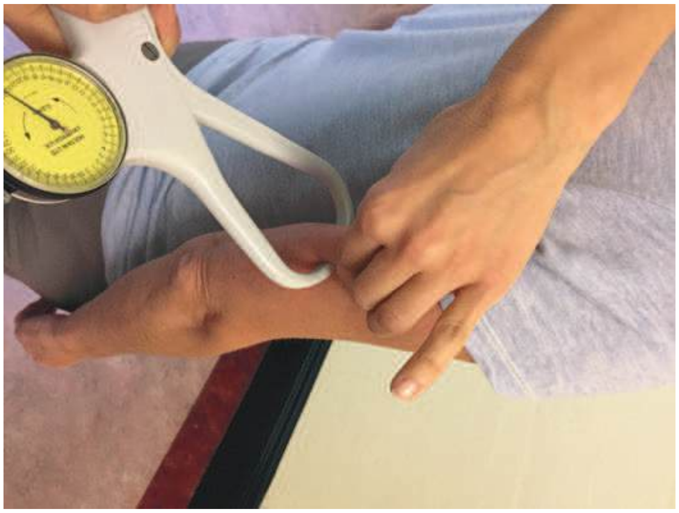

Fig. 86.5 **Routine measurement of skinfold thickness.** The dominant arm, which does not have an arteriovenous fistula or graft, is used in patients with renal failure.

dietary protein intake in the short term. However, results need to be interpreted with caution (urea kinetic modeling and adequacy of dialysis are further discussed in Chapters 94 and 96). Equations for estimation of nPNA have been recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI).[32]

Body Mass Index

The BMI (BMI = weight [kg]/height [m^2]) is the most commonly used parameter for nutritional assessment. BMI cannot distinguish muscle from fat mass and is affected by hydration status.

Body Composition

A range of techniques can distinguish body compartments on the basis of physical characteristics, which can provide information about nutritional state (body lean tissue and fat content) and hydration. Some are costly, less accessible, and used more for research purposes. A couple of the more widely available techniques are mentioned in the following discussion.

Skinfold thickness can be used to assess body fat, and muscle mass can be assessed by measurement of mid–upper arm muscle circumference (MAMC; Fig. 86.5). The midpoint of the upper dominant arm is used because this is the arm less likely to have an arteriovenous fistula.

$$\begin{aligned}\text{MAMC (cm)} &= \text{Midarm circumference (cm)}\\ &\quad - [3.14 \times \text{Triceps skinfold}]\ \text{(cm)}\end{aligned}$$

The measurement is taken after dialysis for patients on HD. Although these anthropometric parameters are inexpensive and relatively easy to measure, they are limited by intervariability and intravariability. Nevertheless, serial measures over time can be useful to track changes in the same patient when they are used in conjunction with other nutritional indices.

Observation of trends using serial measures of bioelectrical impedance are increasingly being used as an adjunct to the day-to-day clinical assessment of hydration status and body composition management of dialysis patients. However, bioelectrical impedance is not without its limitations and further prospective controlled trials are required to determine the best role for this technology in clinical practice.[33,34,52]

Visceral Protein

Fluid status, impaired liver function, age, and acute inflammatory conditions can affect albumin levels. However, despite its relatively long half-life (20 days), albumin remains an important measure of nutritional status and health of the patient. Clinically, it may be possible to observe the growth of white nails when there has been a transient period of hypoalbuminemia (Fig. 86.6). Other serum protein markers of nutritional status are difficult to interpret because of the influence of factors other than nutrition. Serum transferrin is linked to body iron stores and may be altered with changes in iron status. Prealbumin levels can be increased by CKD because of impaired metabolism in the kidney. Levels of prealbumin also decline rapidly during episodes of acute inflammation.

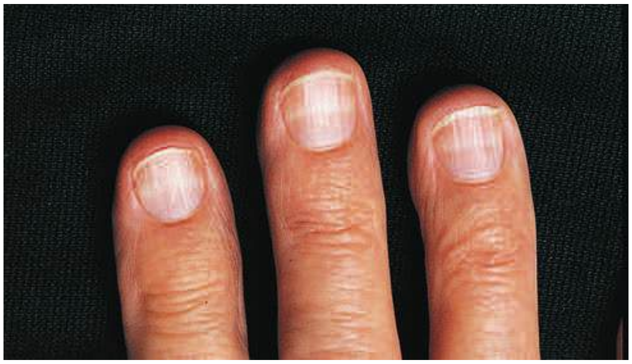

Fig. 86.6 **White nails in hypoalbuminemia.** The white band grew during a transient period of hypoalbuminemia caused by nephrotic syndrome.

Tools to Diagnose Protein-Energy Wasting and Assess Nutritional Status

Given the low specificity and sensitivity of many of the anthropometric and biochemical markers, a range of measurements along with evaluation of the subjective well-being of the patient is needed to assess nutritional status (Table 86.5).

Four main established categories are recommended for the diagnosis of PEW: serum biochemistry, body mass, muscle mass, and dietary intake.[23] Subjective global assessment (SGA) is a reliable nutritional assessment tool for patients on dialysis.[35] Questions about recent changes in nutrient intake are used with simple observations of the patient's body weight and muscle mass to assess the nutritional status of the individual; patients are classified as well nourished, mildly malnourished or with suspected malnutrition, or severely malnourished. Figs. 86.7 and 86.8 show muscle wasting in a patient on HD who was classified by SGA as severely malnourished. SGA is by definition subjective and has been criticized for being insufficiently sensitive to define the degree of malnutrition. The malnutrition inflammation score (MIS), the PEW definition criteria, and the geriatric nutritional risk index are alternative tools used by some centers and continue to be evaluated.

Nutritional Guidelines

Guidelines are useful, but it is important that dietary restrictions are not unnecessarily imposed and that advice be tailored to the individual and altered as circumstances dictate. Table 86.6 summarizes the nutritional recommendations for CKD.

Hyperlipidemia

Although disturbances in lipid metabolism are commonly seen in CKD, there is a paucity of data on the effect of diet therapy in this group. A diet low in fat (particularly saturated fat) with an increased intake of soluble fiber may be helpful in reducing cholesterol levels, although the role of cholesterol lowering in CKD patients is controversial (see Chapter 81). Losing weight if overweight and consuming a diet lower in sugar may improve hypertriglyceridemia, but a balance needs to be

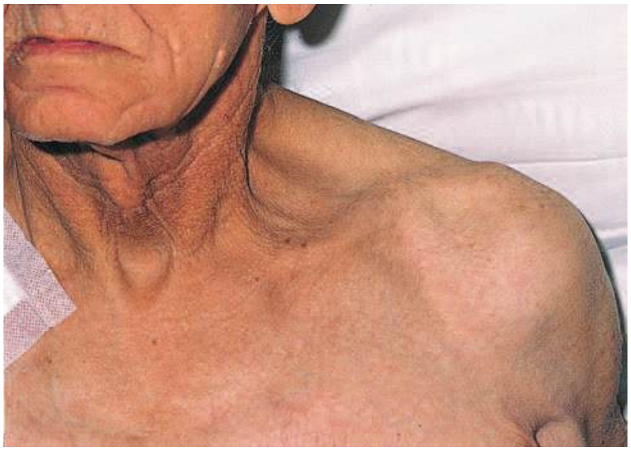

Fig. 86.7 **A severely malnourished hemodialysis patient.** There is marked wasting of the quadriceps and calf muscles. In addition, note skin lesions from scratching due to uremic pruritus.

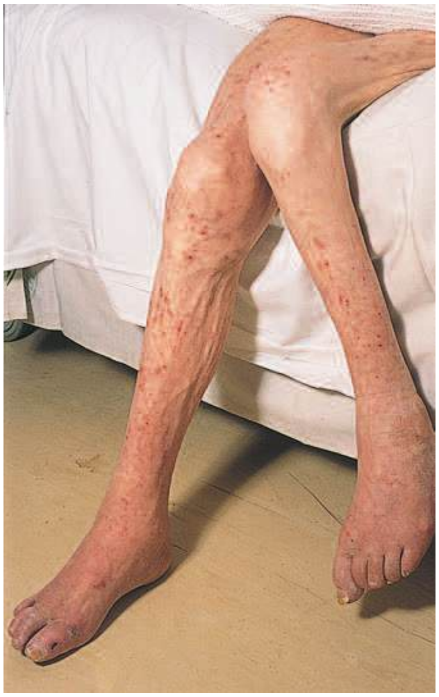

Fig. 86.8 **A severely malnourished hemodialysis patient.**

TABLE 86.5 Some Indices of Malnutrition

Assessment	Indices
Biochemical parameters	Serum albumin below the normal range Serum prealbumin <300 mg/l (30 mg/dl) (for maintenance dialysis patients only, because levels may vary according to GFR level for CKD 2-5) Low predialysis serum creatinine, phosphate, potassium, urea levels Serum cholesterol <150 mg/dl (3.8 mmol/l) Low creatinine index Low PNA, PCR
Anthropometric parameters	Continuous decline in weight, skinfold thickness, midarm muscle circumference BMI <20 kg/m^2 (note ISRNM suggest a lower threshold of 23 kg/m^2 is used)[23] Body weight <90% of ideal Abnormal muscle strength

BMI, Body mass index; *GFR,* glomerular filtration rate; *ISRNM,* International Society of Renal Nutrition and Metabolism; *PCR,* protein catabolic rate; *PNA,* protein equivalent of total nitrogen appearance.

struck between healthy eating concepts and nutritional adequacy. Additional fiber has the benefit of helping regulate bowel function, which is particularly important in PD patients.

Hypertension

The role of diet in the prevention and treatment of hypertension is discussed fully in Chapter 35.

Vitamins, Minerals, and Trace Elements

Vitamin, mineral, and trace element abnormalities in CKD relate to dietary restriction, dialysate losses, and the necessity of intact kidney function for normal metabolism of certain vitamins. However, the dietary requirements for patients with CKD are not clear-cut.

Protein and potassium restrictions can lead to inadequate intakes of pyridoxine, vitamin B_{12}, folic acid, vitamin C, iron, and zinc. The use of recombinant human erythropoietin may increase the requirement for iron and folic acid (see Chapter 82).

Increased serum homocysteine is a known risk factor for cardiovascular morbidity in CKD (see Chapter 81). However a cochrane review showed that lowering of serum homocysteine concentration with folic acid, vitamin B_{12}, and pyridoxine supplements has no effect on mortality or risk of cardiovascular events in dialysis patients.[36]

A variety of vitamin preparations are available that contain a recommended water-soluble vitamin profile for dialysis patients. The preparations vary slightly, but the following is one example: vitamin C, 120 mg; vitamin B_{1}, 3.0 mg; vitamin B_{2}, 1.7 mg; vitamin B_{6}, 10 mg; vitamin B_{12}, 6 μg; biotin, 300 μg; folic acid, 1 mg; nicotinamide, 20 mg; and pantothenic acid, 10 mg.

In the absence of firm guidance, it is prudent to have a low threshold for commencing such a water-soluble vitamin preparation. The European Best Practice (www.european-renal-best-practice.org) on nutrition gives opinion-based recommendations for patients on HD.[37]

High-dose vitamin C supplements (although popular in the general population) should not be taken in CKD because of the increased risk for secondary tissue oxalate deposition.

A review on fat-soluble vitamins in advanced CKD concluded there is universal agreement that supplementation with vitamin A is generally not recommended (unless a patient is receiving total parenteral nutrition) because deficiencies are rare, dialysis losses are minimal, and accumulation leading to toxicity can occur.[38] Vitamin E has been suggested to have antioxidant properties and beneficial effects for patients with CKD.[39] However, appropriately powered studies with longer follow-up are needed for confirmation.

Vitamin K functions as a cofactor for the enzyme γ-glutamyl carboxylase and may have a role in inhibiting vascular calcification (see Chapter 84). Evidence suggests most dialysis-dependent patients have subclinical vitamin K deficiency, and there is no known toxicity. Research is ongoing to determine if supplementation of vitamin K may have a beneficial role in preventing vascular calcification and reducing mortality in patients with advanced CKD.

Guidelines for vitamin D, phosphorus, and calcium are summarized in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (see Chapter 84).

TABLE 86.6 **Nutritional Recommendations in Chronic Kidney Disease**

Recommendations Are for Typical Patients but Always Should Be Individualized on the Basis of Clinical, Biochemical, and Anthropometric Indices.

Daily Intake	Predialysis CKD	Hemodialysis	Peritoneal Dialysis
Protein (g/kg ideal BW) (see KDOQI[32] for estimation of adjusted edema-free BW)	0.6-1.0 Level depends on the view of the nephrologist. 1.0 for nephrotic syndrome.	min ≥1.1[51]	min 1.0-1.2[51]
		Recommendations are in conjunction with an adequate energy intake. Requirements may be higher during illness because of multiple comorbidities or during acute periods of infection, including peritonitis.	
Energy (kcal/kg BW)	35[32] (younger than 60 y) 30-35[32] (older than 60 y)	35[32] (younger than 60 y) 30-35[32] (older than 60 y) 30-40 kcal/kg ideal BW[37]	35[32] including dialysate calories (younger than 60 yr) 30-35[32] including dialysate calories (older than 60 yr)
Sodium (mmol)	<100 (more if salt wasting)	<100	<100
Potassium	Reduce if hyperkalemic	Reduce if hyperkalemic	Reduce if hyperkalemic; potassium restriction is generally not required. May need to increase potassium intake if hypokalemic.
	If hyperkalemic, advice will take the form of decreasing certain foods (e.g., some fruits and vegetables) and giving information about cooking methods.		
Phosphorous	Reduce because of phosphate retention. Monitor levels. Advice will take the form of reducing certain foods (e.g., dairy, offal, some shellfish) and processed foods with high content of added phosphates, and giving information about the timing of binders with high-phosphorus meals and snacks.		

BW, Body weight; *CKD,* chronic kidney disease; *KDOQI,* Kidney Disease Outcomes Quality Initiative.

Recommendations for sodium, potassium, and phosphorus are shown in Table 86.6.

Monitoring and Treatment

Monitoring of patients with CKD involves a combination of nutritional assessment, noting relevant biochemistry (potassium, phosphate, lipids), checking dialysis adequacy, and observation of fluid status. The challenge comes in balancing the restrictions of the kidney diet against the risk for compromising nutritional status. When anorexia is present despite optimal management, nutrient intake may be maximized by one or more of the methods discussed in the following sections.

Enteral Supplementation

If food fortification advice is insufficient, supplements, in the form of high-protein, high-calorie drinks, powders, and puddings, should be considered. Enteral tube feeding is also an option if nutrient intake cannot be increased sufficiently by use of oral supplements. Renal-specific tube feeds and supplements are available that have lower fluid and electrolyte contents. A systematic review suggested that enteral multinutrient support increases serum albumin concentration and improves total dietary intake in patients receiving maintenance dialysis.[40] In addition, maintenance HD patients with albumin levels of 3.5 g/dl or lower received intradialytic oral nutritional supplements in a recent large retrospective matched-cohort study. Despite limitations, the results indicated significantly better survival in the supplemented group versus similarly matched patient controls.[41,42]

Supplementation of Dialysate Fluids

The GI route is the preferred choice for nutritional supplementation. However intradialytic parenteral nutrition (IDPN) has been used to provide intensive parenteral nutrient therapy with use of concentrated hypertonic solutions infused into the venous blood line three times weekly during HD treatments for patients who cannot tolerate oral or enteral administration of nutrients. IDPN typically provides 800 to 1200 kcal three times weekly, in the form of glucose and fat emulsion and 30 to 60 g of protein and so will only supplement rather than provide full nutritional needs.

A systematic review concluded that the evidence from clinical studies is insufficient to demonstrate either a net benefit or a net harm associated with providing IDPN to malnourished HD patients and that further clinical research is needed in this area.[43] The high cost of the therapy is a barrier to performing adequately powered clinical trials.

Intraperitoneal amino acids (IPAAs) can be used in PD. A 1.1% amino acid solution is substituted for glucose in PD fluid, and about 80% of the amino acids are absorbed in a 4-hour period.[44] The long-term effects of IPAAs on nutritional status and clinical outcomes are not known, and the solution is often used primarily to reduce glucose exposure.

Expert opinion on the use of these approaches is inconsistent. The KDOQI has suggested that IPAAs (for PD) or IDPN (for HD) should be considered for patients who have evidence of protein or energy malnutrition and inadequate protein or energy intake and who are unable to tolerate adequate oral supplements or tube feeding.[32] The European Society of Enteral and Parenteral Nutrition has provided criteria for use of IDPN.[45] However, the American Society for Parenteral and Enteral Nutrition recommends that IDPN not be used as a nutritional supplement in malnourished HD patients because studies so far do not offer strong support for IDPN.[46]

Appetite Stimulants

Megestrol acetate, a progesterone derivative, moderately improves appetite in HD patients in small studies. However, megestrol acetate has adverse effects, and larger trials are required before recommendations can be made for CKD patients.[47] More studies are also required for ghrelin, an orexigenic hormone, and melanocortin-receptor antagonists.

Gut-Targeted Therapeutics

There is accumulating evidence that the GI tract maybe a major source of chronic inflammation in CKD. It is hypothesized that altered diets (low potassium, phosphorus, and fiber) may affect the gut microbiome, resulting in overgrowth of bacteria that produce uremic toxins and a leaky epithelial barrier that allows toxins to get into the circulation.

It has been suggested that prebiotic and probiotic formulations may lower serum levels of uremic toxins. However more trials investigating gut-targeted therapeutics are needed before they could be recommended for use in clinical practice.

Metabolic Acidosis

Although some trials have shown no detrimental effect of mild metabolic acidosis, many others have reported that normalization of serum bicarbonate concentration (see Chapter 12) is beneficial for protein nutritional status and bone metabolism. Current guidelines recommend the correction of acidosis in dialysis-dependent patients.[37,48,49]

Exercise

There is a large body of research on exercise training for adults with CKD that shows significant benefits on physical fitness, CV parameters, well-being, and nutritional markers.[50] Trials are ongoing, and the future is likely to hold more guidance in this area for clinical practice.

Potassium Binders

Novel, orally administered potassium-exchanging compounds are being investigated as possible treatment options for the management of hyperkalemia. Sodium zirconium cyclosilicate and patiromer act by enhancing potassium removal, predominantly through the GI tract.

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SELF-ASSESSMENT QUESTIONS

1. A 60-year-old woman commenced hemodialysis 6 years ago. At a recent outpatient appointment she reported breathlessness. Predialysis blood pressure (BP) is 150/80 mm Hg.
   - Dialysis: 4 hours three times per week
   - Target weight: Stable for last 2 years at 55 kg
   - Height: 1.47 m
   - Body mass index (BMI): 25 kg/m^2
   - Intradialytic weight gain average 0.9 kg
   - Passes small amounts of urine

   Monthly laboratory testing reveals blood results as follows:

	Creatinine (mg/dl)	Urea (mg/dl)	Phosphate (mg/dl)	Potassium (mmol/l)	Albumin (g/dl)	Cholesterol (mg/dl)	Hemoglobin (g/dl)
Predialysis	5.3	27	3.16	4.5	3.5	100	13.85
Postdialysis	1.54	7.86	1.30	2.9			

   What would your next course of action be?

   A. Reduce the dialysis time because she is receiving more dialysis than required.
   B. Investigate dietary intake, in particular protein and calorie intake, and assess target weight.
   C. Increase target weight.
   D. Start diuretics and fluid restriction.

2. A 38-year-old White man with progressive chronic kidney disease is feeling tired, reporting weight loss, nausea, and a metallic taste in the mouth. His BP is 156/90 mm Hg, and urinalysis reveals +++ protein and traces of blood. There are no signs of peripheral edema. He trains at the gym three times per week.
   - Weight: 78 kg
   - Height: 1.7 m
   - BMI: 27 kg/m^2
   - Amlodipine 5 mg/day commenced
   - Sodium bicarbonate commenced
   - Diet history reveals an average daily protein intake of 120 g, an approximate calorie intake of 2600 kcal, and sodium intake of 190 mmol/day.

   Laboratory findings are as follows:

GFR (ml/min)	Creatinine (mg/dl)	Urea (mg/dl)	Phosphate (mg/dl)	Calcium (mg/dl)	Potassium (mmol/l)	Bicarbonate (mEq/L)
13	5.1	74	4.96	10.02	5.1	16

   What would your next course of action be?

   A. Put the patient on a reduced-calorie diet.
   B. Start dialysis.
   C. Moderate protein and salt intake.
   D. Start a low-potassium diet.

3. A 59-year-old man with end-stage renal disease resulting from type 1 diabetes has been treated with continuous ambulatory peritoneal dialysis for 12 months. He reports reduced appetite, occasional nausea, and feeling full only midway through modest-sized meals; he has lost 3.3 kg over the previous 2 months. He weighs 79.2 kg and he has a BMI of 34 kg/m^2. He dialyzes with four exchanges of volume, 2 liters each. Measurement of dialysis clearances shows a weekly Kt/V for urea of 1.8 (target minimum 1.7). What would your next course of action be?

   A. Reduce dialysis fluid volumes in case they are contributing to his gastrointestinal symptoms.
   B. Advise weight reduction because BMI may be contributing to feelings of fullness.
   C. Start amino acid-containing peritoneal dialysate.
   D. Start a prokinetic agent.

87

Dermatologic Manifestations of Chronic Kidney Disease

Pieter Evenepoel, Dirk R. Kuypers

Cutaneous disorders are common in patients with chronic kidney disease (CKD). Many of these cutaneous disorders are caused by the underlying renal disease, whereas others relate to the severity and duration of uremia. Skin lesions associated with cutaneous aging have a high incidence in CKD patients, including wrinkling, senile purpura, actinic keratoses, and hair loss.

Improved treatments in dialysis patients have resulted in changes in the frequency and types of skin disorders observed in conjunction with end-stage renal disease (ESRD). Dermatologic conditions such as uremic frost, erythema papulatum uremicum, uremic roseola, and uremic erysipeloid now rarely occur. Pigmentary alterations, xerosis, ichthyosis, half-and-half nails, acquired perforating dermatosis, bullous dermatoses, pruritus, and calcific uremic arteriolopathy (CUA) remain prevalent, whereas nephrogenic systemic fibrosis (NSF) is a rare and waning entity now that the causative agent has been identified (Fig. 87.1). The last four prevalent skin disorders are the focus of this chapter because they are associated with significant morbidity or mortality and/or represent an ongoing diagnostic or therapeutic challenge.

UREMIC PRURITUS

Clinical Manifestations

Uremic pruritus (UP) is a frequent symptom of ESRD, with a reported prevalence ranging from 22% to 48%. Although its incidence in adult dialysis patients has declined as a result of improved dialysis efficacy and the introduction of so-called “biocompatible” dialysis membranes, pruritus remains a frustrating problem for patients, causing serious discomfort and skin damage, often in association with disturbance of day and night rhythm, sleeping disorders, depression, anxiety, and diminished quality of life.[1,2] The intensity and spatial distribution of UP vary significantly among patients and over time throughout the course of renal disease. Excoriations, induced by uncontrollable scratching with or without superimposed infection, are frequently encountered in severely affected patients and, rarely, lead to prurigo nodularis—a treatment-resistant lichenified or excoriated papulonodular chronic skin eruption (Fig. 87.2). The most frequently involved body areas are the back, limbs, chest, and face; 20% to 50% of patients report generalized pruritus.[3]

Pathogenesis

Many uremic factors are thought to contribute to UP. Parathyroid hormone (PTH) and divalent ions (calcium, phosphate, magnesium) have been implicated because itching is a frequent symptom accompanying severe secondary hyperparathyroidism and elevated calcium-phosphate product. However, the lack of consistent correlations between serum and skin levels of PTH, calcium, phosphorus, and magnesium with the severity of UP indicates that other factors contribute to its development. Histamine released by mast cells has been implicated in UP. The number of dermal mast cells is increased in uremic patients, and higher tryptase and histamine plasma concentrations are reported in severe cases. Histamine release is triggered by substance P, a neurotransmitter involved in itch sensation. The role of elevated serotonin (5-hydroxytryptamine [5-HT$_3$]) levels in dialysis patients with UP is debated; clinical trials using a selective inhibitor of 5-HT$_3$ have yielded conflicting results (see later discussion). Xerosis is a common skin problem in dialysis patients (60% to 90%) that predisposes to UP. Skin dryness is caused by primary dermal changes associated with uremia, such as atrophy of sweat glands with impaired sweat secretion, disturbed stratum corneum hydration, sebaceous gland atrophy, and abnormal arborization of free cutaneous nerve fiber endings.

There are two major hypotheses of the pathogenesis of UP. The opioid hypothesis proposes that UP is caused by overexpression of opioid μ receptors in dermal cells and lymphocytes. Consistent with this hypothesis, activation of the κ opioid system using a κ-receptor agonist was efficient in reducing pruritus in a mouse model. In contrast, the immune hypothesis considers UP an inflammatory systemic disease rather than a local skin disorder. Studies examining the beneficial effects of ultraviolet B (UVB) exposure on pruritus showed that UVB attenuates the development of Th1 T-helper cells in favor of Th2 T-helper cells. Indeed, the number of CXCR3-expressing and interferon-γ–secreting CD4$^+$ cells (indicating Th1 differentiation) is significantly increased in the circulation of dialysis patients with pruritus compared with those without. Levels of serum markers of inflammation, such as C-reactive protein, interleukin-2 (IL-2), IL-31, and IL-6, are also higher in patients with UP.

Treatment

Common causes of UP in CKD and dialysis patients, such as primary skin disorders (e.g., urticaria, psoriasis, atopic and contact dermatitis), liver disease (e.g., hepatitis), and endocrine diseases (e.g., hypothyroidism, diabetes mellitus) should be ruled out and adequately treated. The treatment approach to UP is shown in Fig. 87.3.

Optimizing Dialysis and Mineral Metabolism Therapy

Optimizing dialysis biocompatibility and efficacy and improving nutritional status may result in a reduced prevalence and severity of UP. Adequate control of calcium and phosphorus serum concentrations by short-term use of dialysate with low calcium and magnesium concentrations ameliorated pruritus symptoms in only a few small studies

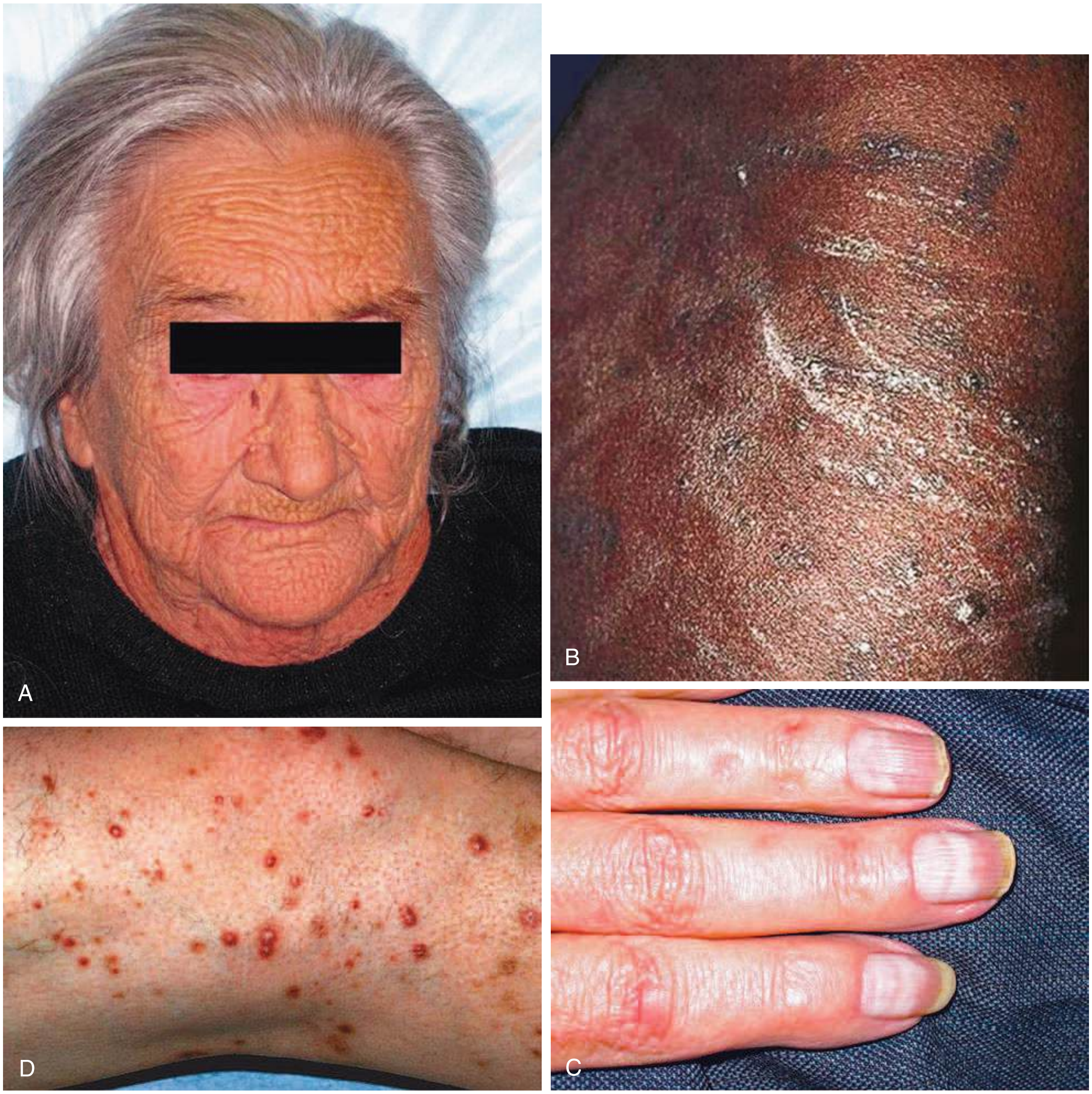

Fig. 87.1 **Cutaneous disorders in patients with end-stage renal disease.** (A) A spectrum of pigmentary alterations occurs in dialysis patients, with brownish hyperpigmentation in sun-exposed areas being the most prevalent. (B) Xerosis, a dry or roughened skin texture, is seen in up to 75% of dialysis patients. (C) Half-and-half nails (also termed *red and white nails*) occur in as many as 40% of patients on dialysis. The nails exhibit a whitish or normal proximal portion and an abnormal brown distal portion. (D) Acquired perforating dermatosis affects approximately 10% of the dialysis population. The lesion is usually asymptomatic and consists of grouped dome-shaped papules and nodules, 1 to 10 mm in diameter. The trunk and the extremities are most commonly involved.

and may lead to worsening of renal osteodystrophy in cases of prolonged use. Parathyroidectomy is not advocated for relief of UP because no consistent beneficial effects have been demonstrated.

Skin Emollients

Emollients continue to be the primary treatment given by nephrologists, although the literature is mixed on the overall efficacy of this approach. The use of simple emollients without perfumes or other additives is preferred. Continuous bath oil therapy containing polidocanol, a mixture of monoether compounds of lauryl alcohol and macrogol, seems to be of value for some patients. Sericin, a biopolymer protein from the silkworm *(Bombyx mori)* contains 32% serine, is the main amino acid of the natural moisture factor in human skin, and suppresses the release of proinflammatory cytokines. Sericin was shown to effectively reduce UP in a randomized, double-blind, placebo-controlled 6-week study in 50 dialysis patients.[4]

Antihistaminic Drugs

Classic antihistamines have similar efficacy compared with emollients; newer, second-generation antihistamines (e.g., desloratadine) might have some effect in UP. Ketotifen (2 to 4 mg/day), a putative mast cell stabilizer, was beneficial in one small study.

Phototherapy

Ultraviolet light, especially UVB (wavelength, 280 to 315 nm), is effective for treatment of UP and is well tolerated except for occasional sunburn. The duration of the antipruritic effect of thrice-weekly total body UVB therapy (total, 8 to 10 sessions) is variable but may last for several months. Potential carcinogenic effects of UV radiation require serious consideration, and its prolonged use is contraindicated in patients with a fair complexion (skin phototypes I and II).

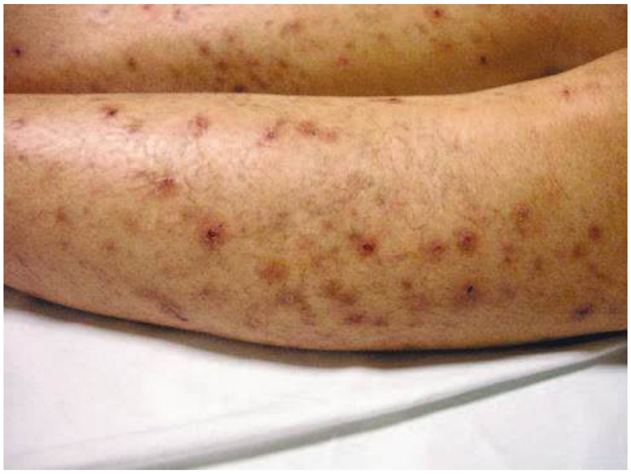

Fig. 87.2 **Prurigo nodularis.** (Courtesy I. Macdougall, London, United Kingdom.)

5-Hydroxytryptamine Antagonist

Ondansetron, a selective 5-HT$_3$ antagonist, was used successfully in a small study in peritoneal dialysis patients. However, a subsequent larger randomized, placebo-controlled study failed to show superiority over placebo in patients on hemodialysis (HD).

Opioid Receptor Agonists

A κ-opiate receptor agonist, nalfurafine, given intravenously after HD, was tested in two randomized, double-blind, placebo-controlled trials comprising 144 patients. Itching intensity, excoriations, and sleep disturbances were significantly reduced in patients receiving the active compound without an excess of drug-related side effects compared with placebo.[5] Oral daily doses of 2.5 to 5 mg nalfurafine were equally effective in reducing UP scores compared with placebo during a 2-week treatment period in 337 dialysis patients.[6] A subsequent 1-year study (n = 211) confirmed the sustained beneficial effect of 5 mg nalfurafine on UP, with the most frequently reported adverse events being insomnia (19%), constipation (7%), and increased blood prolactin concentrations.[7]

Gabapentin

Gabapentin, an anticonvulsant drug, administered after dialysis (300 mg) was effective in reducing pruritus. A reduced dose is required if it is given chronically to patients with ESRD, because it has a narrow therapeutic window and can accumulate and cause neurotoxic side effects.[8] The UP score was significantly reduced in two controlled studies after 4 weeks of gabapentin therapy at a dose of 100 to 300 mg administered thrice weekly after dialysis. Gabapentin was well tolerated; no patients stopped therapy because of side effects, which were limited to dizziness, somnolence, fatigue, and nausea. Similar effects were demonstrated in a smaller study using pregabalin and recent randomized trials comparing gabapentin with doxepin and ondansetron.[9,10]

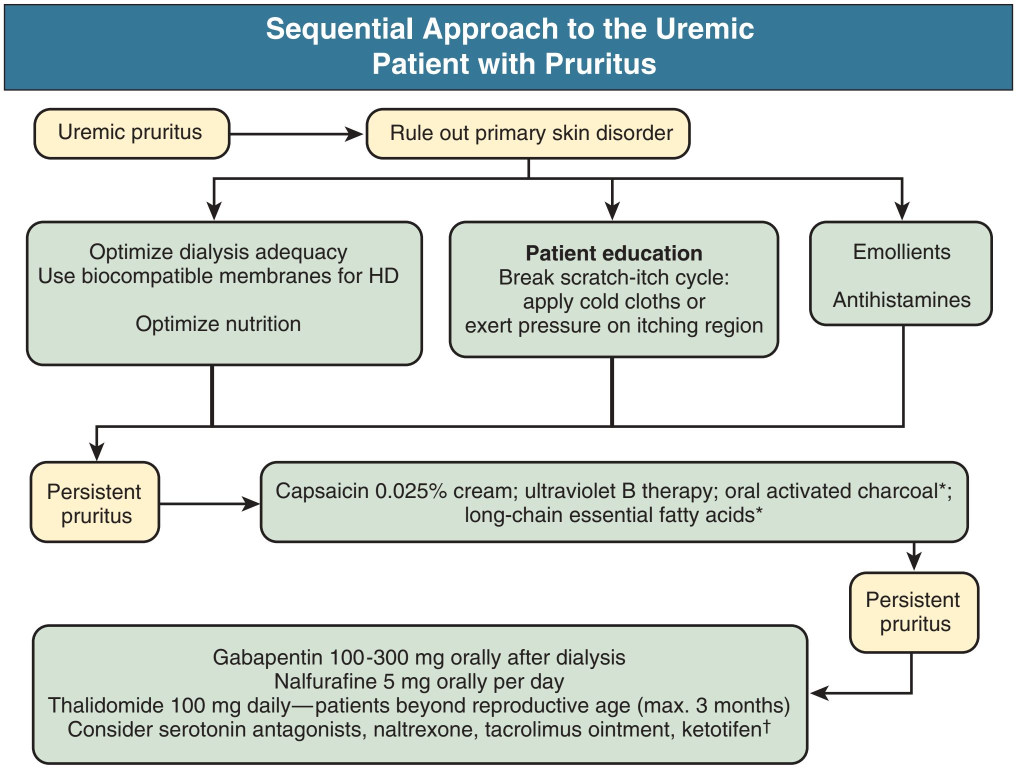
Sequential Approach to the Uremic Patient with Pruritus
Uremic pruritus
Rule out primary skin disorder
Optimize dialysis adequacy
Use biocompatible membranes for HD
Optimize nutrition
Patient education
Break scratch-itch cycle:
apply cold cloths or
exert pressure on itching region
Emollients
Antihistamines
Persistent pruritus
Capsaicin 0.025% cream; ultraviolet B therapy; oral activated charcoal*;
long-chain essential fatty acids*
Persistent pruritus
Gabapentin 100-300 mg orally after dialysis
Nalfurafine 5 mg orally per day
Thalidomide 100 mg daily—patients beyond reproductive age (max. 3 months)
Consider serotonin antagonists, naltrexone, tacrolimus ointment, ketotifen†

Fig. 87.3 **Sequential approach to the uremic patient with pruritus.** *See text for details. †Therapeutic benefit in studies has been described variably; see text for details. *HD,* Hemodialysis.

Immunomodulators and Immunosuppressive Agents

A 7-day course of thalidomide reduced the intensity of UP by up to 80% in a placebo-controlled crossover study of 29 HD patients. Because of its strong teratogenic properties, thalidomide should probably be reserved for therapy-resistant severe UP in individuals outside the reproductive-age category. Adverse effects of thalidomide, such as peripheral neuropathy and cardiovascular side effects, limit its continuous longer use. A prospective, single-center study of 25 chronic dialysis patients with UP demonstrated that 6 weeks of treatment with tacrolimus ointment (0.1%) significantly reduced the severity of UP. Tacrolimus was well tolerated in this trial and caused no detectable systemic exposure or side effects.[11] However, a subsequent, smaller vehicle-controlled trial showed equal relief of UP with vehicle and tacrolimus. The risks of long-term topical use of these agents are currently unknown, and their prolonged use is not recommended until more data are available.

Long-Chain Essential Fatty Acids

Oral administration of γ-linoleic acid (GLA)-rich primrose oil resulted in significant improvement of UP in chronic dialysis patients. Supplementation of GLA-rich primrose oil is thought to augment synthesis of antiinflammatory eicosanoids. Similar effects could be obtained through use of fish oil, olive oil, and safflower oil.

Capsaicin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is a natural alkaloid found in the pepper plant that depletes the cutaneous type C sensory nerve endings of substance P. Two clinical studies showed that application of a 0.025% capsaicin cream significantly alleviated UP in dialysis patients, who exhibited no side effects.

Oral Activated Charcoal

Pruritus symptoms completely disappeared or were significantly reduced in chronic dialysis patients treated with activated charcoal (6 g/day) for 8 weeks. In two different clinical studies, comparable results were obtained with this inexpensive and well tolerated compound, rendering it a valuable alternative for patients with UP.

Miscellaneous

Various other types of therapies have been examined in the treatment of pruritus but are, despite the effectiveness of some, not considered first choice in chronic HD patients because of undesirable side effects, cumbersome use, or incompatibility with renal replacement therapy (sauna, cholestyramine, nicergoline). Other therapies that have not reduced UP convincingly in a controlled setting and are therefore not advocated include acupuncture, low-protein diet, intravenous lidocaine, sertraline, zinc sulfate, topical vitamin D, and mexiletine.

BULLOUS DERMATOSES

Bullous dermatoses are reported in up to 16% of patients on maintenance dialysis. This skin disease entity mainly comprises pseudoporphyrias (e.g., secondary to nonporphyrinogenic drugs and chemicals) and other photodermatoses, whereas true porphyrias (e.g., porphyria cutanea tarda [PCT], variegate porphyria) remain a rare entity.[12] Pseudoporphyrias, true porphyrias, and photodermatoses are clinically and histologically similar and are characterized by a blistering photosensitive skin rash. The dorsal hands and the face are the most affected areas (Fig. 87.4).

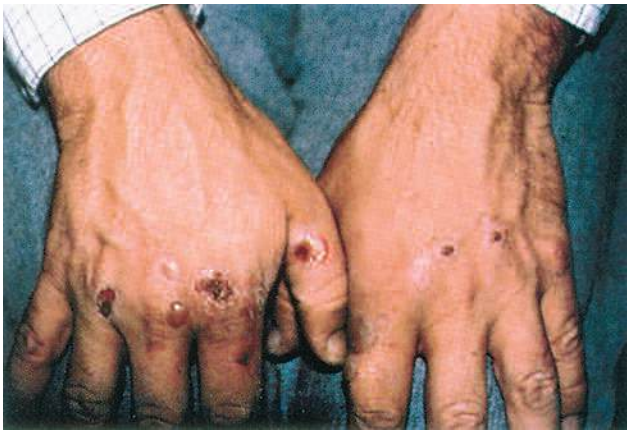

Fig. 87.4 **Porphyria cutanea tarda.** Tense bullae, erosions, and crusts of the dorsal hands. (With permission from reference 12.)

PCT is caused by abnormalities in the porphyrin-heme biosynthetic pathway, leading to an accumulation of highly carboxylated uroporphyrins in the plasma and skin. Phenotypic expression of the disease also requires one or more of a number of external contributory factors, including alcohol, estrogens, iron overload, and infection with hepatitis B and C viruses. It is important to distinguish PCT from other porphyrias in which patients are at risk for development of potentially fatal neurologic attacks if they are exposed to porphyrinogenic drugs and other precipitants. Therapeutic options include avoidance of environmental triggers, HD with high-flux membranes, repeated small-volume phlebotomies, and iron chelators.

The term *pseudoporphyria* was originally used for patients with normal plasma porphyrins who exhibited PCT-like skin lesions secondary to drugs and chemicals. However, some dialysis patients also develop similar skin lesions that spontaneously heal and leave a hypopigmented area; this entity is known as *dialysis porphyria;* a proportion of these patients have raised plasma porphyrins but without the disturbances in porphyrin metabolism classically found in the porphyrias. In rare patients, an offending medication can be identified. However, in most dialysis patients, protection from sun exposure appears to be the only preventive measure.

CALCIFIC UREMIC ARTERIOLOPATHY (CALCIPHYLAXIS)

Definition

CUA, or calciphylaxis, is a devastating and life-threatening ischemic vasculopathy confined primarily to patients with CKD.[13,14] There are also reports of this disease in nonuremic patients. The ischemia may be so severe that frank infarction of downstream tissue develops. The most common and most noticeable damage is in the skin and subcutaneous tissues.[12,13] CUA should be distinguished from benign nodular calcification (calcinosis cutis), which can develop in patients with very high serum calcium-phosphate product (Fig. 87.5).

Epidemiology, Pathogenesis, and Risk Factors

Although hard epidemiologic data are lacking, it is generally believed that the incidence of CUA is increasing. This might in part result from increased physician awareness and the high-risk profile of contemporary dialysis patients. The estimated incidence ranges from 1 to 4 per 100 patient-years. The pathogenesis of CUA is complex and incompletely understood.[13,15] Recent data suggest that CUA involves a cell-mediated, bone morphogenetic protein-2–driven osteogenic process with extensive subcutaneous extracellular matrix remodeling and deposition of hydroxyapatite.[16] A cascade consisting of matrix remodeling, calcification, endothelial damage and thrombus formation, luminal obstruction, and finally full-blown CUA has been postulated.[16] Female gender, White race, obesity, diabetes, dialysis vintage, and last but not least vitamin

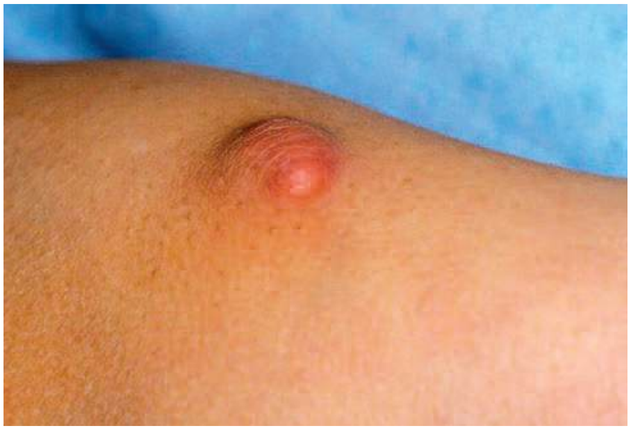

Fig. 87.5 Benign nodular calcification (calcinosis cutis). Firm subcutaneous nodule adjacent to the elbow.

K antagonism are established risk factors. In a case control study, the incidence of CUA was 10-fold higher in dialysis patients treated with vitamin K antagonists (warfarin or coumarins). Endogenous inhibitors of vascular calcification, such as matric Gla protein are dependent on vitamin K for their activation. Patients treated with warfarin or coumarins may thus not be able to appropriately inhibit vascular calcification. CUA prevalence is higher in patients with hyperphosphatemia and those receiving calcium-containing phosphate binders. In acute CUA, serum calcium and phosphate levels can be low. Although data from the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial indicate cinacalcet may reduce the incidence of CUA in HD patients who have moderate to severe secondary hyperparathyroidism,[17] registry data fail to confirm a key role for uncontrolled hyperparathyroidism in the pathogenesis of CUA.[18] Finally, both low- and high-turnover bone disease have been associated with CUA.

Clinical Manifestations

CUA is typically characterized by areas of zoster-like tenderness and ischemic necrosis of the dermis, subcutaneous fat, and, less often, muscle.[13] These ischemic changes lead to livedo reticularis or violaceous, painful, plaque-like subcutaneous nodules on the trunk, buttocks, or proximal extremity—that is, in areas of greatest adiposity (proximal CUA; Fig. 87.6A). The early purpuric plaques and nodules progress to ischemic or necrotic ulcers with eschars that often become infected. Proximal CUA is frequently precipitated by a specific event, such as local skin trauma or a hypotensive episode. CUA also can affect the hands, fingers, and lower extremities, thereby mimicking atherosclerotic peripheral vascular disease (distal CUA; see Fig. 87.6B). Peripheral pulses are preserved distal to the area of necrosis. Myopathy, hypotension, fever, dementia, and infarction of the central nervous system, bowel, or myocardium have been described in association with cutaneous necrosis. This condition is termed *systemic CUA*.

Pathology

The histologic features of CUA are suggestive but not pathognomonic.[13] Specimens from incisional biopsies of early lesions show subtle histologic changes. Late lesions characteristically show epidermal ulceration, dermal necrosis, and mural calcification with intimal hyperplasia of small and medium-sized blood vessels in the dermis and subcutaneous tissue (Fig. 87.7).

Diagnosis and Differential Diagnosis

Many clinicians base the diagnosis of CUA on physical examination findings only. Although ulceration is an obvious presentation of CUA, increasing awareness of the condition should allow diagnosis at an earlier, nonulcerative stage when a distinct subcutaneous tenderness can be felt below the early skin lesions. Biopsies are discouraged by most but not all experts because of potential ulceration in the region of the incision and the risk for sampling error. Other potentially useful diagnostic procedures include measurements of transcutaneous oxygen saturation, bone scintigraphy (Fig. 87.8), and xeroradiography.[19]

BOX 87.1 Treatment Options in Patients With Calcific Uremic Arteriolopathy*

1. **Reduction of procalcifying factors**
   Intensified dialysis (e.g., daily hemodialysis, switch from peritoneal dialysis to hemodialysis, low-calcium dialysate)
   Avoidance of vitamin D and calcium supplements; administration of calcium-free phosphate binders; bisphosphonate administration (caution if adynamic bone disease is suspected)
   Parathyroidectomy (in the case of hyperparathyroidism) or administration of cinacalcet
2. **Improving the status of calcification inhibitors**
   Halt vitamin K antagonists (warfarin)
   Aggressive treatment of infections or other proinflammatory stimuli to increase fetuin-A levels
   Experimental:
      Administration of high-dose vitamin K_2, and if unavailable, vitamin K_1?
      Administration of fetuin-A (e.g., by fresh frozen plasma or plasma exchange?)
3. **Prevention or reversal of calcium-phosphate precipitation**
   Administration of sodium thiosulfate
4. **Supportive measures**
   Avoidance of additional local tissue trauma by atraumatic wound care with gentle debridement of necrotic tissue and avoidance of subcutaneous injections
   Anticoagulation (heparin and low molecular weight heparin)
   Adequate pain management
   Adequate infection control

Modified from reference 20.
*Theoretical options based on pathophysiologic considerations that have not been tested in clinical practice are printed in italics.

The following conditions should be considered in the differential diagnosis: herpes zoster, systemic vasculitis, peripheral vascular disease, pyoderma gangrenosum, atheroemboli, cryoglobulinemia, warfarin-induced skin necrosis, and systemic oxalosis. A skin biopsy should be performed when clinical circumstances do not suggest CUA or when clinical and laboratory examinations, including the assessment of coagulation and immunologic parameters, point to an alternative diagnosis.

Natural History

Despite intensive combined treatments, the prognosis of patients with CUA remains poor; the overall 1-year survival is 45% and the 5-year survival is 35%, with a relative risk for death of 8.5 compared with that for other dialysis patients. Patients with ulcerative or proximal CUA have the worst prognosis. Infection accounts for up to 60% of the mortality.[13]

Prevention and Treatment

Preventive approaches include controlling bone and mineral metabolism and optimizing nutritional state.[13] Specific therapeutic regimens have been limited to uncontrolled case series (Box 87.1). Intervention should include an aggressive program of wound care and prevention of superinfection, adequate pain control, and correction of underlying abnormalities in serum calcium and phosphorus concentrations. This includes

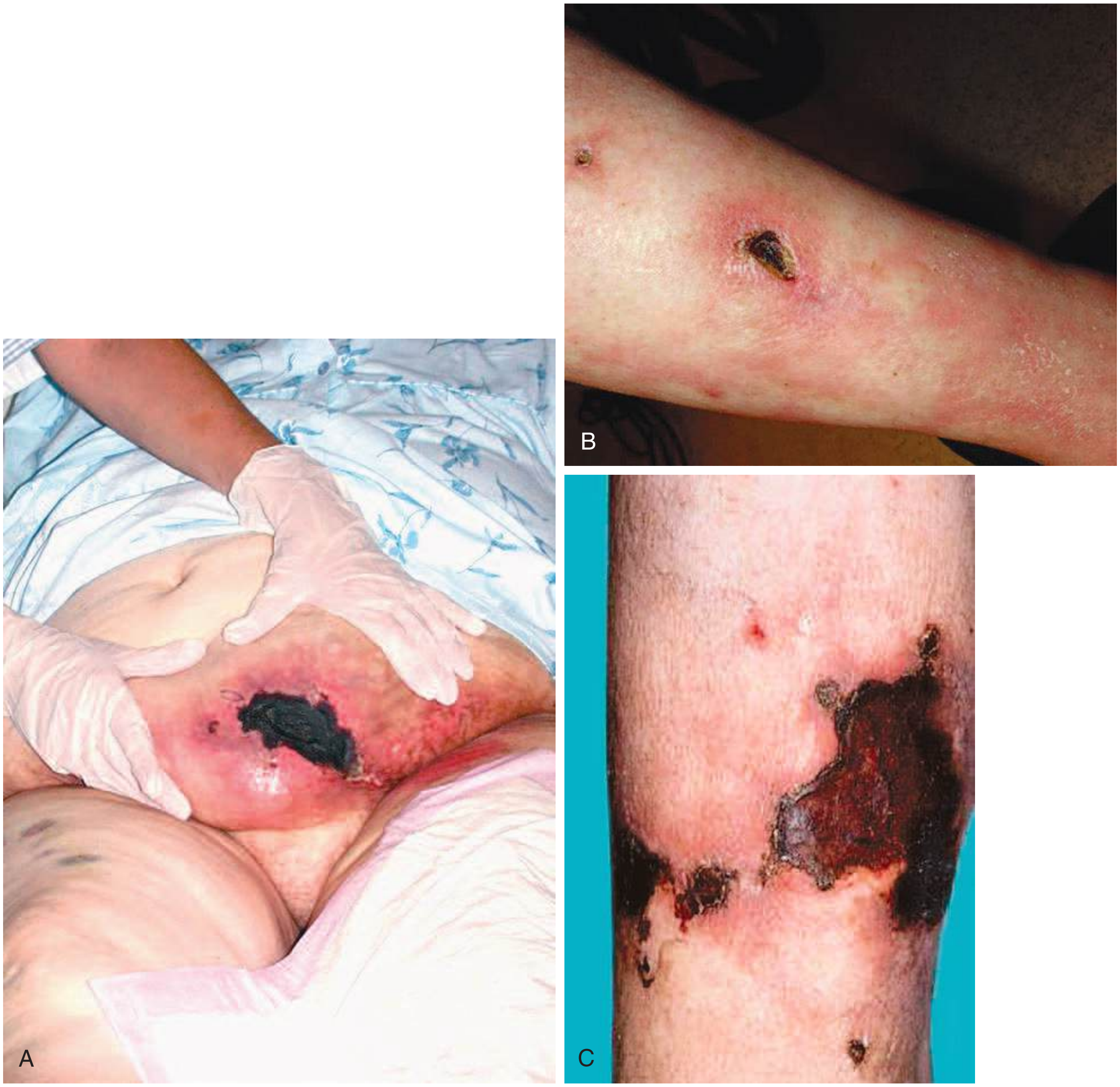

Fig. 87.6 Proximal (A) and distal (B and C) calcific uremic arteriolopathy.

cessation of vitamin D supplementation, intensification of the dialysis regimen, and use of a low-calcium dialysate and non–calcium-containing phosphate binders (e.g., sevelamer, lanthanum carbonate). Furthermore, local tissue trauma, including subcutaneous injections, should be avoided. Parathyroidectomy is effective in the control of CUA in some series but not in others and should be reserved for patients with severe hyperparathyroidism. In such patients, calcimimetic agents may be a suitable noninvasive alternative. Vitamin K (preferentially vitamin K_1) supplementation is advised, especially in patients with warfarin- or coumarin-associated CUA. Novel and promising therapies include sodium thiosulfate and bisphosphonates. Sodium thiosulfate has recently been licensed as an orphan drug for CUA by the European Medicines Agency. It enhances the solubility of calcium deposits[20] because exchange of calcium for sodium results in extremely soluble calcium thiosulfate. Besides being a chelator of calcium, sodium thiosulfate is also a potent antioxidant. Sodium thiosulfate is given intravenously at the end of every HD session (12.5 to 25 g over 30 to 60 minutes). Apart from nausea and vomiting, the therapy is well tolerated. The major side effect of sodium thiosulfate infusion is the development of metabolic acidosis. The optimal duration of treatment and potential effects of long-term treatment on bone are unknown. Efficacy has been suggested by several case-series, but definite proof by a randomized controlled trial is lacking.

NEPHROGENIC SYSTEMIC FIBROSIS

Definition

NSF, formerly known as *nephrogenic fibrosing dermopathy*, is a scleroderma-like fibrosing disorder that develops in the setting of renal failure. The fibrotic process affects the dermis, subcutaneous tissues, fascia, and other organs, including striated muscles, heart, and lungs.[21]

Pathogenesis

Gadolinium-based contrast (GBC) agents have been identified as the cause of NSF; exposure to gadolinium before the onset of disease was

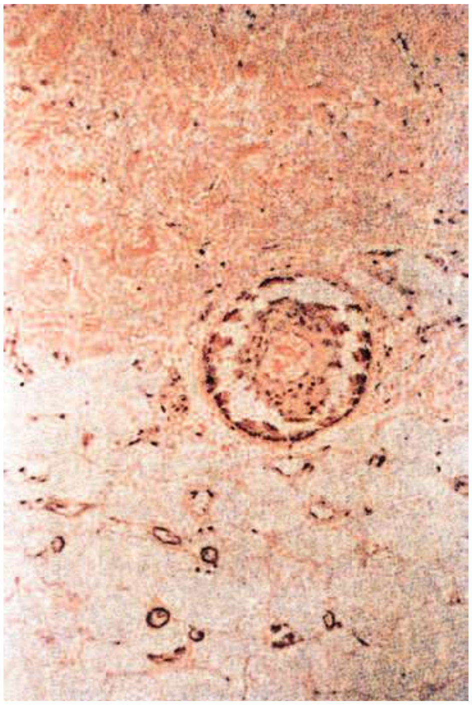

Fig. 87.7 **Histopathologic features of calcific uremic arteriolopathy.** Medial calcification and intimal hyperplasia of an arteriole at the dermal-subcutaneous junction. Note calcification of interlobular capillaries in the subcutaneous tissue. (Van Kossa stain.) (With permission from reference 12.)

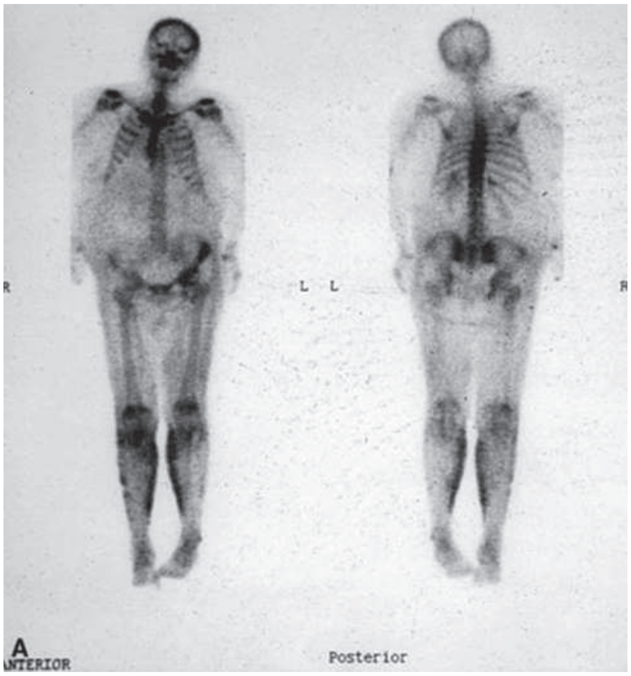

Fig. 87.8 **Bone scintigraphic abnormalities in calcific uremic arteriolopathy.** Calf calcification in a patient with gross ulcerations in both legs from the popliteal fossae to the ankles. (With permission from reference 14.)

confirmed in more than 95% of reported cases. Free gadolinium ions are highly toxic to tissues. The toxic effects of gadolinium are circumvented by sequestration of the metal by chelates, large organic molecules that form a stable complex with gadolinium and make the ion biochemically inert and nontoxic. Under normal circumstances, GBC agents are eliminated by the kidney through glomerular filtration. Evidence points toward aberrant activation of circulating fibrocytes as a central event in the genesis of NSF. Other investigators have suspected that the strongly profibrotic mediator transforming growth factor-β may be involved in the pathogenesis of NSF.

Epidemiology

NSF is a rare disorder. Since the identification of the first patients with NSF in 1997, the NSF registry (www.icnfdr.org) has confirmed more than 380 patients from medical centers worldwide. NSF equally affects men and women. The risk for development of NSF after GBC agent exposure is related to the degree of renal failure and stability of the chelate. The incidence of NSF in patients with severe renal dysfunction (glomerular filtration rate [GFR] <30) varies from 0.2% to 4%. Gadodiamide (marketed as OmniScan in the United States), the linear nonionic chelate–based formulation, appears to be associated with the highest risk for NSF on the basis of epidemiologic data and animal studies. Gadopentetate, the linear ionic chelate–based product, probably has a medium risk, less than linear nonionic chelates but more than macrocyclic chelates. Other factors reported to be associated with NSF (without definitive proof) include coagulation abnormalities and deep venous thrombosis, recent surgery (particularly vascular surgery), hyperphosphatemia, and the use of high doses of recombinant erythropoietin. Angiotensin-converting enzyme inhibitors might protect against NSF. After warnings issued by the U.S. Food and Drug Administration and European Medicines Agency regarding the association of linear GBC agents with NSF in individuals with renal dysfunction, the incidence of NSF declined and in recent years, no new cases of NSF have been reported.

Clinical Manifestations and Natural History

The lesions of NSF are typically symmetric and develop on limbs and trunk. A common location is between the ankles and midthighs and between the wrists and mid-upper arms bilaterally. On occasion, swelling of the hands and feet, sometimes associated with bullae, is noted. The primary lesions are skin-colored to erythematous papules that coalesce into erythematous to brawny plaques with a peau d'orange appearance (Fig. 87.9A). These plaques have been described as having an ameboid advancing edge. Nodules are sometimes also described. Involved skin becomes markedly thickened and woody in texture. Joint contractures may develop rapidly, with patients becoming wheelchair-dependent within days to weeks of onset (see Fig. 87.9B). Patients often report pruritus, causalgia, and sharp pains in the affected areas.[21] Although NSF has not been reported as a cause of death, this disorder has led to reduced mobility and/or superinfection that ultimately resulted in a protracted hospital course and death.

Pathology

The histopathologic changes in affected skin include marked proliferation of spindle cells, the presence of numerous dendritic cells, and accumulation of mucinous material and thick collagen bundles (Fig. 87.10). Most dermal spindle cells in NSF have the immunophenotype of a circulating fibrocyte, a recently characterized circulating cell that expresses markers of both connective tissue cells and circulating leukocytes. Metastatic calcification and NSF may be found in the same lesion.

Diagnosis and Differential Diagnosis

The gold standard of diagnosis is histopathologic examination of skin biopsy specimens from an involved site. Skin lesions also can be visualized by [^{18}F]-fluorodeoxyglucose whole-body positron emission tomography. NSF resembles other fibrosing skin disorders, including

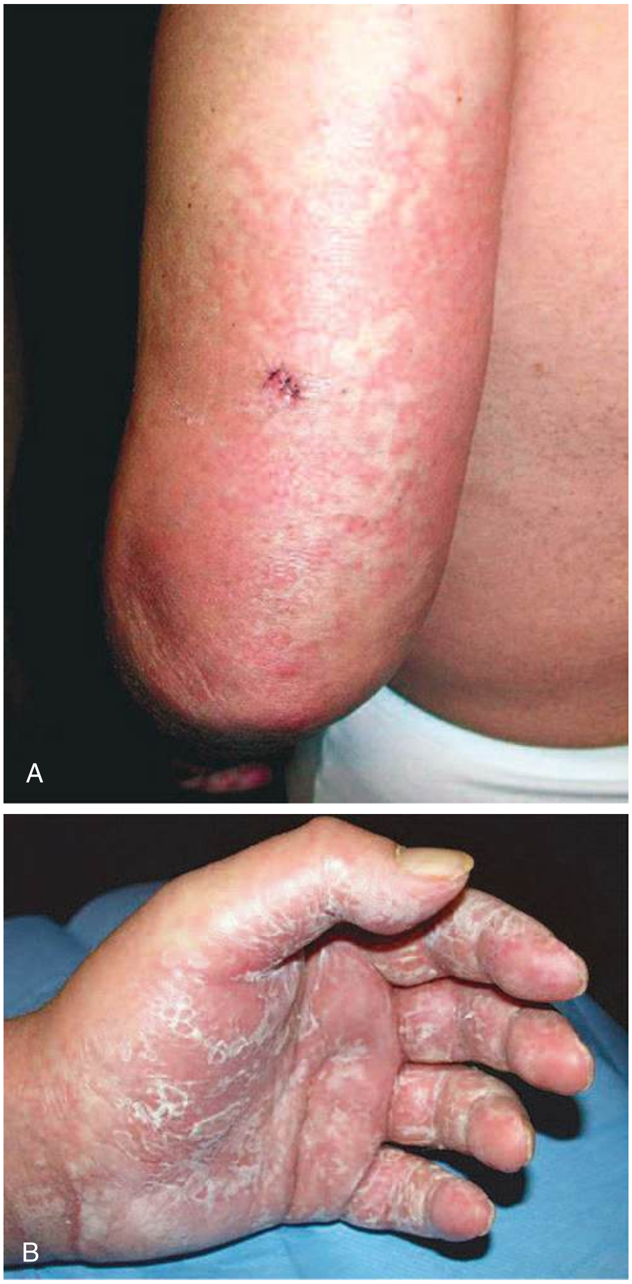

Fig. 87.9 Nephrogenic systemic fibrosis. (A) Peau d'orange appearance. (B) Swelling of the hands, accompanied by palmar erythema, blisters, and contracture of the fingers.

scleromyxedema, scleroderma, eosinophilic fasciitis, eosinophilia-myalgia syndrome, and Spanish toxic oil syndrome. The specific distribution of cutaneous involvement, the occurrence in the setting of renal failure, the history of recent exposure to linear GBC agents, and the unique histopathologic features distinguish NSF from the other fibrotic disorders.

Treatment and Prevention

There is no consistently effective therapy for NSF. There is variable evidence for the efficacy of plasma exchange. Other therapeutic modalities that have been used (or are under investigation) include imatinib, oral and topical corticosteroids, selective histamine blockade, calcipotriene ointment, cyclophosphamide, cyclosporine, thalidomide, interferon-α, photopheresis, and psoralen ultraviolet A therapy. Intensive physiotherapy is advised in every patient to prevent or to reverse limb disability related to contractures of the joints. At present, prevention of NSF seems more important than any of the currently available interventions, and widespread clinical awareness of this condition is required. Avoidance of linear GBC agents in high-risk patients (acute kidney injury and patients with CKD with estimated GFR [eGFR] rate <30 ml/min/1.73 m^2) is the best measure to prevent this catastrophic complication. If GBC agent exposure is required, use of the smallest dosage of a macrolytic chelate is strongly advised (www.esur.org/guidelines/). HD (three sessions within 72 hours) should be considered after GBC agent exposure in patients who are already on this modality.

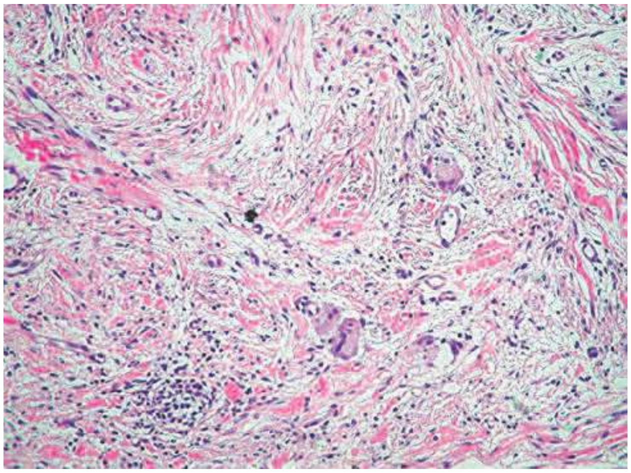

Fig. 87.10 Histopathologic features of nephrogenic systemic fibrosis. Haphazardly arranged dermal collagen bundles with surrounding clefts and a strikingly increased number of similarly arranged spindled and plump fibroblast-like cells.

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SELF-ASSESSMENT QUESTIONS

1. Uremic pruritus in dialysis patients is:
   - **A.** A local skin disorder
   - **B.** A systemic disorder caused by uremia
   - **C.** A neurologic disorder caused by overexpression of opioid skin receptors
   - **D.** An inflammatory systemic disorder caused by dysregulation of the immune system
   - **E.** All of the above
2. Skin emollients in dialysis patients should be used:
   - **A.** Only in patients without underlying primary skin diseases
   - **B.** Only in patients with proven xerosis
   - **C.** Only in patients without skin defects
   - **D.** Only in patients with therapy failure
   - **E.** In all patients
3. Treatment of uremic pruritus with oral nalfurafine:
   - **A.** Is limited to patients with proven overexpression of μ receptors in their skin
   - **B.** Is limited to patients free from sleeping disturbances
   - **C.** Is limited to patients with therapy failure
   - **D.** Is limited to patients with baseline normal blood prolactin concentrations
   - **E.** Is not limited to any subgroup of patients with uremic pruritus
4. Which of the following drugs predisposes to calcific uremic arteriolopathy?
   - **A.** Acetylsalicylic acid
   - **B.** Heparin
   - **C.** β-Blocker
   - **D.** Warfarin and coumarins
   - **E.** Calcium-free phosphate binders
5. Nephrogenic systemic fibrosis:
   - **A.** Is a self-limiting disease with benign prognosis
   - **B.** Is related to exposure to linear gadolinium chelates
   - **C.** Is painless
   - **D.** Is especially prevalent in renal transplant recipients
   - **E.** Is related to exposure to iodine radiocontrast agents

88

Acquired Cystic Kidney Disease and Malignant Neoplasms

Anja S. Mühlfeld, Peter Boor

DEFINITION

Acquired cystic kidney disease (ACKD) was first recognized in 1847 by John Simon in patients with chronic Bright disease. He described the development of cystic renal changes with cysts ranging from "mustard seed to as large as cocoa nuts" and also noted that they "run a slow and insidious progress during life, and often leave in the dead body no such obvious traces as would strike the superficial observer." ACKD was "rediscovered" by Dunnill and colleagues[1] in 1977 in kidneys from dialysis patients.

ACKD is a specific entity of chronic kidney disease (CKD) of any etiology and has to be differentiated from other types of cystic kidney disease (see Chapters 44 and 45). It is usually defined as more than three macroscopic cysts in each kidney of a patient who does not have a hereditary cause of cystic disease. Some authors consider ACKD preneoplastic.[2,3]

PATHOGENESIS

The exact mechanisms of tubule transformation into cysts in ACKD are unknown. Responses to CKD with slow, progressive parenchymal (nephron) loss are believed to be involved. Progressive nephron loss results in initial tubular hypertrophy followed by hyperplasia and is likely aggravated by tubular distortion and distal tubular outflow obstruction, such as by advanced tubular atrophy, interstitial fibrosis, or calcium oxalate crystals, which are all common in ACKD (Fig. 88.1).[4] ACKD can appear before dialysis is started and does not correlate with dialysis modality or underlying renal disease. The cysts seem to develop from various tubular segments. Most cysts are lined by a single layer of flat to cuboidal epithelial cells, but also cuboidal cells with eosinophilic, foamy, and occasionally also clear cytoplasm, with particularly the latter being considered precursor lesions of renal neoplasias.[2,3,5,6] Other factors implicated in the development of tubular hyperplasia include plasticizers, ischemia, or uremic or other humoral metabolites. In some instances the cysts size decreased after renal transplantation.

With the continuing presence of mitogenic stimuli, intracystic epithelium becomes multilayered or forms micropapillary proliferates. Further accumulation of mutations, activated protooncogenes, or chromosomal abnormalities, in conjunction with additional factors such as genetic background, environmental chemicals, and sex hormones, most likely accounts for the transition to renal cell carcinoma (RCC) (see Fig. 88.1).[7]

EPIDEMIOLOGY

Among adult and pediatric patients starting maintenance dialysis treatment, prevalence of ACKD ranges from 5% to 20%. In both chronic hemodialysis (HD) and peritoneal dialysis patients, prevalence then increases at a similar rate and reaches 80% to 100% after 10 years of treatment (Fig. 88.2).[8-11] Several but not all studies have reported an increased frequency or faster progression in men than in women. The rate of progression appears to slow after 10 to 15 years of dialysis.

The frequency of ACKD as well as of renal tumors in dialysis patients may be underestimated on the basis of imaging alone. Renal cysts are detectable by ultrasound, with a minimum size of 0.5 cm. Data obtained in native nephrectomy specimens at the time of transplantation identified ACKD in 33%, renal adenomas in 14%, and RCCs in 4% of the cases.[12] In unselected series of chronic dialysis or transplant patients, the cumulative incidence of RCC complicating ACKD as demonstrated by imaging is below 1%, although rates up to 7% have been reported in some small studies. These data indicate an up to 40- to 100-fold increased risk for RCC in ACKD patients compared with RCC in the general population. Risk factors include male gender (male-to-female ratio, 7 : 1), African American ethnicity, long duration of dialysis, and severe ACKD with marked organ enlargement.

CLINICAL MANIFESTATIONS

ACKD can manifest as unilateral or bilateral cysts, which are mostly cortical and variable in size and number. Rarely, severe ACKD can become macroscopically indistinguishable from adult polycystic kidney disease (PKD). In contrast to hereditary cystic diseases, the cysts of ACKD are strictly confined to the kidneys. The disease is usually asymptomatic and discovered accidentally during abdominal imaging procedures. Alternatively, it may be manifested by the following potential complications or consequences of ACKD[13]:

- Cystic hemorrhage with or without hematuria; bleeding may occur with cyst rupture with subsequent perinephric hemorrhage or retroperitoneal hemorrhage, which can rarely lead to hypovolemic shock.
- Calcifications in or around cysts and in rare cases stone formation (calcium-containing stones or β_2-microglobulin stones).
- Cyst infection, abscess formation, or sepsis.
- Erythrocytosis in advanced cases, similar to the erythrocytosis observed in PKD.
- Malignant transformation.

Acquired Cystic Kidney Disease–Associated Renal Cell Carcinoma

About 85% of RCCs in ACKD are asymptomatic at the time of diagnosis. The remaining cases mostly manifest with bleeding, usually gross hematuria. In cases in which nephrectomy had to be performed in dialysis patients for intractable hematuria, previously undetected RCCs were diagnosed in about one third of the patients. Compared with sporadic

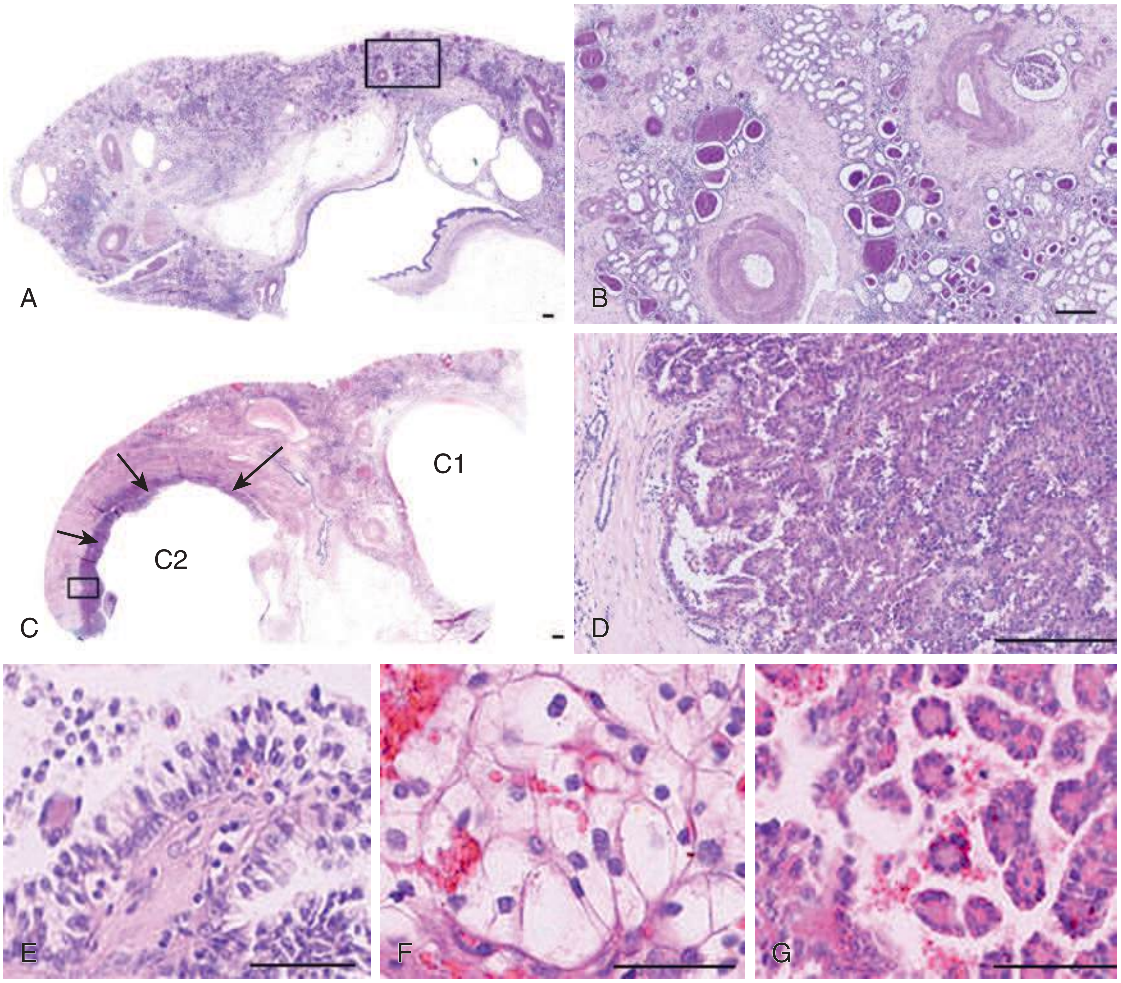

Fig. 88.1 Typical histomorphologic appearance of acquired cystic kidney disease (ACKD) and commonly found renal cell carcinomas (RCC) in ACKD. (A) The kidney shows numerous cysts of different sizes and a prominent atrophy of renal parenchyma. At higher magnification in (B) global glomerulosclerosis, tubular atrophy with typical focal areas of thyroidization (i.e., intratubular periodic acid–Schiff [PAS]-positive casts), interstitial fibrosis, and arteriosclerosis (PAS-stained section) are noted. (C) Another area of the same kidney specimen as shown in A, with two cysts. The right cyst is lined by inconspicuous and at this magnification invisible single-layered epithelium (C1). The left cyst (C2) is lined by a thick cell-dense layer *(arrows),* which at higher magnification (D) is characterized by tubular and papillary proliferates of atypical epithelial cells, characteristic for intracystic ACKD-associated RCC (hematoxylin-eosin–stained section). (E) Another tumor often found in ACKD is composed of well-differentiated clear cells in a papillary arrangement, characteristic for clear cell papillary RCC. (F) A clear cell RCC, a tumor commonly found in ACKD and the most common renal tumor in the general population. It is composed of nests and sheets of atypical cells with clear cytoplasm. (G) Papillary RCC, another tumor commonly found in ACKD and the second most common RCC in the general population. It is composed of eosinophilic epithelial cells in a papillary arrangement. In this case the tumor size was 3 cm; therefore the diagnosis of papillary RCC (type 1) was made; if the size were less than 1.5 cm, the same histologic tumor pattern would be classified as papillary adenoma. In the presented cases and typical for ACKD, most clear cell and papillary RCCs in ACKD are well-differentiated, that is, the nuclei show little or no nucleoli and little nuclear pleomorphy. The scale bars in A through D represent 250 µm and in E through G 50 µm. The insets in A and C represent areas shown in higher magnification in B and D, respectively.

RCCs, ACKD-associated RCCs are characterized by younger age of the patient, male predominance, more frequent multicentric and bilateral manifestation, and less frequent metastases.[2]

PATHOLOGY

Cystic changes in ACKD are typically bilateral but may vary between kidneys. Most ACKD kidneys are smaller than normal, and all show advanced parenchymal atrophy and chronic injury. An increase in size of the ACKD kidneys above normal may result from cyst hemorrhage or malignant transformation. The cysts are usually restricted to the renal cortex. The size of the cysts ranges from microscopic to about 2 cm; about 60% of the cysts are smaller than 0.2 cm.[2] Preneoplastic changes include atypical cyst-lining cells with clear cell morphology, forming multiple cell layers and intracystic papillary or nodular proliferates.

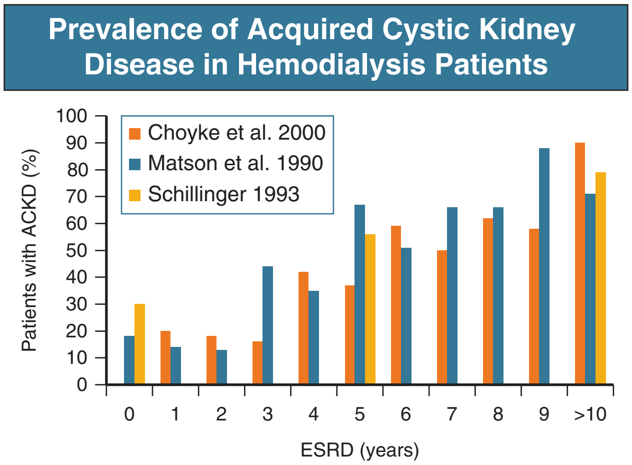

Fig. 88.2 Prevalence of acquired cystic kidney disease (ACKD) in hemodialysis patients. Summary of reported ACKD prevalences in chronic hemodialysis (HD) patients in relation to the length of HD treatment. (Modified from references 9 to 11.)

Up to 25% of kidneys with ACKD harbor tumors when examined histologically. About one quarter to one third of these are carcinomas. Adenomas are only defined for well-differentiated papillary tumors and are arbitrarily considered adenomas when less than 1.5 cm, whereas those greater than 1.5 cm are considered carcinomas, given the higher metastatic probability of larger tumors. All other tumors showing typical histology of RCCs regardless of size (e.g., invasive groups of clear cells) are diagnosed as RCCs.

The most common type of RCC that is specific for ACKD is ACKD-associated RCC, which accounts for about 36% of RCCs found in ACKD. The histologic appearance of ACKD-associated RCCs varies from tubular, papillary, acinar, microcystic, to solid. They are mostly composed of eosinophilic tumor cells with prominent nucleoli and frequent intratumoral calcium oxalate crystals (see Fig. 88.1).[6] The second most common ACKD-specific RCCs (24%) are clear cell papillary RCCs, which show papillary, tubular, or cystic arrangement of relatively well-differentiated clear cells.

Other commonly observed RCCs in ACKD are those commonly observed in the general population, such as papillary (18%), clear cell (10%), and chromophobe RCCs (6%). RCCs arising from ACKD are multicentric in about 50% of cases and bilateral in about 10%. Multiple histologic subtypes may occur in the same kidney. Clear cell RCCs contain cells in solid, tubulocystic or alveolar arrangement, whereas papillary RCCs show eosinophilic, papillary arranged tumor cells (see Fig. 88.1). In difficult cases with overlapping histologic appearance, immunohistochemistry helps differentiate between these entities. The precise diagnosis is important because ACKD-associated RCCs and clear cell papillary RCCs seem to be more indolent than classic RCCs, but in rare cases can metastasize. In addition, all RCCs in ACKD tend to have a better clinical course most likely as a result of early detection given close follow-up of these patients.

RCCs in renal transplant patients tend to be smaller, exhibit a lower T stage and a lower grade at diagnosis compared with RCCs in patients with end-stage renal disease. Tumors are more often multifocal, bilateral, and papillary.[14,15] Likely because of the earlier stage at detection the prognosis of RCCs after renal transplantation generally is more favorable.

No imaging modality is able to distinguish between the different benign and malignant subtypes of renal neoplasms found in ACKD; therefore histopathologic analysis remains the only means for their diagnosis.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnostic approach to ACKD usually involves ultrasound (Fig. 88.3).[4,9] However, the differentiation between simple cysts and RCCs can be difficult given the echogenicity of end-stage kidney parenchyma and the complexity of cysts in ACKD. Computed tomography (CT) scanning, in particular with early contrast enhancement, is superior to ultrasound in detecting small malignant lesions (see Fig. 88.3).[4,9,16] A classification of renal cysts (Fig. 88.4) based on their appearance in CT scans, introduced by Bosniak,[17,18] is now widely accepted and is also applied to ultrasound and magnetic resonance imaging (MRI) (see Table 59.5). Criteria that favor the diagnosis of RCC as opposed to a simple cyst include thickened and irregular walls, the presence of septa or renal tissue within the lesions, contrast enhancement, multilocularity, and large size (≥4 cm). Given the risk for nephrogenic fibrosis after exposure to gadolinium-containing contrast agents (see Chapter 5), MRI without contrast enhancement has was shown in a pilot study in renal transplant recipients to be superior to renal ultrasound alone.[19] Another small study found that contrast enhanced ultrasound for the assessment of complex cysts in renal transplant recipients was better than standard ultrasound in correctly characterizing Bosniak I and II cysts.[20]

Because of the risk for malignant transformation, screening for ACKD and follow-up imaging when ACKD is detected have both been advocated. A proposal for ACKD and tumor screening is outlined in Fig. 88.5. However, the cost of screening has to be weighed against the risk-to-benefit ratio of nephrectomy in dialysis patients. A decision analysis[21] concluded that screening for ACKD (by either ultrasound or CT scanning) in young patients with a life expectancy of 25 years offers as much as a 1.6-year gain in life expectancy. This is similar to the gain obtained in young healthy people who stop smoking. In contrast, in ACKD patients older than 60 years, no significant gain in life expectancy is achieved by regular screening.[22] In a different analysis of 797 dialysis patients who had developed RCCs (90% identified by screening), screening provided a mean survival benefit of 3.3 years after adjustment for age and dialysis vintage.[22] Screening during transplant evaluation by ultrasound followed by CT in the case of suspicious lesions is recommended on the basis of recent data showing a prevalence of renal cancer in up to 4% of the patients and concerns about the role of immunosuppression in accelerating tumor growth.[23]

NATURAL HISTORY

Cystic dilations of renal tubules may develop at a glomerular filtration rate lower than 70 ml/min.[24] ACKD thereafter progresses and reaches a prevalence of nearly 100% after more than 10 years of dialysis (see Fig. 88.2). The constant increase in kidney volume seems to reach a plateau after about 20 years of HD, and at least partial regression may occur after very-long-term HD.[25] In malignant transformation, tumor growth rates are highly variable. Death is usually associated with widespread metastases and accounts for about 2% of the deaths in renal transplant patients.

It is not established whether renal transplantation affects the natural history of RCC complicating ACKD, although immunosuppression has been suggested as a risk factor for RCC in transplant patients with ACKD.[13] A prospective, single-center ultrasound screening of the native kidneys in 561 renal transplant recipients identified ACKD in 23%.[26] The mean duration of dialysis was 4 to 5 years, and the mean time after transplantation was 9 years. In this cohort, ACKD was slightly less frequent than had been reported in dialysis patients, possibly indicating that renal transplantation might inhibit the development of ACKD.[26] The prevalence of RCCs among all 561 patients was 4.8%. However,

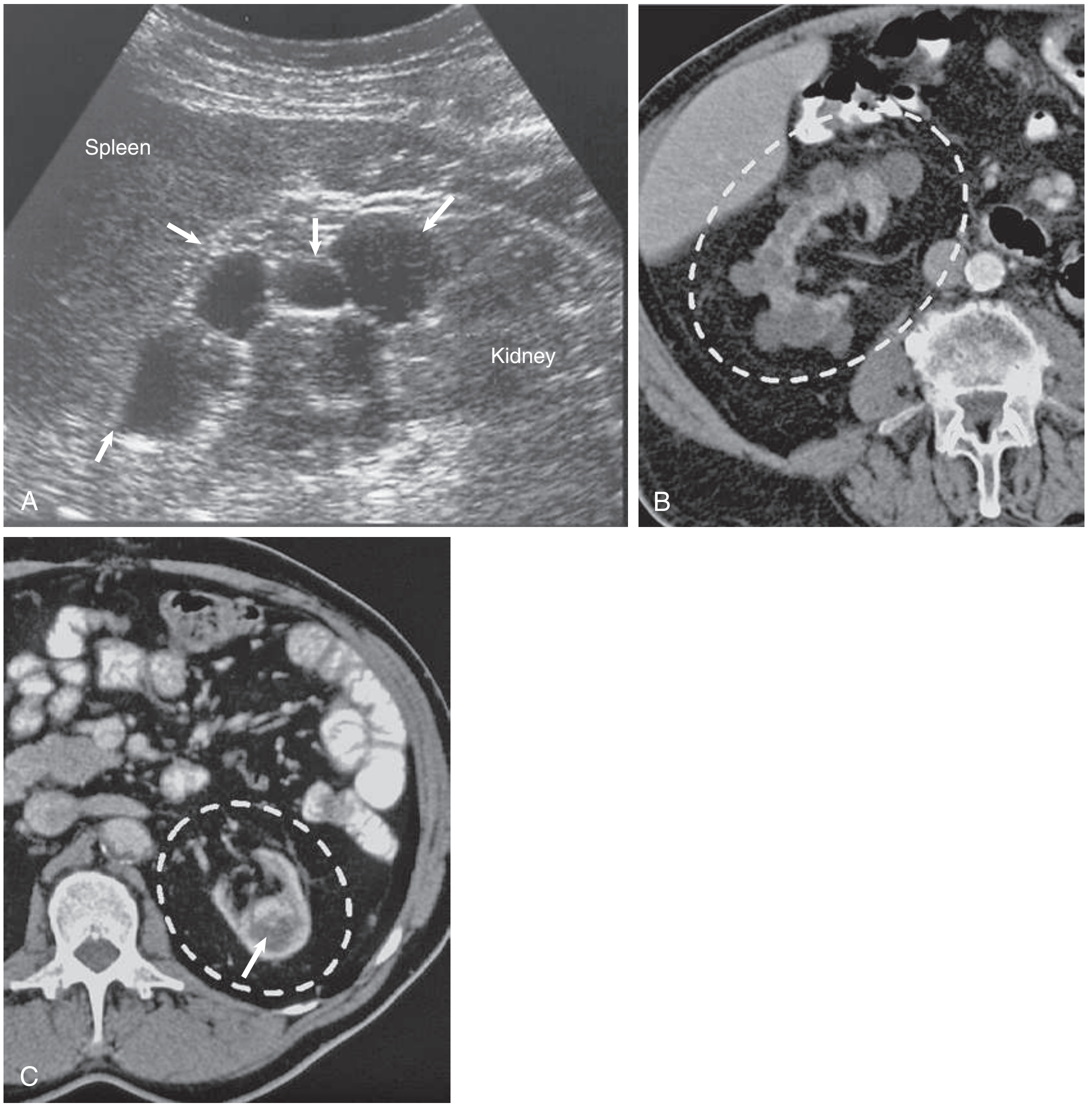

Fig. 88.3 **Imaging studies in acquired cystic kidney disease (ACKD).** (A) Ultrasound image of the left native kidney of a patient after 16 years of chronic hemodialysis (HD). Multiple cysts are present in the renal cortex *(arrows).* (B) CT image of a patient after 5 years of chronic HD demonstrating multiple cysts within the right kidney *(dashed circle).* (C) Contrast-enhanced CT image of a renal transplant patient who developed a renal cell carcinoma *(arrow)* originating from the left native kidney with ACKD *(dashed circle).*

among patients with ACKD, RCCs were detected in almost 20%, but in only 0.5% of patients without ACKD.[26]

TREATMENT

Treatment of ACKD is warranted only when complications such as hemorrhage, cyst infection, or malignant transformation develop. Whereas the first two complications may be handled conservatively and only rarely require surgery, malignant transformation should raise the question of nephrectomy. Given the perioperative morbidity and mortality of nephrectomy, in particular in multimorbid dialysis or transplant patients, it is not surprising that the threshold for surgical intervention in cases of RCC is still controversial.

Most agree that tumors larger than 3 cm in diameter justify nephrectomy because above this size, RCCs in the general population frequently metastasize (see Fig. 88.4).[11] However, this strategy is based on an extrapolation from otherwise healthy persons and a more aggressive approach may be required under certain circumstances. This is particularly true because tumor size in ACKD is often difficult to establish given its frequent multilocular development and because metastases have been described in ACKD even when renal tumors were not detected by imaging studies.

In the case of tumors of less than 3 cm in diameter with no complications, the slow tumor growth may justify observation with repeated imaging studies (see Fig. 88.4). Patients with high life expectancy or listed for transplantation might be considered for nephrectomy also in case of tumors with diameters less than 3 cm. In general, tumor enlargement should be used as an indication for nephrectomy if it is permitted by the patient's status.

A prophylactic contralateral nephrectomy, in the case of unilateral tumors, is not routinely recommended because of the morbidity associated with the procedure, the worsening of anemia, and the loss of residual renal function in those who are not considered transplant candidates. A delay of transplantation is generally not suggested in patients who have had an asymptomatic RCC associated with ACKD in their nephrectomy. In such a setting, a contralateral nephrectomy

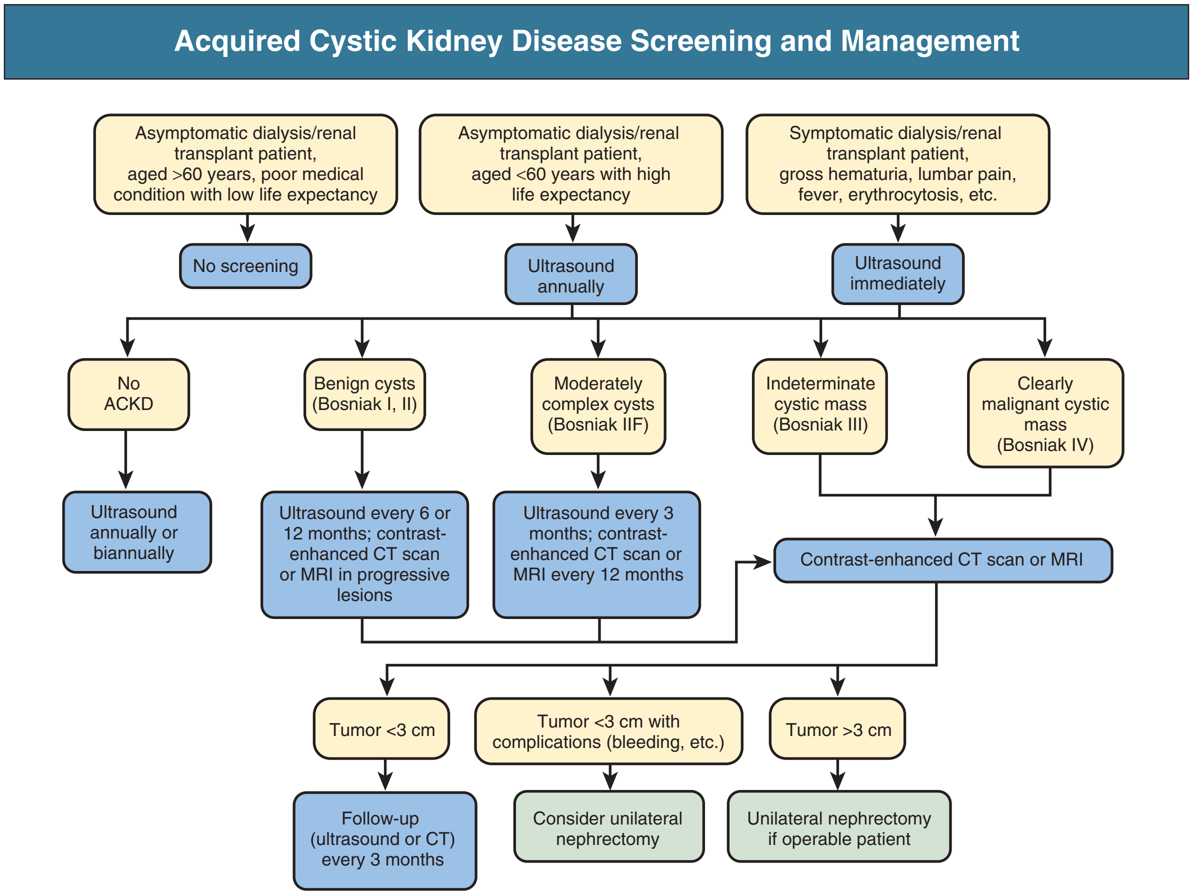
Acquired Cystic Kidney Disease Screening and Management
Asymptomatic dialysis/renal transplant patient, aged >60 years, poor medical condition with low life expectancy
Asymptomatic dialysis/renal transplant patient, aged <60 years with high life expectancy
Symptomatic dialysis/renal transplant patient, gross hematuria, lumbar pain, fever, erythrocytosis, etc.
No screening
Ultrasound annually
Ultrasound immediately
No ACKD
Benign cysts (Bosniak I, II)
Moderately complex cysts (Bosniak IIF)
Indeterminate cystic mass (Bosniak III)
Clearly malignant cystic mass (Bosniak IV)
Ultrasound annually or biannually
Ultrasound every 6 or 12 months; contrast-enhanced CT scan or MRI in progressive lesions
Ultrasound every 3 months; contrast-enhanced CT scan or MRI every 12 months
Contrast-enhanced CT scan or MRI
Tumor <3 cm
Tumor <3 cm with complications (bleeding, etc.)
Tumor >3 cm
Follow-up (ultrasound or CT) every 3 months
Consider unilateral nephrectomy
Unilateral nephrectomy if operable patient

Fig. 88.4 Proposed approach to acquired cystic kidney disease (ACKD) screening and management of suspected renal cell carcinoma. *ACKD,* Acquired cystic kidney disease; *CT,* computed tomography; *MRI,* magnetic resonance imaging. (Modified from references 13, 21, and 26.)

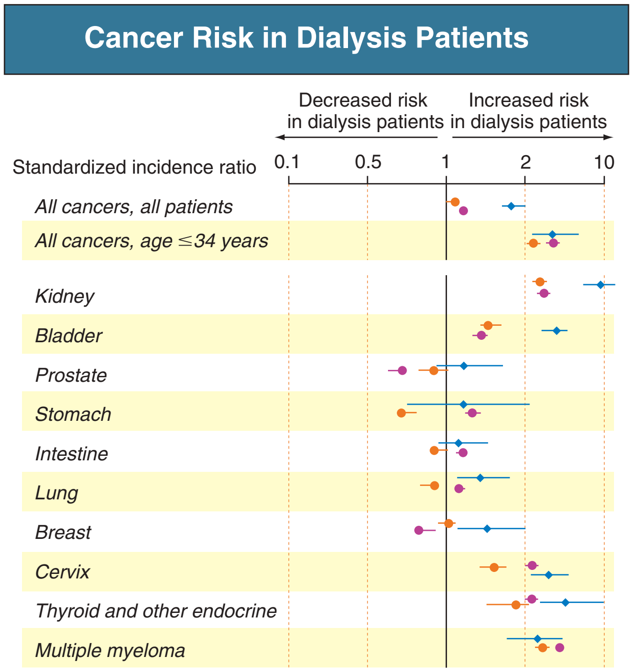

Fig. 88.5 Cancer risk in dialysis patients. Relative risk for cancer (plus 95% confidence interval) compared with the general populations in 831,804 dialysis patients from Australia/New Zealand *(blue diamonds),* Europe *(orange circles),* and the United States *(purple circles).* (Modified from reference 29.)

can be recommended to decrease the potential risk for neoplastic growth and avoid a delay of transplantation.

We recommend performing screening for renal masses in transplant recipients on a yearly basis using ultrasound. In suspicious cases, contrast-enhanced CT scanning or MRI might help differentiating blood-filled cysts from solid tumors. In the case of a suspicious mass or RCC in the native kidneys, nephrectomy should be performed. However, although immunosuppression is possibly associated with the development of RCC, it does not seem to diminish the likelihood of cure, especially because RCCs in transplant patients, possibly as a result of regular screening for malignancy, tend to be detected at an earlier stage.[27] In addition, nephrectomy in renal transplant recipients can be safely performed without a high risk for surgical complications.[28]

CANCER IN DIALYSIS PATIENTS

Even if the risk for malignant transformation of ACKD is disregarded, dialysis patients have a slightly higher cancer risk compared with the general population. Analysis of more than 800,000 dialysis patients in three registries from the United States, Europe, and Australia/New Zealand revealed that most of the increased risk was due to cancers of the kidney, bladder, and endocrine organs (see Fig. 88.5).[29] Besides the specific risk associated with malignant transformation of ACKD, some of the increased risk is directly related to the underlying renal disease or to the immunosuppression that may have been administered to patients with immune-mediated renal disease. Cyclophosphamide therapy, for example, may predispose to bladder and ureteral cancer that manifests after patients have been initiated on dialysis. Renal disease or immunosuppressive therapy may underlie the apparent risk in dialysis patients for development of multiple myeloma (see Fig. 88.5). In addition, patients with analgesic nephropathy or aristolochic acid nephropathy are at high risk for development of transitional cell carcinoma (TCC) of the upper urinary tract.[30] Particularly after renal transplantation, these tumors tend to be less differentiated and in an advanced stage and therefore the patients have a relatively poor outcome. For this reason, patients with analgesic nephropathy or aristolochic acid nephropathy should be evaluated for the presence of TCC before transplantation and annually after transplantation. It has been advocated that testing should include cystoscopy, retrograde ureteral catheterization with washings and brushings, and sonography imaging.[31] Other malignancies that have been observed at increased frequencies in dialysis patients include carcinoma of the cervix, thyroid and other endocrine neoplasias (see Fig. 88.5), and, at least in the U.S. Renal Data System database, a 1.5- to 2-fold increase in the risk for non-Hodgkin's lymphoma, Hodgkin's disease, and leukemias.[29]

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SELF-ASSESSMENT QUESTIONS

1. A 52-year-old White man comes to your clinic with new onset of hematuria. He is on chronic hemodialysis (HD) treatment for end-stage renal disease (ESRD) because of diabetic nephropathy. Ultrasound of his kidneys reveals four cysts on the left side and five cysts on the right. On the right side, two of the cysts are not echo free and have a thickened wall with multiple calcifications. Which of the following statements is correct?
   - **A.** His previous diagnosis of diabetic nephropathy causing ESRD is false. Renal ultrasound clearly depicts the typical picture of autosomal dominant polycystic kidney disease (ADPKD).
   - **B.** Acquired cystic kidney disease (ACKD) is a common finding in patients on maintenance HD treatment and is a possible cause of hematuria.
   - **C.** This patient needs to be carefully evaluated for the presence of renal cell carcinoma (RCC) because renal cysts in patients on renal replacement therapy (RRT) almost always undergo malignant transformation.
   - **D.** Most patients with ACKD have cystic disease outside of the kidneys (liver, pancreas) and need to be screened for cerebral aneurysms.
   - **E.** ACKD is associated with exposure to toxic compounds such as benzidine and 2-naphthylamine.
2. A 45-year-old African American woman on maintenance HD because of lupus nephritis is asking for your advice. She has heard about an increased risk for malignant tumors in HD patients. Which of the following statements is *false*?
   - **A.** The increase in risk for tumor development in patients on RRT is in part related to the underlying renal disease or to the immunosuppression that may have been administered to patients with immune-mediated renal disease.
   - **B.** Most of the increased risk is due to cancers of the kidney, bladder, and endocrine organs.
   - **C.** Cyclophosphamide therapy may predispose to cancer of the bladder.
   - **D.** Patients with analgesic nephropathy or Chinese herbs/aristolochic acid nephropathy are at increased risk for development of transitional cell carcinoma (TCC) of the upper urinary tract.
   - **E.** Data from large registries reveals a nearly 10-fold increase in the risk for colorectal cancer in patients on HD treatment.
3. A renal transplant recipient with ESRD secondary to focal segmental glomerulosclerosis presents for a regular checkup. He reports that his primary care physician had ordered an abdominal ultrasound because of recurrent right upper quadrant pain. As an incidental finding, multiple cysts in his native kidneys were noted. Which of the following statements about his condition is *false*?
   - **A.** ACKD is a common finding in patients with ESRD.
   - **B.** Up to 25% of kidneys with ACKD harbor tumors, about one third of which are carcinomas.
   - **C.** ACKD is mostly asymptomatic; however, clinical manifestations include cyst hemorrhage, cyst infection, and malignant transformation.
   - **D.** Bilateral nephrectomy is the treatment of choice for asymptomatic ACKD in renal transplant recipients because malignant transformation occurs in almost 90% of cases.
   - **E.** Contrast-enhanced CT and MRI are the methods of choice to detect small malignant lesions in patients on RRT.

89

Geriatric Nephrology

Mitchell H. Rosner, Emaad Abdel-Rahman, Antonelli Pani

Aging is associated with a decline in kidney function that which can manifest as early as the fourth decade of life and accelerates between the fifth and sixth decades. These changes affect glomerular and tubular function, systemic hemodynamics, and body homeostasis. This chapter focuses on the management of the population older than 65 to 70 years.

AGING-ASSOCIATED STRUCTURAL CHANGES

Anatomic Changes

The human kidney reaches a maximum size of approximately 400 g (12 cm in length) in the fourth decade of life. A natural decline of approximately 10% in renal mass per decade then follows. This natural decline is associated with cortical thinning and decrease in the number of functional nephrons. An analysis of living kidney donors examined the changes in nephron number and structure over time.[1] Between the youngest and oldest age groups (18 to 29 years vs. 70 to 75 years), the number of nonsclerotic glomeruli decreased by 48%, whereas cortical volume decreased by only 16% and the proportion of globally sclerotic glomeruli on biopsy increased by only 15%. The authors concluded that the incomplete representation of nephron loss with aging by either increased glomerulosclerosis or cortical volume decline is consistent with atrophy and reabsorption of globally sclerotic glomeruli and hypertrophy of remaining nephrons.

Glomerular Changes

Structural glomerular changes with age include basement membrane thickening and development of focal and segmental or global glomerulosclerosis, which increases to 10% to 30% and in some studies even exceeding 70% of glomeruli by the eighth decade (Figs. 89.1 and 89.2).[2] Preserved glomeruli often show an increase in overall tuft cross-sectional area, consistent with glomerular hypertrophy. Neither kidney function nor chronic kidney disease (CKD) risk factors can explain the strong association between age and glomerulosclerosis in healthy adults.

Tubular and Interstitial Changes

Tubulointerstitial injury associated with aging is most pronounced in the outer medulla, with tubular dilation and atrophy, mononuclear cell infiltration, and interstitial fibrosis. Some tubules (especially in the distal tubule and collecting duct) may develop small diverticuli; it has been suggested that these diverticuli may play a role in the development of upper urinary tract infections (pyelonephritis) by harboring bacteria.[3]

Vascular Changes

Arterioles often develop hyalinosis with aging. Thickening of the arterioles with an increase in the ratio of medial thickness to lumen diameter is common with aging but is observed almost exclusively in hypertensive individuals.[3] The arcuate arteries become more angulated and irregular with aging, and there is increased tortuosity and spiraling of the interlobar vessels. These changes occur independently of hypertension but are augmented in its presence. With aging, some afferent arterioles, particularly of juxtamedullary glomeruli, develop vascular shunts to the efferent arterioles, thereby bypassing glomeruli, leading to "aglomerular arterioles."[4]

AGING-ASSOCIATED CHANGES IN RENAL FUNCTION

Glomerular Filtration Rate

Inulin clearance studies document a progressive fall in glomerular filtration rate (GFR) after the age of 40 years, with a relatively greater decline in men (Fig. 89.3).[5] However, the fall in GFR is not inevitable; in as many as one third of patients who remain normotensive, there is no decrease in creatinine clearance with age.[3]

In addition to the decrease in GFR with aging, there may be a reduction in renal "reserve." Whereas some studies suggest that aging humans show a normal increase in GFR after amino acid infusion, others have shown a marked reduction in increases in renal plasma flow (RPF) and GFR in response to concurrent infusion of amino acids and dopamine in healthy older individuals.[6,7]

Renal Plasma Flow

RPF also decreases from a mean of 650 ml/min in the fourth decade to 290 ml/min by the ninth decade, with increasing renal vascular resistance (Fig. 89.4).[3] Because RPF decreases relatively more than GFR, filtration fraction (defined as GFR/RPF) increases with age. Studies have demonstrated that there is a true reduction in renal blood flow when it is factored for renal mass.[8] The decrease in renal blood flow especially involves the cortex, and blood flow to the medulla is relatively preserved.

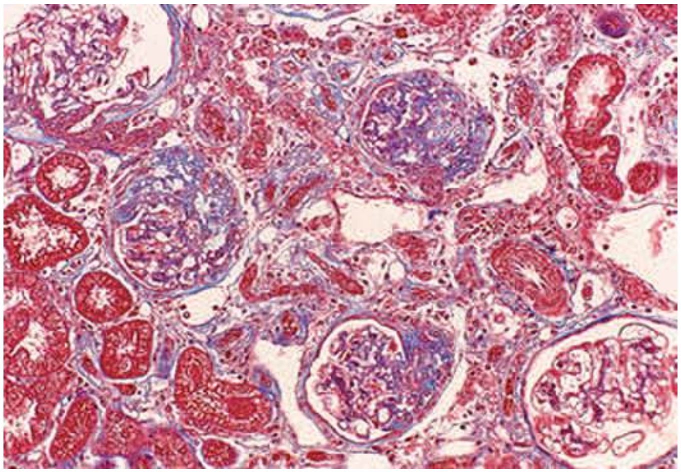

Fig. 89.1 Glomerulosclerosis and tubulointerstitial fibrosis in an aging rat. Similar changes, consisting of focal segmental glomerulosclerosis, tubular atrophy, and interstitial fibrosis, occur in humans. (Trichrome stain; original magnification ×400.)

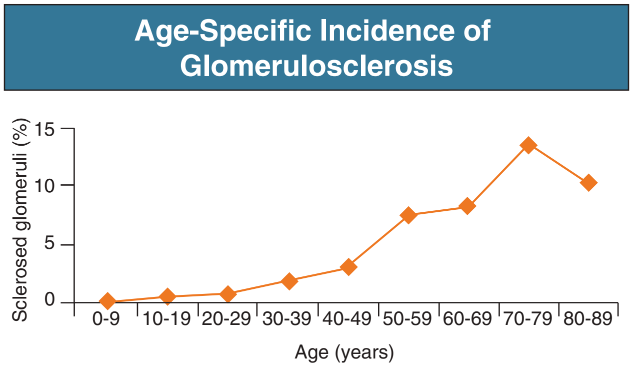
Age-Specific Incidence of Glomerulosclerosis

Fig. 89.2 Glomerulosclerosis increases with aging. (Modified from reference 2.)

ASSESSMENT OF RENAL FUNCTION IN THE ELDERLY

Serum creatinine is a less reliable indicator of renal function in the aging population. After the age of 60 years, there is a progressive decrease in urinary creatinine excretion, which largely reflects muscle mass decreases with aging (Fig. 89.5).[9]

There is no consensus on the optimal approach to estimation of GFR in elderly people. Whereas the Modification of Diet in Renal Disease (MDRD) study equation and the Cockcroft-Gault formula for estimating GFR use age in their calculations (see Chapter 3), neither has been validated in people older than 70 years and both underestimate true GFR in those older than 65 years compared with gold-standard techniques. Although the MDRD equation may be more accurate than the Cockcroft-Gault formula,[10] serum cystatin C, which is independent of muscle mass, may be superior to both.[11] A new GFR-estimating equation was derived from patients who were older than 70 years using iohexol clearance as the gold standard. This Berlin Initiative Study equation worked particularly well in classifying patients with CKD stage 2 to 4 kidney function.[12] Most recently, a full age spectrum estimated GFR (eGFR) equation was developed that has improved validity across the full age-spectrum, allowing less bias at the extremes of age and perhaps allowing for improved clinical decision making.[13]

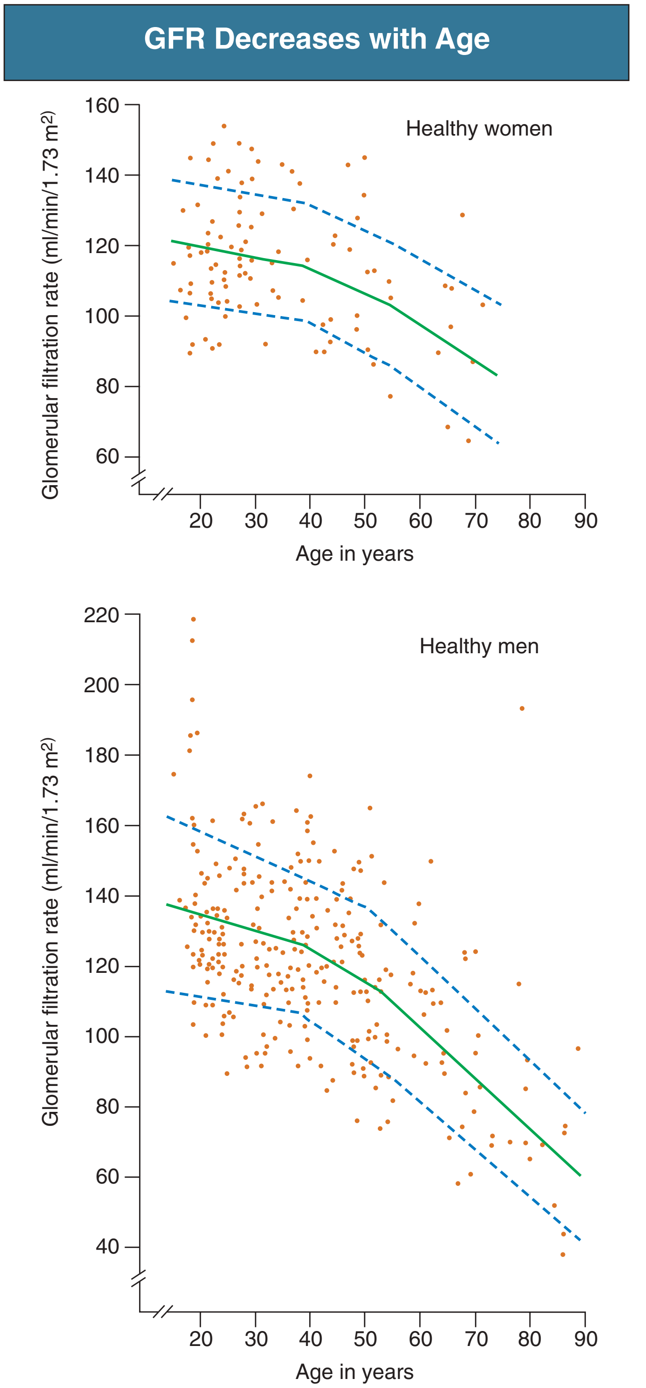
GFR Decreases with Age

Fig. 89.3 Glomerular filtration rate (GFR) decreases with age. GFR (inulin clearance) begins to fall at age 40 years, and the rate of decline is more rapid in men than in women. (Modified from reference 5.)

Albuminuria

The prevalence of albuminuria increases progressively after the age of 40 years. The increased prevalence is most marked in diabetic and hypertensive patients but is also observed in patients lacking these risk factors; whether age per se is associated with proteinuria is debatable.[14]

Hematuria

Malignant neoplasms of the urinary tract are more common in older patients, and so the diagnostic workup for hematuria in patients aged

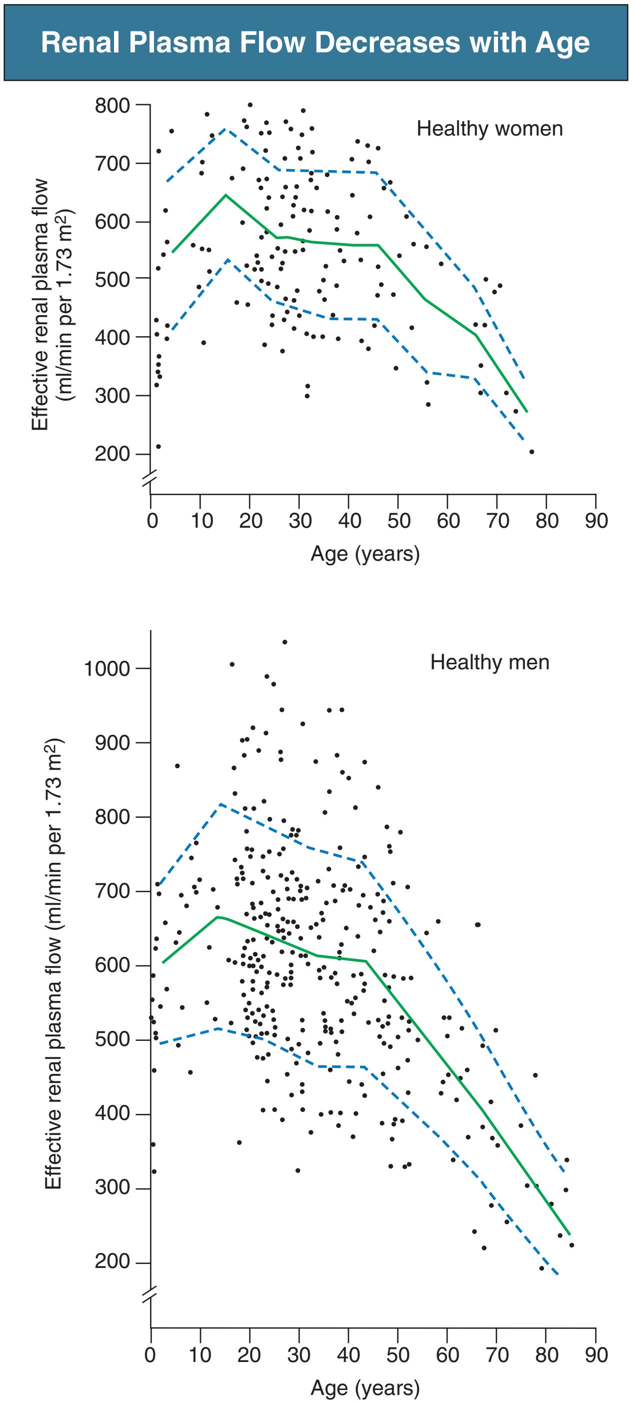

Fig. 89.4 **Renal plasma flow (RPF) decreases with age.** RPF (*p*-aminohippurate clearance) begins to fall rapidly after the age of 50 years, and the rate of decline is more rapid in men than in women. (Modified from reference 5.)

50 years should include cystoscopy and urinary tract imaging. Renal cell carcinomas (RCCs) are most commonly diagnosed in the seventh decade. RCC is more aggressive in the elderly, and treatment decisions can be difficult, especially in the setting of significant CKD in which nephrectomy may lead to dialysis dependence.[15] However, increased use of biopsy to determine whether a mass lesion is cancer and localized resection of the mass alone or surveillance over time have become more common and the preferred approach to RCC in patients with CKD.

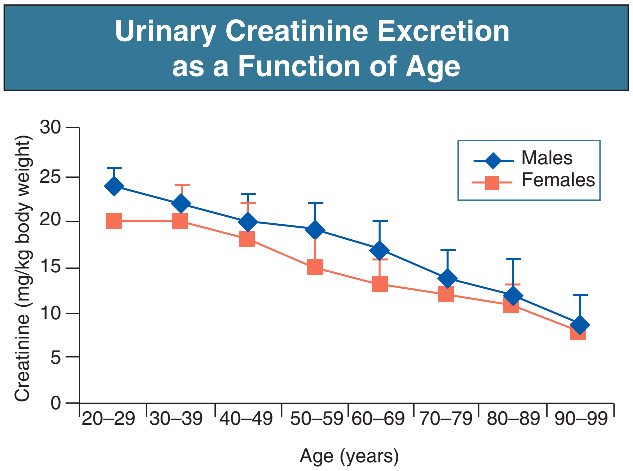

Fig. 89.5 **Urinary creatinine excretion (factored for body weight) decreases with age.** (Modified from reference 9.)

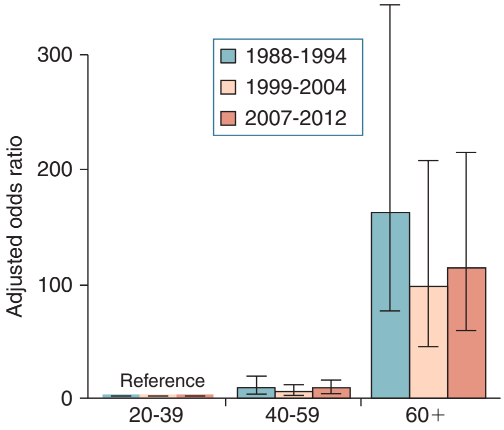

Fig. 89.6 **Adjusted odds ratios of estimated glomerular filtration rate less than 60 ml/min/1.73 m^2 in NHANES participants, by age, 1998-2012.** (Data from reference 47.)

Other causes of hematuria may need to be considered, as discussed in Chapter 4.

PREVALENCE OF CHRONIC KIDNEY DISEASE IN THE ELDERLY

According to the U.S, Renal Data System's Annual Data Report and the National Health and Nutrition Examination Survey (NHANES) study, the incidence of CKD is increasing most rapidly in people aged 65 years and older (Fig. 89.6).[16] Importantly, an eGFR of 50 to 59 ml/min/1.73 m^2 does not increase mortality among patients age 65 years or older compared with patients with eGFR of more than 60 ml/min/1.73 m^2 and the significance of this mild reduction in eGFR is uncertain among older people.[17] These observations have led to debate about the clinical significance of mild decreases in eGFR among older people and whether the term *chronic kidney disease* in such cases should be replaced with *age-related reduced kidney function.*[18]

RISK FACTORS FOR CHRONIC KIDNEY DISEASE IN THE ELDERLY

The variability in the severity of aging-related renal disease in humans has suggested that there may be specific risk factors for its development and for declines in GFR greater than would be expected from aging alone. According to a community-based survey, age, annual income, use of oral analgesics, metabolic syndrome, hyperuricemia, and hemoglobin were risk factors for CKD in both elderly and nonelderly patients.[19] In elderly patients, medical history of diabetes mellitus (DM), CKD, stroke, and analgesic use positively correlated with CKD.[24] In another prospective study, increased levels of physical activity correlated with a lower risk for rapid GFR decline (defined as loss greater than 3 ml/min/1.73 m^2 per year, as estimated by longitudinal measurements of cystatin C levels) in a general population of older adults.[20]

PATHOGENESIS OF AGE-RELATED CHRONIC KIDNEY DISEASE

A variety of mechanisms have been proposed for aging-related renal changes (Box 89.1). The kidney is the only known source of the antiaging hormone Klotho. Mice with Klotho deficiency recapitulate features of systemic and renal aging. Klotho is synthesized by the distal nephron and is secreted as a circulating hormone.[21] The mechanisms whereby Klotho (and its deficiency) regulates the aging process are being elucidated in animal models, but this protein may be a future target for antiaging strategies.

BOX 89.1 Proposed Mechanisms for Aging-Associated Kidney Disease

Hemodynamic
- Glomerular hypertension and hyperfiltration
- Intrarenal activation of renin-angiotensin system
- Endothelial dysfunction (loss of nitric oxide)
- Renal ischemia
- Decreased renalase

Metabolic
- Accumulation of advanced glycation end-products
- Chronic effects of uric acid
- Chronic metabolism of endogenous and exogenous fructose

Cellular dysfunction
- Oxidative stress
- Decreased Klotho
- Senescence (with telomere shortening and loss of mitochondria)

Renal transformation growth factor β (TGF-β) expression

Additional mechanisms of renal aging may involve telomere shortening of chromosomal DNA, loss of mitochondria, and accelerated apoptosis. Aging-associated renal disease also may be mediated by activation of the renin-angiotensin system, which may lower renal Klotho expression. Other mechanisms may include hyperfiltration injury and glomerular hypertension as well as vascular changes associated with arteriolar stiffening and higher pulse wave velocity, progressive reduction in nitric oxide production by endothelial cells, progressive capillary loss with ischemia, and accumulation of advanced glycation end-products.[22-26] A more recent finding is that endogenous metabolism of fructose can lead to aging-associated kidney disease because mice deficient in fructokinase did not develop kidney damage with age.[27]

FLUID AND ELECTROLYTES IN AGING

Sodium Balance and Hypertension

Aging is associated with impaired excretion of a salt load and defective conservation in the setting of sodium restriction.[28] Proximal sodium reabsorption is increased in aging, whereas distal sodium reabsorption may be reduced.[29] Because the diet of most individuals in developed countries contains excess sodium (8 to 10 g of salt daily), there is a tendency in the elderly population for total body sodium excess. This relative defect in sodium excretion and increased total body sodium may be predisposing factors for the development of hypertension, the prevalence of which increases with age. After the age of 60 years, most people are hypertensive (Fig. 89.7).[30] Salt sensitivity occurs in more than 85% of aging people, and sodium restriction will result in a significant fall (>10 mm Hg) in mean arterial pressure.[31] Populations that ingest low-sodium diets, such as the Yanomamö Indians of southern Venezuela, do not show an increase in blood pressure with age.[32] Loss of vascular compliance also may contribute to aging-associated hypertension, as may endothelial dysfunction, perhaps mediated by oxidative stress. Aging-associated renal and vascular changes may explain why correction of secondary forms of hypertension (e.g., primary aldosteronism, Cushing syndrome, and renovascular hypertension) is less effective at curing hypertension in older patients. In one study, diastolic blood pressure fell to below 90 mm Hg in 24 of 25 patients younger than 40 years after treatment of the mechanism responsible for the secondary hypertension

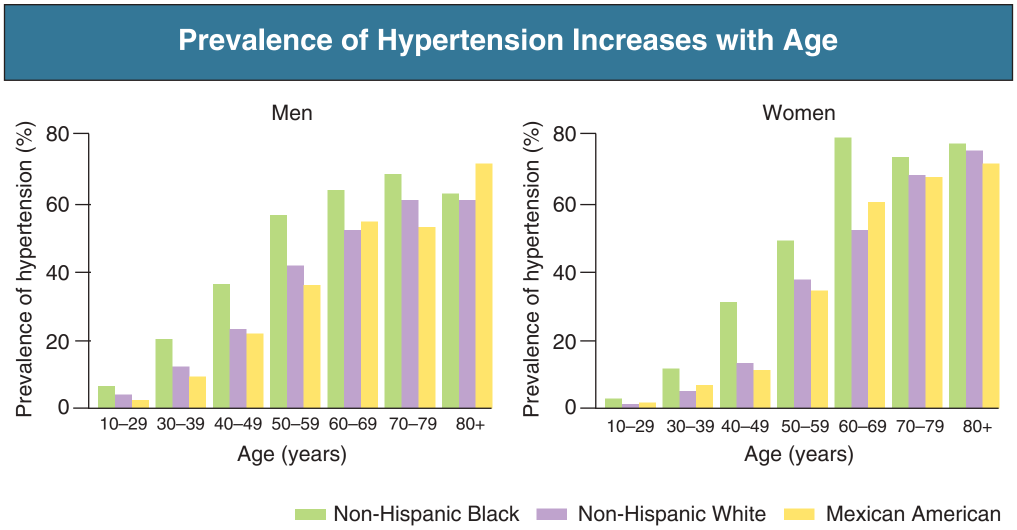

Fig. 89.7 Prevalence of hypertension based on age, gender, and race. (Modified from reference 30.)

but in only 38 of 61 patients older than 40 years.[33] Recent data suggest that treatment of hypertension in the elderly (older than 75 years) should be similar to that in the younger population because treating to a systolic blood pressure (SBP) target of less than 120 mm Hg (compared with an SBP target of less than 140 mm Hg) resulted in significantly lower rates of fatal and nonfatal major cardiovascular events.[34] Reaching these lower BP goals in the elderly may be more difficult, require more medications, and have risk for orthostatic and diastolic hypotension.

Osmoregulation and Water Handling

The most common electrolyte abnormalities in the elderly are the consequence of impaired water handling with aging. Hyponatremia has been found in up to 11% of the ambulatory geriatric population and 5.3% of hospitalized elderly patients.[35] Hypernatremia is found in about 1% of patients older than 60 years admitted to the hospital.[35] Both concentration and dilution of the urine are affected by aging and account for part of the susceptibility to dysnatremias.

In the elderly, the maximal urinary osmolality and thirst response to hyperosmolality are reduced, which may predispose to dehydration and hypernatremia. The impairment in urine concentrating ability results from a defect in the concentrating gradient in the medullary region and can lead to nocturia.[36] Compounding the risk for hypernatremia is that the ill elderly patient may not have ready access to water.

The elderly also have an impaired ability to dilute the urine and thus have a decreased ability to excrete a water load, leading to an increased predisposition to hyponatremia that is often compounded by the use of medications such as thiazide diuretics and selective serotonin reuptake inhibitors.[37] Whether age per se is an independent risk factor for the development of hyponatremia has been questioned, because after adjustment for frailty, the relationship between age and sodium disorders is no longer significant.

Other Tubular Defects and Electrolyte Problems

Potassium excretion is impaired in the elderly, and the transtubular potassium gradient is decreased.[38] Hyperkalemia occurs more frequently in elderly patients treated with drugs that interfere with potassium excretion (such as potassium-sparing diuretics). Other factors contributing to hyperkalemia in the elderly include decreased GFR, lower basal levels of aldosterone, and tubulointerstitial scarring. Hypokalemia is also common because of renal or extrarenal losses.

Most elderly individuals can maintain acid-base balance under normal conditions. However, during conditions of stress when acid production is increased (sepsis or acute kidney injury [AKI]), an inability to excrete an additional acid load may be uncovered. This is supported by a study demonstrating that elderly patients could not increase net acid excretion to the same level as younger adults in response to a protein meal.[39]

Hypercalcemia occurs in 1% to 3% of elderly patients. Causes include malignant tumors, hyperparathyroidism, immobilization, and use of thiazide diuretics. Hypocalcemia is less common and is observed mainly in patients with advanced CKD (in association with vitamin D deficiency and hyperphosphatemia), chronic malabsorption, and severe malnutrition. Hypomagnesemia is reported in 7% to 10% of elderly patients admitted to the hospital; most commonly, this is the result of malnutrition or laxative or diuretic use. Hypermagnesemia is less common and is found primarily in patients with CKD or who are taking large doses of magnesium-containing antacids. Gout (as well as an elevation in serum uric acid levels) is also more common in older people.

ENDOCRINE FUNCTION AND RENAL HORMONES

Elderly women with eGFR below 60 ml/min have lower calcium absorption and lower 1,25-hydroxyvitamin D levels, probably because of diminished conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the aging kidney.[40]

The kidney removes about 50% of insulin in the peripheral circulation by filtration and proximal tubular uptake and degradation. The decline of renal function in the elderly leads to a decrease in insulin clearance. This is in part offset by diminished glucose tolerance, which may relate to the increasing frequency of obesity observed in aging individuals. However, the risk for hypoglycemia related to insulin use is increased in the elderly.

CLINICAL MANIFESTATIONS

General Considerations

Aging is associated with declines in renal function that ultimately limit the ability to defend against destabilizing events. Moderate fluid loss (e.g., an episode of diarrhea) and moderate fluid loading (e.g., inappropriate perioperative intravenous fluids) may be poorly tolerated and lead to hypovolemia and fluid overload, respectively. Hypovolemia in those taking multiple medications, including ACE inhibitors, may lead to AKI. Overzealous administration of water as 5% dextrose or 0.45% saline may result in hyponatremia especially in patients taking selective serotonin reuptake inhibitors, which may increase levels of antidiuretic hormone. The use of nonsteroidal antiinflammatory drugs (NSAIDs) in the elderly is associated with increased risk for hyponatremia, hyperkalemia, hypertension, and impaired renal function.

Glomerular Diseases

Elderly patients may have treatable kidney diseases identifiable on renal biopsy.[41] In a study of 235 biopsy specimens in patients older than 80 years, 67% of the patients had treatable lesions.[42] The pathologic spectrum of glomerular disease seen in elderly people is similar to that seen in the general population, although the prevalence of various pathologies differs. For example, diabetic kidney disease is seen with increasing frequency in the aging population. Among patients with nephrotic syndrome who are older than 60 years, membranous nephropathy is the most common diagnosis (32.1% of patients), followed by amyloidosis (typically light chain derived) and minimal change disease (Fig. 89.8).[42] Other important causes of AKI as a result of glomerular disease in the elderly include rapidly progressive glomerulonephritis (GN) resulting from pauci-immune (antineutrophil cytoplasmic antibody-associated) GN (accounting for about 30% of elderly patients with AKI who undergo kidney biopsy).[41] A recently described entity, immunoglobulin G4 (IgG4)-related renal disease is seen with a higher frequency in men older than 65 years.[43] In contrast, certain glomerular disorders, such as lupus nephritis and IgA nephropathy, are uncommon in elderly people. Only 2% of patients with lupus nephritis present after the age of 60 years.[41,42]

Renovascular and Atheroembolic Disease

There is an increased frequency of renovascular and atheroembolic disease with aging. In several case series, AKI resulting from atheroembolic disease accounted for 4% to 7% of cases.[44] Atherosclerotic renal artery stenosis is estimated to be present in about 7% of patients older than 65 years and is a major cause of secondary hypertension, ischemic nephropathy, and CKD in the elderly.[44] In elderly people with hypertension, elevated serum creatinine, and a history of vascular disease, testing for renovascular disease with magnetic resonance angiography or renal artery duplex scanning may be considered (see Chapter 41). Percutaneous transluminal renal angioplasty and renal artery stenting are of variable value in the elderly because many patients have significant arteriosclerosis, which may limit the benefits of intervention.[44] Thus an individualized approach to therapy is warranted.

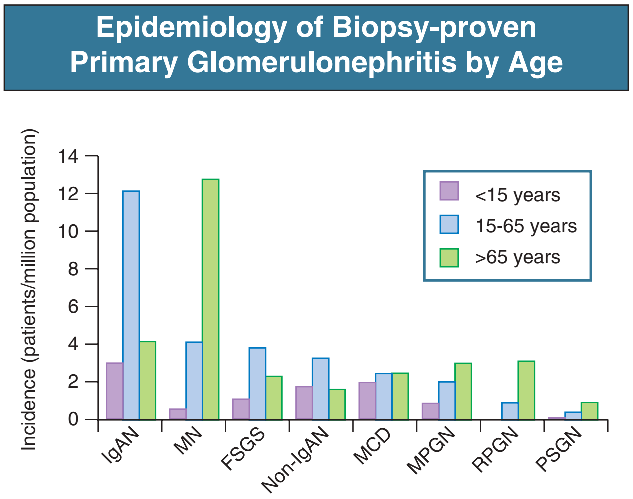

Fig. 89.8 Epidemiology of biopsy-proven primary glomerulonephritis by age. Children presenting with nephrotic syndrome are often treated empirically for minimal change disease (MCD); thus diagnosed MCD is likely underrepresented in data derived from biopsy registries. *FSGS,* Focal segmental glomerulosclerosis; *IgAN,* IgA nephropathy; *MGN,* membranous nephropathy; *MPGN,* membranoproliferative glomerulonephritis; *non-IgAN,* other mesangial proliferative glomerulonephritis; *PSGN,* poststreptococcal glomerulonephritis; *RPGN,* rapidly progressive glomerulonephritis. (Modified from Vendemia F, Gesualdo L, Schena FP, D'Amico G. Epidemiology of primary glomerulonephritis in the elderly. Report of the Italian Registry of Renal Biopsy. *J Nephrol.* 2001;14:340-352.)

Diabetic Nephropathy

DM is a common disease in the elderly; more than half of all diabetic individuals in the United States are over 60 years of age. The prevalence of DM peaks in persons 65 to 74 years of age.[45] Relatively healthy older adults with no major comorbidities may benefit from more intense glucose control (target HbA_{1c} <7%), whereas more lenient targets may be more appropriate for elderly with major comorbidities, established diabetic end-organ damage, or limited life expectancy. The doses of oral hypoglycemic agents and insulin may need to be decreased as the renal function declines, and more so in the elderly, to avoid hypoglycemia and other side effects.[46]

Acute Kidney Injury

Polypharmacy associated with aging greatly increases susceptibility to the development of AKI as a result of drug toxicity.[47] Whereas the causes of AKI in the elderly patient encompass the same spectrum of prerenal, renal, and postrenal causes that are seen in other age groups, the elderly patient has a higher relative risk for developing AKI from obstructive uropathy or sepsis and associated with cancer. Decision making regarding whether to provide active intervention such as with continuous renal replacement therapy (RRT) in elderly patients with AKI and multisystem organ failure will be influenced by comorbidity and the expected likelihood of a good clinical outcome.

Nephrotoxicity and Drug Dosage

Elderly patients are prone to increased nephrotoxicity because they are often administered medicines on the assumption that normal or nearly normal serum creatinine concentration is consistent with normal renal function. Thus the dosage may be inappropriate; it is critical not to rely solely on serum creatinine values for determination of dosages, and eGFR should be used in this regard. Elderly patients with CKD usually are prescribed multiple medications, and this creates a great risk for drug-drug interactions that can be exacerbated when renal clearance is impaired.

End-Stage Renal Disease and Renal Replacement Therapy

The mean age for a patient to initiate RRT is currently over 60 years in the United States and Europe. The mean age of ESRD patients requiring dialysis in most low- and middle-income countries is much lower (32 to 42 years) than that in wealthy countries. In the United States there has been a decline in the incidence of ESRD in patients older than 65 years, with a continued high incidence in those older than 75 years.[48] Despite the frequency of CKD among elderly patients, ESRD is far less common than cardiovascular morbidity or mortality. For example, older patients with CKD stage 3 are more likely to die and less likely to reach ESRD than are their younger counterparts.[49]

The decision to offer RRT should not be based solely on the age of the individual. It is important to recognize that such a decision involving an elderly patient is more complex and fraught with more challenges than in younger patients and requires a multidisciplinary approach that involves family members. Nonmedical barriers may be particularly important in the elderly—for example, limited transportation, family support, and cost. Nursing home patients who began dialysis experienced sharp and sustained declines in their ability to perform basic daily activities.[50] A year after beginning dialysis, 58% of the patients had died and only 13% still functioned at the same level as they had before beginning dialysis. Thus, although dialysis may extend life, it does not necessarily lead to improvements in functional status in older patients. In fact, the increased longevity associated with institution of dialysis may be entirely accounted for by increased days in the hospital without improvements in quality of life.[51]

As with other populations, the survival of arteriovenous fistulas (AVFs) in elderly patients is significantly greater than that of arteriovenous grafts.[52] In fact, successful use of an AVF in the elderly has results similar to those in younger people, with prolonged patencies and low incidence of infections and thromboses, and thus age alone should not preclude AVF creation. Similarly, use of tunneled hemodialysis (HD) catheters is also associated with increased mortality in older HD patients.[52] However, the high prevalence of comorbidities, particularly DM, peripheral vascular disease, and congestive heart failure, usually make vascular access creation more difficult in the elderly. Furthermore, many of these patients may have an insufficient vasculature for fistula maturation. Finally, many fistulas may never be used because of the competing risk for death before dialysis initiation. In these cases, an arteriovenous graft or a central venous catheter becomes a valid alternative form of vascular access. Limitations of HD in the elderly may include their sensitivity to fluid shifts and the presence of significant cardiac dysfunction; hence peritoneal dialysis (PD) may theoretically offer some advantage by offering a slow, sustained degree of ultrafiltration that leads to greater hemodynamic stability. Unfortunately, inherent functional limitations and lack of social support may provide impediments to broader use of PD in the elderly.[53] Studies have demonstrated similar outcomes in elderly patients undergoing HD versus PD.[53] Comprehensive care programs have been designed to support elderly patients to perform PD in their community or at nursing facilities and may offer options to increase the choices patients have regarding treatment options.[54]

Transplantation should be considered in the management of elderly patients with ESRD because selected elderly recipients benefit from renal transplantation by a significant reduction in mortality compared with wait-listed ESRD patients.[55] This survival benefit is most striking for patients with ESRD caused by diabetes or hypertension, but it declines with longer projected waiting times for transplantation. Even when expanded-criteria donor kidneys are used, a 25% mortality reduction has been shown in those who undergo transplantation compared with those who are wait-listed.[55] Overall graft survival for the elderly transplant patient is similar to that in younger patients.[55] It has been argued that lower doses of immunosuppression are sufficient in elderly renal transplant recipients. However, the Eurotransplant Senior Program, allocating kidneys from donors 65 years or older to recipients 65 years or older regardless of human leukocyte antigen (HLA) matching, found 5% to 10% increased rejection rates in this "old to old" group compared with two better HLA-matched groups, the "old to any" and the "any to old," within the Eurotransplant Kidney Allocation System.[56] In a subanalysis of the Efficacy Limiting Toxicity Elimination (ELiTE)-Symphony study, a large prospective, randomized trial comparing immunosuppressive regimens in renal transplant patients, equal rates of rejection in elderly (60 years or older) versus younger (younger than 60 years) recipients were demonstrated.[57] Furthermore, this subanalysis suggested that older recipients who receive a marginal kidney from an older or expanded-criteria donor may fare worse than younger recipients, with an increased likelihood of death, delayed graft function, graft loss, treatment failure, and reduced graft function.

For those who decide not to pursue RRT, symptomatic therapy (supportive management and palliative care) is an option. This concept underscores the importance of individualizing patient goals with a focus on quality of life. For those with severe functional or cognitive impairment or for whom complications of dialysis have negatively affected their quality of life, dialysis discontinuation is an important consideration. Hospice services remain underused for ESRD patients but may provide an important support mechanism for patients and their families who wish to discontinue dialysis.

Depression in Elderly Patients With Kidney Diseases

Depression is common in older adults with CKD, particularly those with ESRD, and almost 24% of older adults reported depressed mood at the start of dialysis. Progressive decline in cognitive function and sleep disorders were also noted in these adults.[58] Undertreatment of depression in the elderly and in patients with CKD is likely related to the difficulty in diagnosing depression in these patients, given the presence of confounding somatic symptoms that mimic those found in depression. Management of depression in the elderly patient with CKD is similar to that in other patient populations in that both pharmacologic and nonpharmacologic interventions are used.

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SELF-ASSESSMENT QUESTIONS

1. An 82-year-old man has a sudden onset of severe lower extremity edema and weight gain (6 kg in 10 days). He has been taking allopurinol for gout prophylaxis, celecoxib for pain associated with osteoarthritis, losartan for hypertension, and metformin for type 2 diabetes. He has smoked half a pack of cigarettes daily for the past 60 years. His blood pressure (BP) is 160/90 mm Hg. Other than the pitting lower extremity edema, the physical examination findings, including findings from a retinal examination, are within normal limits. A chest x-ray examination shows mild emphysematous changes and small bilateral pleural effusions. A urinalysis reveals 4+ protein and 1+ blood. Serum creatinine is 3.6 mg/dl, and serum albumin is 2.1 g/dl. The erythrocyte sedimentation rate is 90 mm/h (Westergren). Blood glucose is 140 mg/dl (nonfasting). Electrolytes show sodium of 132 mEq/l, potassium of 5.5 mEq/l, bicarbonate of 20 mEq/l, and chloride of 98 mEq/l. A renal biopsy is performed. Complete blood count is within normal limits. Which one of the following lesions is *most* likely to be present in the renal biopsy?
   A. Minimal change disease (MCD) with interstitial nephritis
   B. Amyloidosis
   C. Crescentic glomerulonephritis
   D. Membranous nephropathy
   E. Immunoglobulin A nephropathy
2. An 87-year-old woman with hypertensive nephrosclerosis was started on hemodialysis (HD) 3 months ago. Before dialysis initiation, she had significant weight loss and anorexia, with a serum albumin of 2.8 g/dl. Most recently, her appetite has improved and with this her albumin has improved to 3.2 g/dl, with a serum phosphorus of 5.4 mg/dl and a serum calcium of 9.6 mg/dl. She is currently living in a nursing facility and unable to ambulate without assistance. She appears depressed and apathetic and reports that she has little energy and motivation to participate in any exercise. The family has asked you to meet with them to tell them what they can expect for their mother's health in the future. Which *one* of the following statements is correct?
   A. Dialysis will likely continue to improve her energy level and appetite; the family should expect continued improvement over the next few months.
   B. Her inability to ambulate, frailty, and depression will likely not improve with dialysis, and her condition is likely to continue to deteriorate over time.
   C. Home HD should be considered because this modality is associated with improved outcomes in this age group.
   D. Assisted peritoneal dialysis (PD) should be considered as a way to keep the patient at home; this modality is associated with increased survival over in-center HD.
3. A 79-year-old patient who recently started HD for ESRD secondary to drug-induced interstitial nephritis approaches you to discuss his potential for kidney transplantation. His clinical history includes hypertension, mild angina-like symptoms, and hyperlipidemia. He does not smoke and is very active. In your region, the average time for patients with his blood type to be on the wait list is 5 years before transplantation. Which of the following statements would *most* accurately inform the patient with regard to his candidacy for renal transplantation?
   A. He is unlikely to gain any benefit from transplantation because there is a high risk for death in the first year postoperatively in patients older than 75 years.
   B. He would likely benefit from transplantation, and he should consider living donation as the best option.
   C. He should seek transplant listing but not seek a living donor.
   D. He should be advised to avoid going on the extended-criteria donor waiting list.

90

Approach to Renal Replacement Therapy

Hugh C. Rayner, Enyu Imai, Vijay Kher

The number of patients starting renal replacement therapy (RRT) each year varies enormously across countries (Fig. 90.1). The incidence per million population in most countries has risen steadily over the last decade (Fig. 90.2), although some have seen a decline in recent years (Fig. 90.3). The incidence of RRT is influenced by multiple factors: the incidence and prevalence of diseases that may lead to end-stage renal disease (ESRD), especially diabetes; the ability of health care systems to identify chronic kidney disease (CKD) and to slow progression to ESRD[1]; the level of kidney function at which RRT is commenced; and the availability of resources to provide RRT.

RRT is costly and time consuming; once started, it may continue for many years. All patients likely to reach ESRD, their families, and their caregivers require physical and psychological preparation, including education about future treatment options, given in a form that they find accessible.

PREDICTION OF END-STAGE RENAL DISEASE

Preparation for ESRD treatment requires two things: identification of those patients who are at high risk for reaching ESRD and prediction of the likely time when RRT may be needed.[2]

Diabetes, heavy proteinuria, declining estimated glomerular filtration rate (eGFR) and previous episodes of acute kidney injury make it more likely that a patient will progress to ESRD. Prediction of when someone may need RRT is made easier by a graphical display of eGFR. The trajectory of the eGFR accurately reflects changes in the true GFR over time[3] and is easier to understand than columns of figures (Fig. 90.4). The graph should be shared with patients to help them understand how their disease is progressing. If patients with a declining trend in eGFR are systematically identified, the number of patients initiating RRT without adequate preparation may be reduced and the rising trend in RRT incidence slowed.[1]

MULTIDISCIPLINARY CARE IN ADVANCED CHRONIC KIDNEY DISEASE

Advanced CKD care aims to address several issues: preservation of remaining kidney function; prevention or treatment of complications of CKD; involvement of the patient, the family, and caregivers in making an informed choice in regard to peritoneal dialysis (PD), hemodialysis (HD) and conservative kidney management; creation of dialysis access in good time; and, in appropriate patients, preparation for kidney transplantation ideally before dialysis is started. Patients who receive consistent predialysis care have better outcomes[4] and incur lower health care costs.

Patients need time (often months) to understand and make decisions about dialysis and its implications. The best approach is to transfer patients with a declining GFR to a multidisciplinary team at least 12 months before dialysis is started. The start date can be predicted by extrapolating a trendline of the eGFR forward until it reaches 10 ml/min/1.73 m^2.[5] Using the 12-month prediction rather than an arbitrary value of eGFR to prompt referral avoids elderly patients with slowly declining GFR being referred unnecessarily for dialysis preparation.

The trajectory of the eGFR graph may not be linear; intercurrent illness can cause a sudden drop in GFR and precipitate urgent dialysis in patients at stage 5 CKD. It is therefore prudent to refer all patients for multidisciplinary care once the eGFR reaches 15 ml/min/1.73 m^2.

Predialysis Education Programs

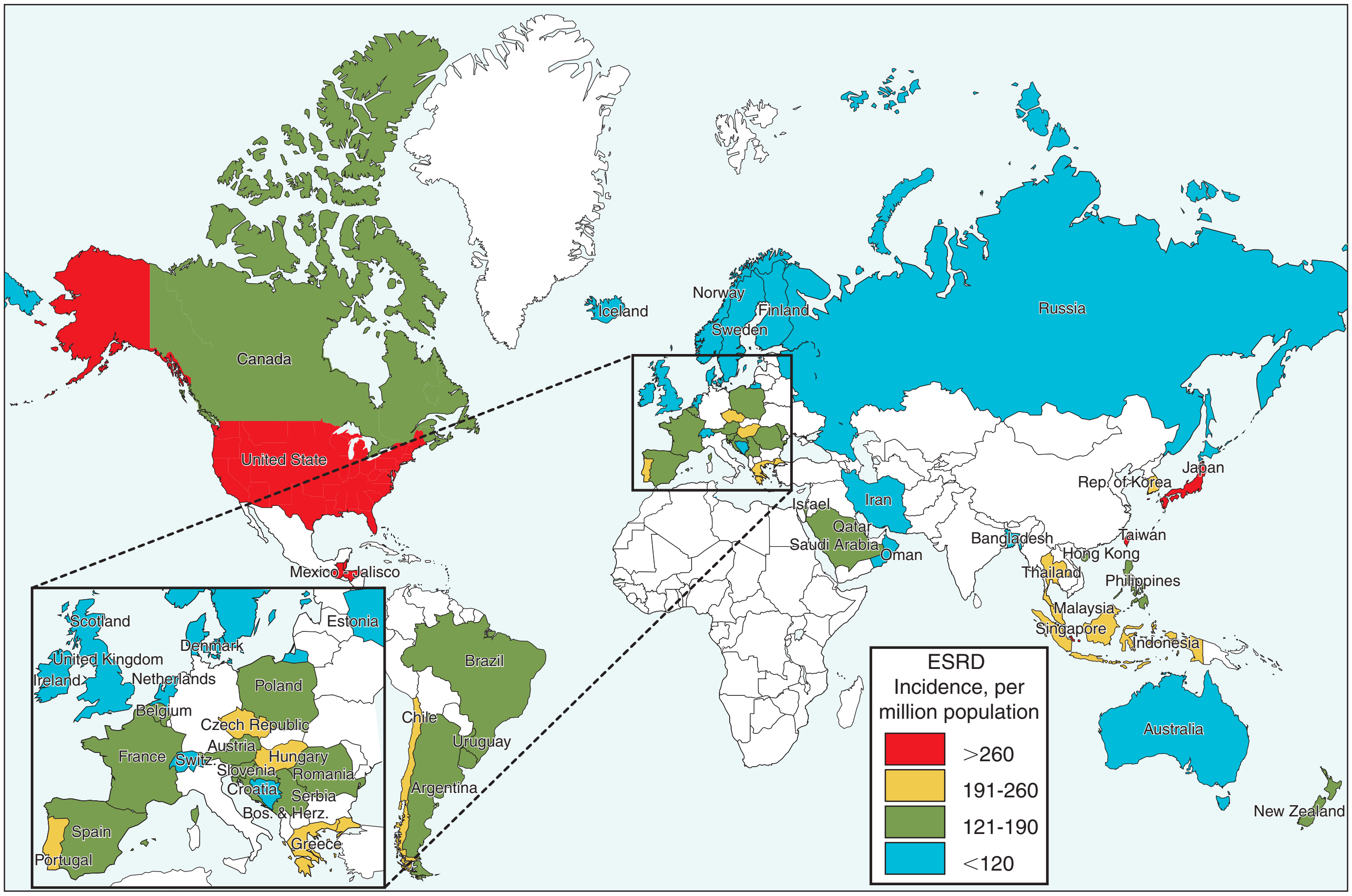
Conventional office consultations with a nephrologist may not enable patients with advanced CKD to gain sufficient knowledge and understanding to make good decisions about RRT.[6] Patients receiving additional care from a predialysis multidisciplinary team have better biochemical results, are more likely to start dialysis in a planned way with less hospitalization, and may even have improved survival rates once they have started dialysis. As well as being good clinical practice, these programs may make good financial sense because the savings in inpatient costs can exceed those required to run the clinics.[7]

Although clinicians are expert in the technical aspects of dialysis and transplantation, patients know best about their own needs and preferences and should be encouraged to share in decision making.

Patient education should follow the principles of adult learning: first, assess the patient's existing level of knowledge and understanding; second, build on this knowledge by delivering appropriate information in an appropriate form; and third, establish that the patient has understood and accepted the information given. Education can be delivered both individually and in groups. In a group education session, patients may learn more from fellow patients than from the group's facilitator. Furthermore, support groups help patients and their relatives appreciate that they are not alone in facing the demands of ESRD.

The team ideally includes a dietician, nurse educator, pharmacist, physical therapist, occupational therapist, social worker, and sometimes a trained peer-support volunteer. A controlled trial in California studied the value of social worker input to the predialysis program in reducing

Geographical Variation in the Incidence of End-Stage Renal Disease


Iceland
Norway
Finland
Sweden
Russia
Canada
United State
Mexico
Jalisco
Israel
Iran
Qatar
Saudi Arabia
Oman
Bangladesh
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Japan
Taiwan
Hong Kong
Thailand
Philippines
Malaysia
Singapore
Indonesia
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New Zealand
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Chile
Uruguay
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United Kingdom
Ireland
Netherlands
Poland
Belgium
Czech Republic
Austria
France
Switz
Hungary
Slovenia
Romania
Croatia
Serbia
Bos. & Herz.
Spain
Greece
Portugal
ESRD Incidence, per million population
🟥 >260
🟨 191-260
🟩 121-190
🟦 <120

Fig. 90.1 **Geographical variation in the incidence of end-stage renal disease (ESRD) per million population, by country, 2013.** Data presented only for countries from which relevant information was available. All rates are unadjusted. Data for Indonesia represent the West Java region. Data for France include 22 regions. Data for Spain include 18 of 19 regions. (Data from Special Analyses, U.S. Renal Data System, ESRD Database.)

unemployment.[8] In the intervention group, patients and their relatives met regularly with a licensed social worker both before and after starting dialysis, to explore strategies for continuing the patient's current employment. Blue-collar workers in the intervention group were 2.8 times more likely to continue working. Patients in work had a better quality of life, greater self-esteem, and a more positive attitude to work. Because it is difficult for dialysis patients to regain jobs once they are lost, this result is particularly valuable for the long-term rehabilitation of patients.

Patients should be directed to the wide range of educational materials available. Many national organizations, such as the National Kidney Foundation in the United States (www.kidney.org), provide web-based patient information and produce printed and audiovisual material. Decision aids can help patients think through their options and choose the treatment that suits them best. A good online example is choosingdialysis.org. Each consultation should be followed by a letter or report, ideally written directly to the patient[9] and copied to the patient's family doctor.

Education About Transplantation

For many, transplantation offers the best prospect for improved survival and quality of life, especially in younger patients. Even in older patients with greater comorbidity, transplantation can improve survival and be cost effective.[10]

The options of transplanting kidneys from a deceased or living donor should be discussed, as well as combined kidney and pancreas transplants for some people with diabetes. Although outcome data from the local transplant center should be made available, published data can be used, such as from the U.S. Scientific Registry of Transplant Recipients (www.srtr.org) or NHS Blood and Transplant in the United Kingdom (www.odt.nhs.uk).

The ideal time for the transplant to be performed is before dialysis has begun—preemptive transplantation. This avoids the need for access surgery and, in most studies, patient survival, graft survival and acute rejection rates are better.[11]

WHEN SHOULD DIALYSIS BE STARTED?

There is no single measure that can be used to determine the right time to start dialysis. A low eGFR, rising serum phosphate, and falling serum bicarbonate may indicate end-stage kidney failure, but these levels are also affected by muscle mass and protein intake. Falling serum albumin may indicate inflammation rather than malnutrition secondary to uremia.

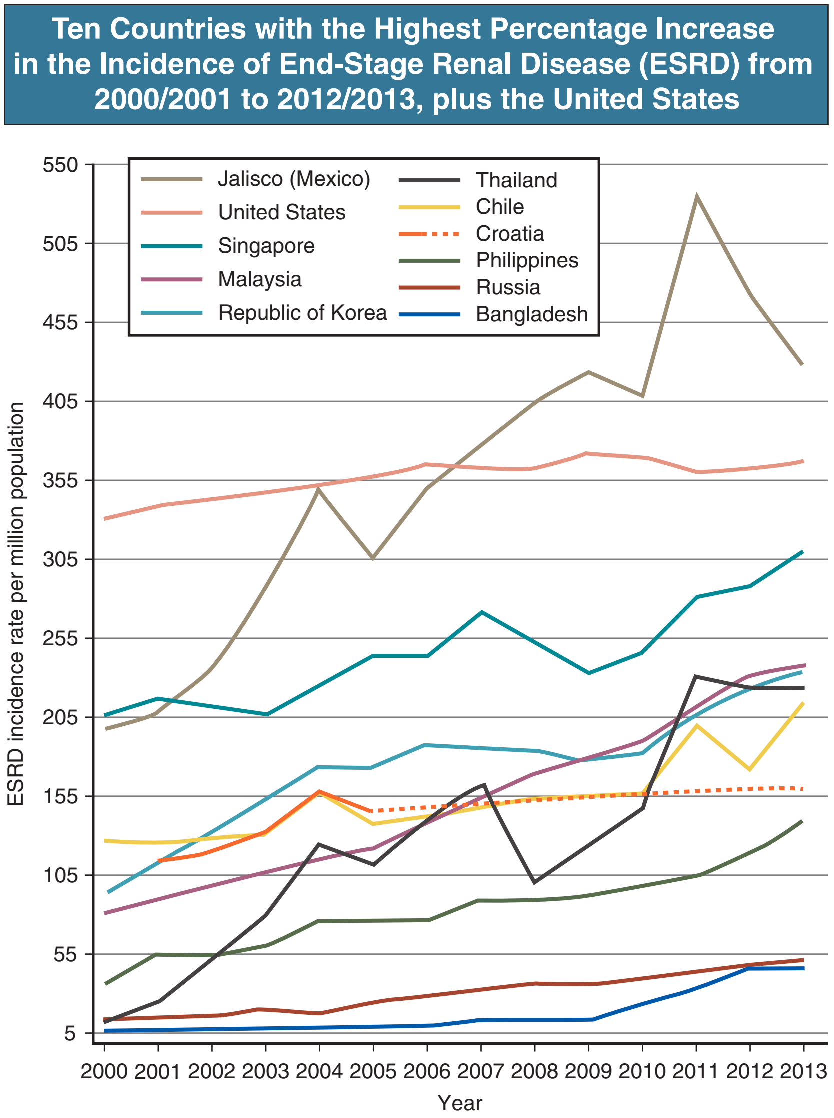


Fig. 90.2 **Ten countries having the highest percentage increase in the incidence of end-stage renal disease (ESRD) from 2000/2001 to 2012/2013, plus the United States.** All data are unadjusted. Data for Croatia are missing from 2006-2011, indicated by the *dashed line.* Data for United States are shown for comparison purposes. (Data from Special analyses, U.S. Renal Data System, ESRD Database.)

The eGFR at the start of dialysis has steadily increased over recent years and varies across countries. Mean eGFR (in ml/min/1.73 m^2) of Japanese patients at the start of dialysis increased from 5.0 in 1989 to 6.5 in 2007.[12] In the United Kingdom, the mean eGFR at the start of dialysis increased from 6 in 1997 to 8.6 in 2014.[13] In the United States in 1996, 13% of incident ESRD cases started RRT with an eGFR of 10 ml/min/1.73 m^2 or greater. This rose to 43% in 2010 but decreased to 39% in 2015.[14] In the United States, dialysis was started at a consistently lower eGFR within the Department of Veterans Affairs, a non–fee-for-service health system, than with other providers.[15] Aging of the CKD population may have contributed to the earlier initiation of dialysis; in Japan the median age at initiation of dialysis increased from 59 to 68 years between 1989 and 2007.[12]

Limitations of a Purely Clinical Approach to the Initiation of Dialysis

Waiting for uremic symptoms to develop before starting RRT carries the risk that the patient will be malnourished when they start dialysis, with an increased risk for mortality. The chronic nature of progressive kidney disease means that patients may remain unaware of the severity of their illness. Protein intake may fall spontaneously so that symptoms of uremia do not develop, at the expense of a loss of lean body mass. Similarly, patients may gradually reduce their activities as their exercise tolerance declines. Many patients appreciate how ill they had become only once they have rehabilitated on a dialysis program. Lack of awareness can be avoided by questioning the patient for insidious symptoms of uremia. For example, patients should be asked to compare their current eating habits and level of activity with those 6 to 12 months previously. Close friends and relatives may provide a useful third-party view of the patient's well-being.

Limitations of a Purely Laboratory Results–Based Approach to the Initiation of Dialysis

Early initiation of dialysis would need to have proven benefits to justify the additional inconvenience to the patient, risk for dialysis-related complications, and cost. Dialysis treatment has a finite life, either from

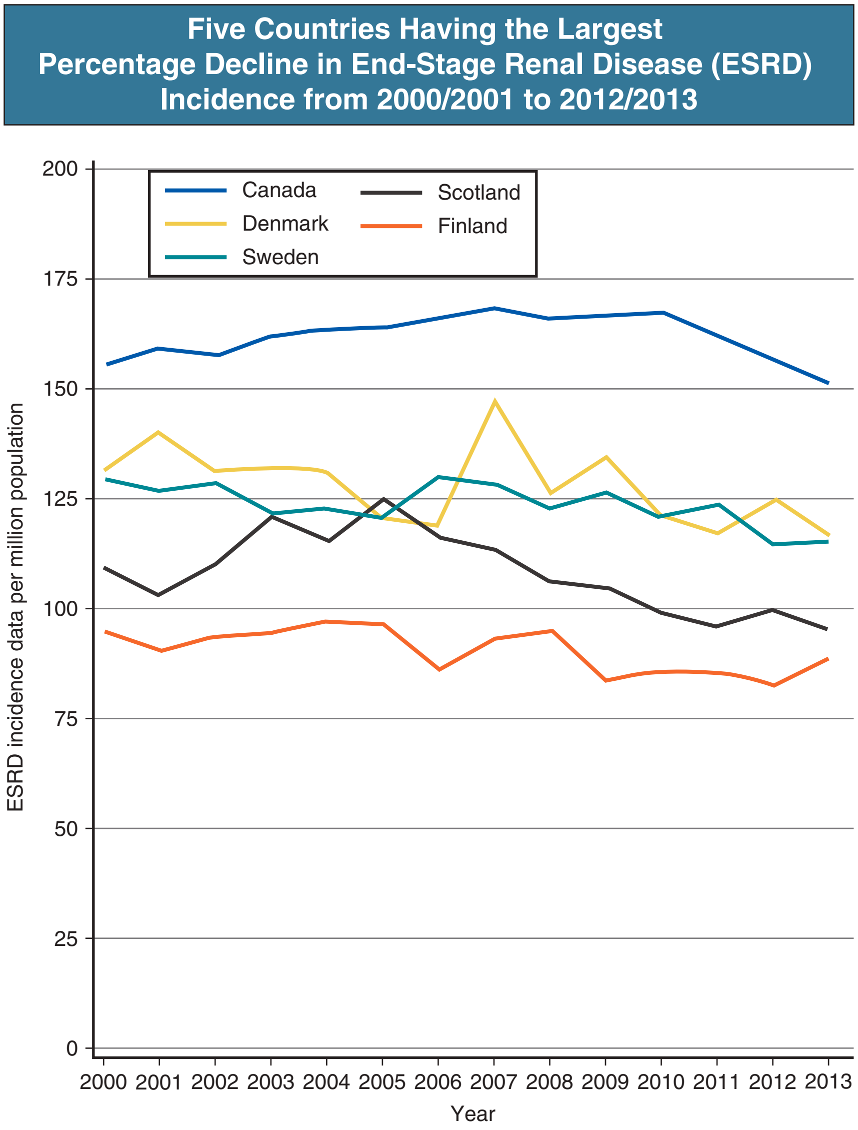


Fig. 90.3 **Five countries having the largest percentage decline in end-stage renal disease (ESRD) incidence data from 2000/2001 to 2012/2013.** All data are unadjusted. The interpretation and reporting of U.S. Renal Data System (USRDS) data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government. (Data from Special Analyses, U.S. Renal Data System, ESRD Database.)

loss of peritoneal function or failure of HD access; thus starting treatment earlier will bring forward the time when further procedures or a change of modality are needed.

Moreover, there is likely to be resistance from many patients to the suggestion that they should start dialysis if they have no symptoms of uremia. Starting dialysis is the first step in a lifelong commitment to RRT, and patients will be asked to comply with a wide variety of inconvenient and sometimes unpleasant treatments. A high level of compliance is required for a successful outcome, and there is concern, particularly in the United States, about the level of noncompliance associated with increased mortality. Commitment to dialysis is likely to be greater if the patient feels better after it has started.

A randomized trial comparing patients who started dialysis at an eGFR of 9.0 ml/min/1.73 m^2 with those who started 6 months later at an eGFR of 7.2 ml/min/1.73 m^2 showed no difference in survival or quality of life (Fig. 90.5).[16] Starting dialysis earlier was not associated with better quality of life and incurred higher health care costs.[17] The one advantage in the earlier-start group was that a higher proportion of those patients who had previously chosen PD actually started dialysis with PD (80% vs. 70%, $P = 0.01$).

Some clinicians advocate an incremental start to HD, using twice rather than three times weekly treatments in patients with sufficient residual kidney function.[18] Less frequent dialysis is popular with patients and may help preserve residual kidney function and prolong vascular access survival. In the developing world, twice-weekly dialysis is often the norm, mostly due to financial constraints. Studies need to be done in these countries to optimize less costly ways of delivering dialysis.[19]

THE CHOICE BETWEEN PERITONEAL DIALYSIS AND HEMODIALYSIS

The mix of PD and HD in the dialysis population varies considerably across countries (Fig. 90.6). Higher expenditure on health care, a larger

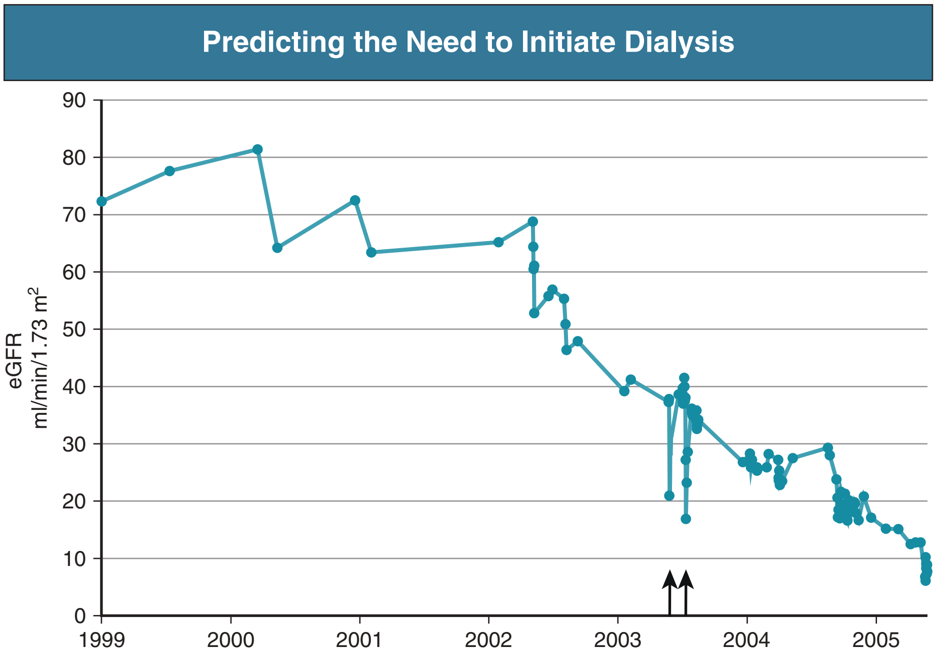

Predicting the Need to Initiate Dialysis

Fig. 90.4 Predicting the need to initiate dialysis. Graph of estimated glomerular filtration rate *(eGFR)* over time for a patient with diabetes and progressive chronic kidney disease. The graph displays sequential eGFR values, telling the story of how the patient's kidney disease progressed. Acute episodes can be distinguished from the underlying chronic progression. 1996: Diabetes mellitus diagnosed. 2000: Blood pressure 196/108 mm Hg and proteinuria detected. 2002: Acute myocardial infarction followed by acute decline in GFR. 2003: Two episodes of radiocontrast-induced acute kidney injury *(arrows)* following a CT scan and a coronary angiogram. 2005: Dialysis started.

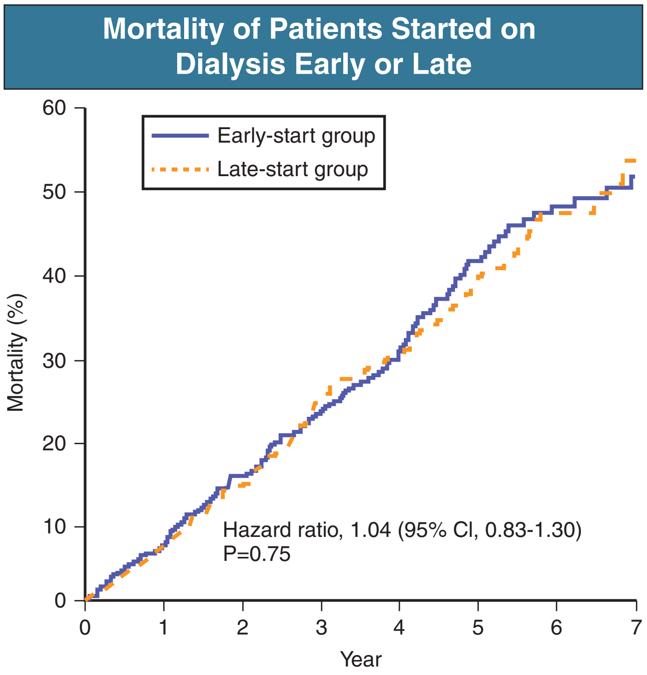

Mortality of Patients Started on Dialysis Early or Late

Fig. 90.5 Mortality of patients started on dialysis early or late. Kaplan-Meier Curves for the time to death.[16]

proportion of dialysis units being private-for-profit, and higher costs of PD consumables relative to staffing, as well as the prevalence of diabetes, are associated with a higher proportion of patients having HD.[20]

Most patients with ESRD are suitable for treatment with either PD or HD. How should one choose between the two? Ideally we would apply evidence from a randomized clinical trial (RCT) of PD versus HD. Variations in the way PD and HD are delivered make designing a balanced comparative trial difficult. One attempted RCT, the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study had to be stopped because of low recruitment. Retrospective and prospective nonrandomized comparative studies have failed to indicate a consistent survival advantage for either modality. There is some evidence that PD may be inferior to HD over the longer term in patients with coronary heart disease and congestive heart failure.[21] This contradicts a commonly expressed opinion that PD is more "gentle" for such patients by avoiding rapid fluid shifts and causing less ischemic "stress" on the heart. Change in treatment from PD to HD is associated with an increased risk for hospitalization and mortality, especially when this is unplanned. Patients having PD for longer than 7 years are at an increased risk for encapsulating peritoneal sclerosis, which may prompt a planned change to HD.

Contraindications to Peritoneal Dialysis

There are a few situations in which PD is contraindicated (Box 90.1). Relative contraindications to PD include those discussed in the following section.

Fresh Intraabdominal Foreign Body

Patients with prosthetic aortic grafts have been successfully treated with PD. HD is usually used for up to 16 weeks to allow the graft to be covered with epithelium and so avoid the risk for graft infection via peritoneal dialysate. However, this risk must be balanced against that of bacterial seeding from the patient's HD access.

Body Size Limitations and Intolerance of Intraabdominal Fluid Volume

Body size can be a problem at both ends of the spectrum. Small patients may be intolerant of the volume of dialysate needed to achieve adequate

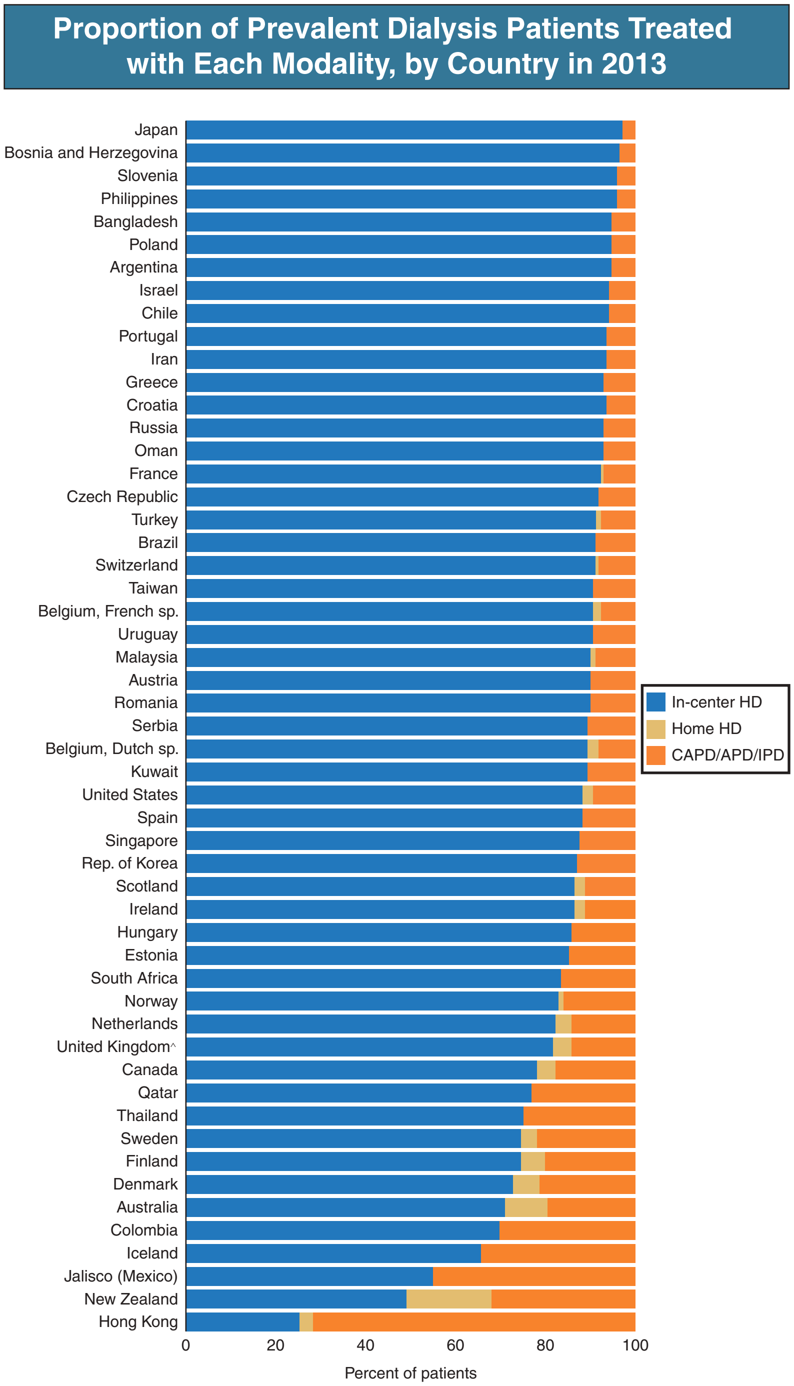


Fig. 90.6 **Distribution of the percentage of prevalent dialysis patients using in-center hemodialysis *(HD),* home HD, or peritoneal dialysis (PD) 2013.** Denominator is calculated as the sum of patients receiving HD, PD, or home HD; does not include patients with other/unknown modality. ^United Kingdom: England, Wales, and Northern Ireland (Scotland data reported separately). Data for Spain include 18 of 19 regions. Data for France include 22 regions. Data for Belgium do not include patients younger than 20. *APD,* Automated peritoneal dialysis; *CAPD,* continuous ambulatory peritoneal dialysis; *ESRD,* end-stage renal disease; *IPD*, intermittent peritoneal dialysis; sp., speaking. (Data were supplied by the U.S. Renal Data System.)

dialysis, particularly if they have negligible residual kidney function. Alternative methods of fluid exchange such as automated PD (APD) can be used to overcome this limitation. Larger dwell volumes or APD are required to achieve adequate solute clearance and ultrafiltration in patients with a body mass index greater than 35 kg/m^2. Discomfort as a result of increased intraabdominal volume can be significant in patients with chronic respiratory disease, low-back pain, or large polycystic kidneys. In general, it is hard to predict a patient's tolerance of intraabdominal fluid and so these limitations usually appear after a patient has started PD.

Bowel Disease and Other Sources of Infection

The presence of ischemic bowel disease, inflammatory bowel disease, or diverticulitis is likely to increase the incidence of peritonitis caused

BOX 90.1 Contraindications to Dialysis Modalities

Peritoneal Dialysis

Absolute

- Loss of peritoneal function producing inadequate clearance
- Adhesions blocking dialysate flow
- Surgically uncorrectable abdominal hernia
- Abdominal wall stoma
- Diaphragmatic fluid leak
- Inability to perform exchanges in absence of suitable assistant

Relative

- Recent abdominal aortic graft
- Ventriculoperitoneal shunt
- Intolerance of intraabdominal fluid
- Large muscle mass
- Morbid obesity
- Severe malnutrition
- Skin infection
- Bowel disease

Hemodialysis

Absolute

- No vascular access possible

Relative

- Difficult vascular access
- Needle phobia
- Cardiac failure
- Coagulopathy

(Modified with permission from *American Journal of Kidney Disease* 2006;48[Suppl 1]:S91-S97. Clinical practice guidelines for peritoneal adequacy, update 2006. PD Adequacy 2006 Work Group.)

by organisms passing through the bowel wall into the peritoneum. Abdominal wall infection may lead to peritonitis via the exit site and catheter tunnel.

Screening for methicillin-resistant *Staphylococcus aureus* (MRSA) before all elective surgical procedures is good practice. Clearance of nasal *S. aureus* with topical mupirocin cream reduces the risk for staphylococcal infection at the exit site.

Severe Malnutrition or Morbid Obesity

Severe malnutrition may lead to poor wound healing and leakage from the catheter tunnel. In addition, peritoneal protein losses during dialysis may exacerbate hypoalbuminemia. At the other end of the spectrum, it may prove difficult to satisfactorily place a peritoneal catheter through the abdominal wall in patients with morbid obesity and the risk for infection is greater. Thereafter, absorption of glucose from the dialysate, which may average as much as 800 calories per day, may contribute to further weight gain.

Contraindications to Hemodialysis

Contraindications to HD are few (see Box 90.1). As discussed in Chapter 91, access to the circulation usually can be obtained, even in patients with extensive vascular disease or previous surgery. An aversion to needle puncture of the atrioventricular fistula (AVF) is common in the early stages but usually can be overcome by careful use of local anesthetic and nursing encouragement. Severe coagulopathy may make management of anticoagulation for the extracorporeal circuit difficult.

HOME HEMODIALYSIS

In the 1960s, maintenance dialysis was mostly done by the patient and the family at home. Because in-center HD programs were established and then PD became available, patients could choose not to have HD at home. This removed the burden of dialysis from the patient and family and avoided the cost of installing a dialysis machine with its associated water treatment. In the United Kingdom the percentage of the dialysis population having home HD fell from 35% in 1984 to 2% in 2005.

However, home HD can provide significant benefits; it removes the inconvenience of traveling to and from the dialysis facility, gives patients the freedom to dialyze at a time that suits them, and reduces the cost of nursing and support staff. Although there is no RCT comparing hospital and home HD, comparative studies in which correction has been made for differences in comorbidity suggest that patients on home HD have lower morbidity and mortality than in-centre HD and PD.[22]

Patients at home often perform more than three treatments per week, and some dialyze overnight. More frequent dialysis significantly reduces the time taken to recover after each treatment, reduces dietary restrictions and antihypertensive medications, and leads to improved quality of life and reduced mortality.[23]

Over recent years there has been increasing recognition of the benefits of home HD, and, along with better technology, this has increased nephrologists' enthusiasm for it,[24] leading to a growth in the proportion receiving home HD in the United Kingdom to 4.2% in 2015.[13] Canada, Denmark, and Finland also have had significant increases, and in 2013 the proportion of patients on home HD in New Zealand was 18.4% (see Fig. 90.6).

Hemodialysis or Hemodiafiltration

Hemodiafiltration (HDF) is increasingly used throughout Europe and elsewhere but is not available in the United States because of regulatory restrictions. HDF adds the removal of fluid containing larger molecules by convection to the clearance of smaller molecules by diffusion. For example, β_2-microglobulin levels are lower in patients treated by HDF than by HD. In this way, HDF theoretically mimics glomerular filtration more closely and potentially may benefit ESRD patients with little or no residual kidney function.

A number of trials comparing outcomes with HD and HDF have been conducted, yielding conflicting results (see Chapter 94). Evidence suggests that high convection volumes (>30 l/week/m^2) need to be removed and replaced to deliver better patient outcomes.[25]

PATIENT CHOICE OF HEMODIALYSIS OR PERITONEAL DIALYSIS

Ideally all patients entering the ESRD program would be given "modality-neutral" counseling and allowed to select their preferred mode of treatment. When this was done in a U.K. center, about 45% of patients without a medical contraindication to PD selected PD.[26] Independent predictors for choosing PD include being married, being counseled before the start of dialysis and increasing distance from the base unit, and predictors for choosing HD are increasing age, comorbidity, and male sex. However, although 45% of patients may choose PD, not all of them start dialysis on this modality. Patients who require urgent dialysis often receive HD rather than PD, although PD can be started urgently if the necessary resources are available.[27] Once started on HD, only a small proportion of patients transfer to PD, even if this was their original preference. Patients presenting late for dialysis should still have access to an education program about their options for long-term treatment.

Frail patients can be assisted to have PD at home by a spouse, family member, or trained assistant. This can avoid the burden of in-center HD and improve quality of life,[28] and patients may progress to independent PD after a month or two of assistance.

The major differences in dialysis modality across countries (see Fig. 90.6) suggest that the type of dialysis patients receive is more often determined by physicians and organizational factors rather than by patients, as discussed in the following section.

Economic Factors

The arrangements by which doctors and dialysis facilities are reimbursed for the cost of providing treatment vary widely around the world, and

Timing of First Nephrology Care before Initiation of Hemodialysis by Country, 2012-2014

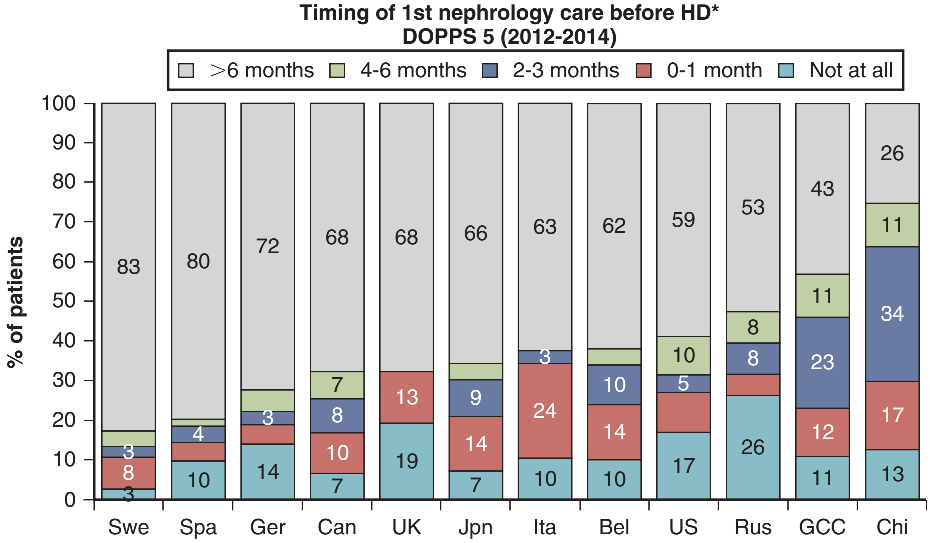


Fig. 90.7 Country differences in timing of first nephrologist care before starting dialysis among patients enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) within 60 days of starting dialysis (2012-2014). Data were calculated among patients on dialysis for <60 days at the time of enrolment in the DOPPS study. *Swe,* Sweden; *Spa,* Spain; *Ger,* Germany; *Can,* Canada; *Jpn,* Japan; *Ita,* Italy; *Bel,* Belgium; *Rus,* Russia; *GCC,* Gulf Cooperation Council countries; *Chi,* China. (Reproduced from Pisoni et al. *Am J Kidney Dis.* 2015;65(6):905-915, with permission.)

there is wide variation in the relative levels of payment for HD and PD. These factors have a profound effect on the mix of dialysis modality within a country.[29] PD is generally less expensive than HD,[30] and some countries, such as Hong Kong, have a deliberate "PD first" policy.[31] In the United States, assisted PD is not reimbursed and so is available only if the patient or the family organizes the assistance. In HD facilities, if payment depends on the number of patients being treated, there will be an incentive to increase patient numbers and fill any unused capacity, especially if the nephrologist has a financial interest in the facility.

Physician Preference

In the past, there has been a clear preference among physicians for HD. When surveyed in 1996, a much greater proportion of U.S. patients on HD than on PD thought that the choice had been made by the medical team rather than either by themselves or by joint decision. Ten years later, only 61% of U.S. dialysis patients remembered having PD discussed with them before they started dialysis. Best practice guidelines emphasize the ethical, and in many countries legal, imperative to advise patients of all their treatment options.[32]

THE IMPORTANCE OF DIALYSIS ACCESS

Before starting dialysis, every patient would ideally have made an informed choice between PD and HD after weeks or months of counseling and preparation, and those choosing HD would have a functioning AVF. Sadly, dialysis is frequently started in less than ideal circumstances. The percentage of patients presenting shortly before starting dialysis varies between dialysis units and countries (Fig. 90.7). This is a particular issue in the United States, where in 2015 36% of new ESRD patients had received little or no nephrology care before beginning therapy.[14]

Patients presenting to a nephrologist shortly before starting dialysis have a longer initial hospital stay and a higher incidence of major complications and death.[4] Late presentation is one reason why HD is started using a catheter rather than an AVF (Fig. 90.8) and a significant part of the increased mortality is related to this.

The timing of AVF placement is complex.[33] If an AVF is created many months before the patient is predicted to reach ESRD the chances that a catheter is used will be reduced. However, elderly patients may die without the AVF ever being used. International data from the Dialysis Outcomes and Practice Patterns Study show that the risk for death is higher for patients dialyzing in units that use central venous catheters in a high proportion of their patients.[34] The risk is also increased if arteriovenous grafts are commonly used. Catheters can cause complications such as infection, pulmonary embolism, and central venous stenosis.

There is wide variation across countries in the time required for permanent access to be created and used. If a fistula can be created swiftly and used as soon as it is mature, perhaps after only 2 weeks, the need for a catheter may be avoided. Details of HD access surgery are discussed in Chapter 91 and PD catheter placement in Chapter 96.

THE DECISION WHETHER TO OFFER RENAL REPLACEMENT THERAPY

The Availability of Dialysis Facilities

Because of its high cost, RRT is not available to most people with ESRD worldwide. The practice of rationing dialysis has been candidly documented in a report from a South African center[35] in which more than half the patients with ESRD assessed between 1988 and 2003 were not offered dialysis. Socioeconomic factors such as age, race, employment, and marital status outweighed medical factors in the decision to begin treatment.

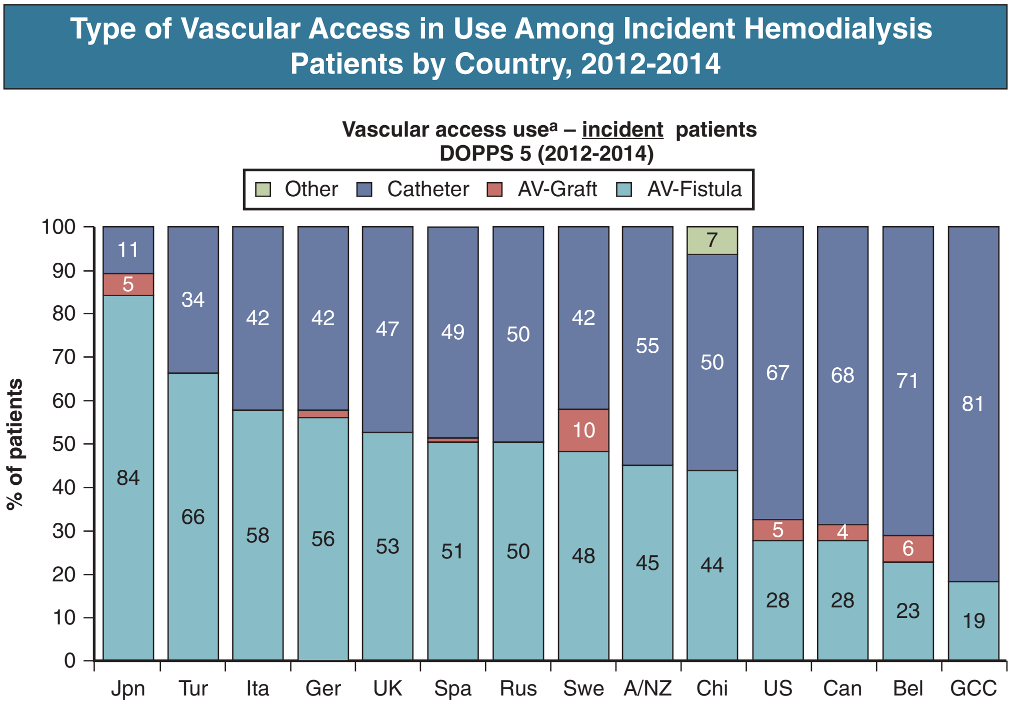


Fig. 90.8 Country differences in type of vascular access in use among incident hemodialysis patients participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS) within 60 days of starting dialysis (2012-2014). Data were calculated among patients on dialysis for <60 days at the time of enrolment in the DOPPS study. *Jpn,* Japan; *Tur,* Turkey; *Ita,* Italy; *Ger,* Germany; *Spa,* Spain; *Rus,* Russia; *Swe,* Sweden; *A/NZ,* Australia/New Zealand; *Chi,* China; *Can,* Canada; *Bel,* Belgium; *GCC,* Gulf Cooperation Council countries. (Reproduced from Pisoni et al. *Am J Kidney Dis.* 2015;65(6):905-915, with permission.)

The phenomenon of "supply-sensitive care" applies to dialysis as it does to health care in general.[36] RRT incidence is independently associated with a country's gross domestic product (GDP), the percentage of GDP spent on health care, and the reimbursement rate relative to GDP for HD dialysis facilities. In more developed countries, those with a greater proportion of private for-profit facilities have a higher incidence of dialysis.[37]

Selection of Patients by Physicians and Nephrologists

Although incidence rates of RRT in most countries have increased over recent decades (see Fig. 90.2), not all of this is due to more patients developing ESRD.[38] In other words, physicians have become more willing to offer dialysis to patients with ESRD. The practice of starting dialysis in patients who are very elderly or dependent on others for their care or who have multiple comorbid conditions varies significantly across countries and among nephrologists within those countries. For example, in 2005 the percentage of patients who were living in a nursing home or who were unable to eat independently within 90 days of starting dialysis was much higher in the United States (11.6%) and Japan (19.2%) than in France (1.3%), Germany (6.4%), Italy (4.7%), Spain (2.0%), and the United Kingdom (1.5%).[39] Severe cognitive impairment in a patient would much more strongly influence a nephrologist in the United Kingdom not to start dialysis than in the United States. Furthermore, nephrologists in the United States were much more likely than those in the United Kingdom and Canada to start dialysis in patients with dementia or in a persistent vegetative state, if pressured to do so by family members. In Japan in 2010, dementia severe enough to require care was present in 9.9% of chronic dialysis patients. Fear of litigation was particularly influential in persuading nephrologists to offer treatment.

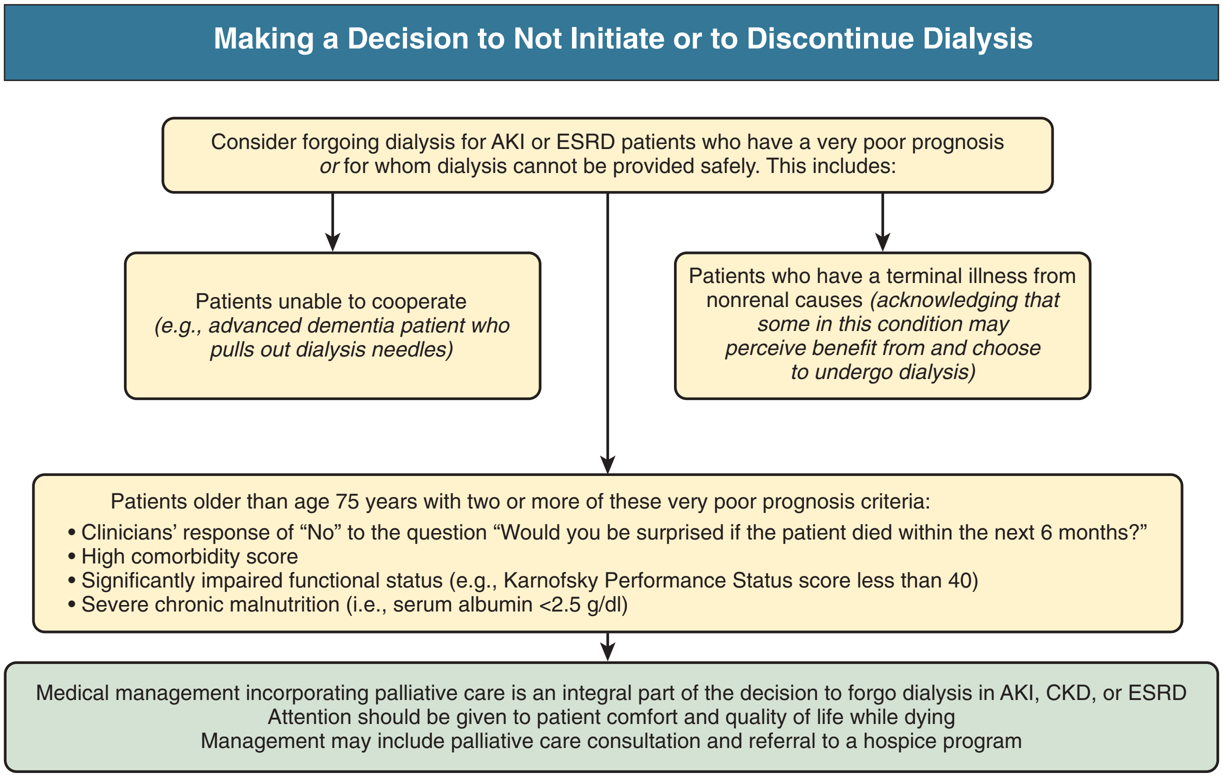
Rationing Versus Rational Dialysis Treatment

How dialysis should be used has raised a range of bioethical issues over the years.[40] In the 1960s, committees would meet to decide who should be offered dialysis, on the grounds that the greatest good should be derived from the limited resources available. Patients who were expected to survive for only a few months would not be offered dialysis. As resources became more widespread, a rationing approach became unacceptable and was replaced by decisions based on the balance of benefit and harm gained from dialysis for each individual.

Predictive Factors

Are there objective criteria that can be applied to identify patients for whom the harms of dialysis will outweigh the benefits? One criterion to be dismissed is age. Although advanced age was used as a simple exclusion criterion in the early days of dialysis, the elderly are now the most rapidly growing section of the dialysis population.

A Canadian study of patients starting dialysis[41] used a comorbidity scoring system to quantify factors likely to predict early death. The predictive value of this scoring system was compared with the value of an estimate made by the patient's nephrologist of the probability that the patient would die within 6 months. It was not possible to predict early death accurately using either the comorbidity scoring system or the clinician's opinion. Indeed, it was impossible even to identify the small proportion of patients with a very poor prognosis. Clinicians were more accurate than the scoring system in identifying patients with less than a 50% risk for death by 6 months, but they tended to overestimate the risk for death in the worst prognostic groups. For example, 30% of patients whose predicted probability of death was considered to be 80% or greater survived for more than 6 months.



Making a Decision to Not Initiate or to Discontinue Dialysis

Consider forgoing dialysis for AKI or ESRD patients who have a very poor prognosis *or* for whom dialysis cannot be provided safely. This includes:

Patients unable to cooperate *(e.g., advanced dementia patient who pulls out dialysis needles)*

Patients who have a terminal illness from nonrenal causes *(acknowledging that some in this condition may perceive benefit from and choose to undergo dialysis)*

Patients older than age 75 years with two or more of these very poor prognosis criteria:

- Clinicians' response of "No" to the question "Would you be surprised if the patient died within the next 6 months?"
- High comorbidity score
- Significantly impaired functional status (e.g., Karnofsky Performance Status score less than 40)
- Severe chronic malnutrition (i.e., serum albumin <2.5 g/dl)

Medical management incorporating palliative care is an integral part of the decision to forgo dialysis in AKI, CKD, or ESRD
Attention should be given to patient comfort and quality of life while dying
Management may include palliative care consultation and referral to a hospice program

Fig. 90.9 Making a decision to not initiate or to discontinue dialysis. *AKI,* Acute kidney injury; *CKD,* chronic kidney disease; *ESRD,* end-stage renal disease.

ADVISING PATIENTS ABOUT PROGNOSIS ON DIALYSIS

Despite these uncertainties, an individual patient should be given an estimate of his or her likely future on dialysis. The Renal Physicians Association (RPA) has suggested the following criteria to help identify patients over 75 years of age who have a poor prognosis on dialysis[42]: (1) clinicians' response of "No, I would not be surprised if my patient died in the next 6 months"; (2) high comorbidity score; (3) significantly impaired functional status (e.g., Karnofsky Performance Status score less than 40); and (4) severe chronic malnutrition (i.e., serum albumin less than 2.5 g/dl using the bromocresol green method). Quality of life is also strongly predictive of mortality, even after statistical correction for these comorbid factors.

For patients whose prognosis is particularly uncertain, or where there is disagreement between the views of the patient and the dialysis team, a time-limited trial of dialysis may be offered. This may give the patient and family a better understanding of what life on dialysis entails and allow time for further discussion between all parties. The duration of the trial should be judged for each individual, and clinical and biochemical parameters such as serum albumin reviewed regularly.

The RPA in the United States has issued guidelines for decisions to not initiate or to discontinue dialysis (Fig. 90.9) and provide a comprehensive toolkit to support shared decision making.[42]

CONSERVATIVE KIDNEY CARE

Conservative kidney care describes the care of patients with ESRD using all necessary and acceptable treatment apart from dialysis. It is increasingly adopted for a subset of patients with ESRD and multiple comorbidities.[43] There is a lack of high-quality evidence to inform discussions about conservative care as an alternative to dialysis. This matters because information provided by clinicians has a strong influence on the beliefs held by patients about their likely outcomes on dialysis or with conservative care.[44]

Most people would agree that patients who are certain to have an unacceptable quality of life should not be subjected to the discomfort of HD. Patients choosing conservative kidney management are spared surgical procedures and the inconvenience and discomfort of traveling to the dialysis unit. Depending on age and the number of comorbidities, survival with dialysis may be no longer, and much of any additional time is made up of days having or recovering from dialysis treatments.[45] Quality of life will be better without dialysis, and more are likely to die at home.

Many of the symptoms and complications of ESRD, such as anemia, acidosis, pruritus, insomnia, depression, fluid overload, and hypertension, can be treated with medication and diet. Patients may not report symptoms such as pain that they do not associate with kidney failure and so should be asked specifically about them. Itching and insomnia are common and, when severe, usually can be relieved by low doses of gabapentin or pregabalin.[46]

Conservative therapy is best delivered by the specialist predialysis multidisciplinary team and should include a dietitian, a social worker, psychological support, and a link to palliative care specialists.

THE PATIENT WHO DOES NOT WANT DIALYSIS

Nephrologists may be presented with the dilemma of a patient who has decision-making capacity and whom they would normally treat but who does not wish to have dialysis. From an ethical viewpoint, a patient's decision not to start dialysis or to discontinue it is justified on the principle of individual autonomy. Legally, in the United Kingdom this is based on the individual's common-law right to self-determination and in the United States on the constitutional right of liberty. Where the patient is able to express a clear wish, the physician is obliged to respect this because to treat a patient against the patient's will constitutes an assault.

The physician must nonetheless ensure that all reversible factors have been addressed, such as unfounded fears about what dialysis will entail or a depressive illness affecting the patient's judgment and ideally request a psychiatric evaluation. It is not uncommon for patients to express a strong desire not to have dialysis, particularly if they are relatively asymptomatic, only to change their mind when they become more symptomatic. At this late stage, the basic "will to survive" comes to the fore. An advance directive not to have dialysis written by the patient should never be held as a reason against a change of mind.

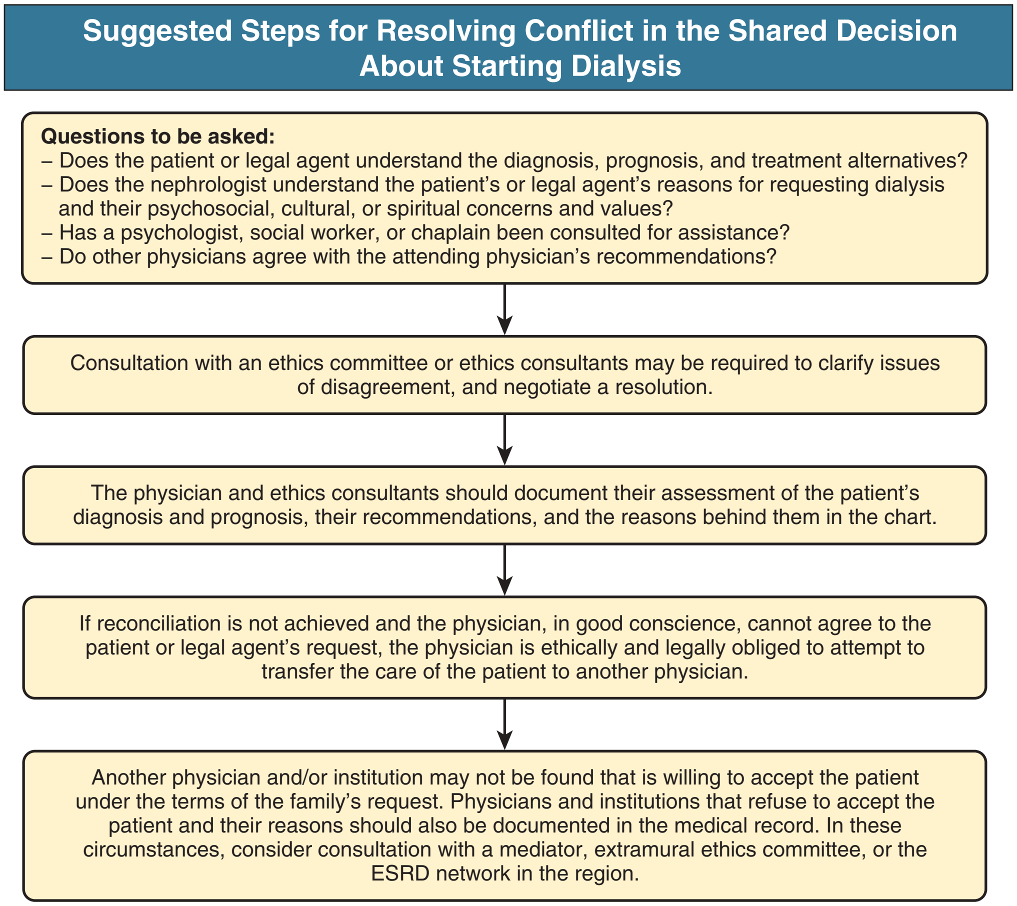
DISAGREEMENT ABOUT A DECISION TO DIALYSE

There will inevitably be differences of opinion about the harms and benefits of dialysis to individual patients. Dialysis nurses may disagree with the nephrologist's decision to treat a patient. If the dialysis nurses and doctors are functioning well as a team, they should feel able to express these reservations and have the issue adequately discussed. It is demoralizing for staff to feel pressured into giving treatment they believe to be inappropriate.

The nephrologist may remain reluctant to offer dialysis despite the insistence of either the patient or, more often, the patient's family or caregivers, the legal agent, or another doctor (see Fig. 90.9). Dialysis must never be given if it is against the patient's clearly expressed wishes, despite the insistence of others. However, if the patient insists on treatment against the nephrologist's advice, dialysis usually should be given while a resolution is reached.

Extensive discussions and explanations of the treatment options and prognosis may be needed to gain a better understanding of the reasons behind the differing views. Helpful advice may be obtained from another physician, particularly the patient's family doctor, who will have a broader understanding of the patient's circumstances. It may be appropriate to involve a psychologist, social worker, or religious counselor.

It may be necessary to refer the case to a formal ethics committee, if one exists locally, to clarify the issues of disagreement and enable a resolution. A physician cannot be compelled to offer treatment against his or her professional judgment, but the physician is ethically and legally obliged to attempt to transfer the care of the patient to another physician. Only as a last resort, if no alternative dialysis unit can be found and after adequate notice has been given, should dialysis be withdrawn. The RPA Clinical Practice Guideline Toolkit provides a systematic approach to conflict resolution if there is disagreement regarding the benefits of dialysis (https://c.ymcdn.com/sites/www.renalmd.org/resource/resmgr/Store/Shared_Decision_Making_Recom.pdf)[42] (Fig. 90.10).



Suggested Steps for Resolving Conflict in the Shared Decision About Starting Dialysis

Questions to be asked:
- Does the patient or legal agent understand the diagnosis, prognosis, and treatment alternatives?
- Does the nephrologist understand the patient's or legal agent's reasons for requesting dialysis and their psychosocial, cultural, or spiritual concerns and values?
- Has a psychologist, social worker, or chaplain been consulted for assistance?
- Do other physicians agree with the attending physician's recommendations?

Consultation with an ethics committee or ethics consultants may be required to clarify issues of disagreement, and negotiate a resolution.

The physician and ethics consultants should document their assessment of the patient's diagnosis and prognosis, their recommendations, and the reasons behind them in the chart.

If reconciliation is not achieved and the physician, in good conscience, cannot agree to the patient or legal agent's request, the physician is ethically and legally obliged to attempt to transfer the care of the patient to another physician.

Another physician and/or institution may not be found that is willing to accept the patient under the terms of the family's request. Physicians and institutions that refuse to accept the patient and their reasons should also be documented in the medical record. In these circumstances, consider consultation with a mediator, extramural ethics committee, or the ESRD network in the region.

Fig. 90.10 Suggested steps for resolving conflict in the shared decision about starting dialysis. *ESRD,* End-stage renal disease. (Modified from reference 42.)

BOX 90.2 Suggested Steps for Dealing With Disruptive Patients

Identify and document problem behaviors and discuss them with the patient.

- Seek to understand the patient's perspective.
- Identify the patient's goals for treatment.
- Share control and responsibility for treatment with the patient.
  - Educate the patient so he or she can make informed decisions.
  - Involve the patient in the treatment as much as possible.
  - Negotiate a behavioral contract with the patient.
- Consult a psychiatrist, psychologist, or social worker for assistance in patient management or determination of decision-making capacity.
- Be patient and persistent, try not to be adversarial.
- Allow the patient to vent concerns but do not tolerate verbal abuse or threats to staff or patients.
- Contact law enforcement officials if physical abuse is threatened or occurs.
- If satisfactory resolution has not occurred with these strategies, contact the local ESRD Network to discuss the situation and ensure due process.
- As a last resort, consider transferring the patient to another facility or discharging the patient.
- Consult with legal counsel before proceeding with plans for discharge and do not discharge without advance notice and a full explanation of future treatment options.

Modified from reference 42.

MANAGEMENT OF DISRUPTIVE PATIENTS ON DIALYSIS

Most nephrologists have had experience of treating a small number of patients who, for one reason or another, will not comply with the discipline required for maintenance dialysis and who become disruptive to the staff and other patients. This behavior can range from noncompliance with treatment, which harms the patient but is merely inconvenient to the staff, to verbal or even physical aggression toward the staff and other patients in the unit. The impact of this small number of patients can be very great.

The strategy for dealing with such patients must be tailored to the individual, particularly the person's decision making capacity. Useful suggestions for resolving conflict have been provided by the RPA (Box 90.2). They emphasize the importance of understanding, information, patience, and persistence. However, the bottom line for patients who have capacity and are aggressive toward staff while on dialysis must be that they are taken off treatment and sent home.

RESUSCITATION AND WITHDRAWAL OF DIALYSIS

Cardiopulmonary Resuscitation

If patients are to be fully involved in decision making about their treatment, two sensitive issues need to be discussed: cardiopulmonary resuscitation (CPR) and the possibility of withdrawal of dialysis. The two are not necessarily linked; patients may wish to continue with dialysis but express a desire that resuscitation not be attempted should they have cardiac arrest. Outcome of CPR in dialysis patients is worse than in the general population, the odds ratio for mortality being 1.24 (95% confidence interval, 1.11-1.3; $P < .001$). In 2011 survival after CPR in the United States was 31% but a greater proportion of patients with ESRD who survived were discharged to skilled nursing facilities.[47]

A decision not to attempt CPR must be documented in the patient's medical and nursing records, and all nursing staff must be made aware of it. It is important to be clear what is meant by "cardiac arrest" and for there to be agreement on how the nursing staff should respond if the patient experiences a hypotensive "crash" while on dialysis. These notes may form part of an advance directive, as discussed later.

Withdrawal of Dialysis

It is not possible to predict accurately which patients will gain prolonged benefit from dialysis; thus many nephrologists offer dialysis to all patients with ESRD who wish to have it. This policy ensures that no patients are denied dialysis but has the inevitable consequence that some patients started on dialysis subsequently have an unacceptable quality of life. The possibility of withdrawing dialysis needs to be addressed if these patients are not to suffer unreasonably.

Rates of withdrawal vary widely between countries and cultures. Withdrawal rates in Eastern and Southern Europe are much lower than those in Northern European countries.[48] In the United States, African Americans have about one third the withdrawal rate of Whites. Rates of withdrawal vary across dialysis units and are significantly associated with the medical director's opinion about whether withdrawal is allowed or facilitated in that unit. This suggests that patients' wishes are not always fully included in these decisions.

Patients may be very reticent to express a wish to withdraw from dialysis. Many see it as their duty as a patient to go along with the treatment recommended by their physician and do not wish to appear ungrateful for the efforts that are being made to keep them alive. Their physician may be the last member of the team to learn about the patient's views, and it is very important that good communication exists within the multidisciplinary team so that any clues that the patient gives are acted upon. Staff should adopt a proactive approach and raise the issue of withdrawal of dialysis with patients who are not thriving.

The willingness of patients to engage in a discussion about planning for the end of their life will be affected by factors such as age, ethnicity, cultural background, and religious beliefs, as well as the circumstances of their daily lives. Qualitative research suggests that, when done sensitively, raising the subject of death with patients does not destroy their hope for the future. Early discussion of these issues can lead to a more satisfactory outcome for patients, relatives and staff when the patient eventually dies. In the United States, formal advance directives play an important part in these discussions and helpful guidance on how to conduct sensitive interviews has been published.[49]

In the United Kingdom, dialysis teams may enter patients on an "at risk" register so they can receive appropriate assessment and care. The dialysis unit should have close links with palliative care specialists so there is a smooth transition from maintenance to palliative dialysis, where priority is given to symptoms and person-centered outcomes. Palliative care for people with kidney disease is discussed further in Chapter 112. Patients who take a long time to recover after a dialysis treatment may benefit from reducing the number of treatments per week.[50]

When a patient is no longer competent to make a decision, an advance directive can provide a clear legal basis for the decision to stop dialysis. Indeed, some American states (e.g., Missouri and New York) insist that dialysis must be continued in the absence of such clear and convincing written evidence. In other U.S. states and the United Kingdom, the physician is given the task of deciding on the patient's behalf. Helpful advice for dialysis staff and patients wishing to complete an advance directive is available in the RPA Clinical Practice Guideline Toolkit (see Fig. 90.9).[42]

Once a patient has expressed a wish for dialysis to be withdrawn, or his or her relatives have raised the issue, the first priority must be to identify any reversible factors that may improve the patient's health sufficiently for the decision to be reversed. In particular, any depression must be identified and treated. Once all these factors have been ruled

BOX 90.3 Key Principles Underlying the Process of Withdrawal of Dialysis

- The ultimate responsibility for the decision rests with the physician, not the relatives or caregivers.
- The patient's interests and dignity should be protected at all times.
- The process should not be rushed. If there is any doubt about the correctness of the decision, treatment should continue.
- There should be an open discussion among the multidisciplinary team to avoid any damaging disagreements.
- The psychological needs of the health care team should not be overlooked.
- Palliative care must be given in the most appropriate environment (e.g., a hospice or, ideally, the patient's own home).

out, the process of withdrawing dialysis should be managed according to some key principles (Box 90.3).

Withdrawing dialysis should not be seen as an admission of failure but as a final stage in the process of RRT. The opportunity for patients to complete unfinished emotional and financial business can make the subsequent bereavement period much less traumatic. Managing this terminal phase can be uniquely rewarding, particularly if it allows a patient and his or her family and caregivers to prepare themselves for the patient's death.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following provides the *best* outcomes in a patient with advanced chronic kidney disease (CKD)?
   A. Deceased donor transplant
   B. Preemptive living donor transplant
   C. Home hemodialysis
   D. Peritoneal dialysis
2. Early initiation of dialysis is associated with:
   A. Improved patient survival
   B. Improved quality of life
   C. Decreased morbidity
   D. Higher health care costs
3. Dialysis should be started in a patient with advanced CKD when:
   A. Estimated glomerular filtration rate (eGFR) is less than 15 ml/min/1.73 m^2 (CKD stage 5)
   B. Urine output is decreased
   C. The patient develops clinical and biochemical features of azotemia
   D. Serum bicarbonate is less than 20 mEq/L
4. A decision to transfer a patient to multidisciplinary renal care should be made when:
   A. The patient develops symptoms of renal failure
   B. The eGFR reaches 10 ml/min/1.73 m^2
   C. The patient is in CKD stage 4 with stable eGFR
   D. The trajectory of eGFR indicates a likely need to start RRT within the next 12 months
5. The nephrologist may withhold dialysis from a patient with end-stage renal disease:
   A. If the patient has verbally expressed his or her wish not to have dialysis
   B. If it is against the judgement of the nephrologist
   C. If the patient is disruptive on dialysis
   D. If the dialysis nurses do not wish to continue dialysis
6. Which of the following is *not* predictive of a poor prognosis on dialysis?
   A. Karnofsky performance status score less than 40
   B. Severe chronic malnutrition
   C. Age older than 75 years
   D. Physician would not be surprised if the patient died within the next 6 months

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Vascular Access for Dialytic Therapies

Jan H. M. Tordoir

Functional vascular access is needed for all extracorporeal dialytic therapies and remains the lifeline for patients treated with chronic hemodialysis (HD). The ideal HD access should have a suitable superficial vein that allows for cannulation in two places more than 5 cm apart and delivers blood flow for effective dialysis, usually of the range 400 to 1500 ml/min. A vascular access should have good primary patency, have a low risk for complications and side effects, and leave opportunities for further procedures in the event that patency or flow rates are compromised. Ideally, a first access should be an arteriovenous fistula (AVF) placed peripherally at the wrist. However, upper arm and lower limb access sites are increasingly used because the contemporary dialysis patients (typically older and with multiple comorbidities) often have poor and diseased arm vessels that may be unsuitable for the creation of a simple wrist fistula.

Vascular access should be created with minimal delay by a surgeon experienced in vascular access creation and ideally in time to avoid the use of a central venous catheter (CVC) for initiation of dialysis. CVC use should be minimized because of the increased risk for sepsis and the development of central venous stenosis or thrombosis, which compromises further access in the upper limbs. Dialysis catheters are also associated with excess mortality compared with arteriovenous access, although it is uncertain whether this association is causal. Unfortunately, many patients require a CVC either to start dialysis or as a bridge between the failure of a permanent access and the creation of a new AVF.[1]

Many accesses eventually require surgical revision to manage access-related complications, including thrombosis, central venous obstruction, and ischemia. A multidisciplinary approach to access creation and maintenance (involving nephrologists, interventional radiologists, access surgeons, and dialysis nurses) appears helpful for optimizing HD access–related outcomes and minimizing costs.

EVALUATION OF THE PATIENT FOR VASCULAR ACCESS

The earlier a patient with chronic kidney disease (CKD) is seen by a vascular access surgeon, the better the chance for the patient to have a well-functioning access at the initiation of HD. An early decision on the type, side, and site of the first vascular access will be based on the following:

- *Clinical examination* with careful palpation of arterial pulses and venous vasculature. Particular attention is paid to the venous filling capacity, with use of a blood pressure cuff and variable pressures, and to the presence of venous collaterals and swelling. The nondominant arm is not necessarily the preferred side, and the decision should be based on the quality of the vessels.
- *Vascular mapping by Doppler ultrasound.* This provides information about the venous vasculature (particularly in obese patients and in the upper arm) and the diameter of the brachial, radial, and ulnar arteries; detects vascular calcifications; and reveals the blood flow volume in the brachial artery. The resistance index (a measure of arterial compliance) can be calculated from the differences between the high-resistance triphasic Doppler signal with clenched fist and the low-resistance biphasic waveform after the fist is released. A preoperative resistance index of 0.7 or higher in the feeding artery indicates insufficient arterial compliance (often associated with arterial calcification), so the chance of successful creation of an AVF is reduced. Current guidelines recommend ultrasound mapping in all patients. Additional angiography and/or phlebography is needed only in very difficult cases or in patients with previous ipsilateral CVCs to rule out central vein obstruction; the use of radiocontrast media should be minimized.

Preservation of veins during the earlier stages of CKD is crucial for the success of vascular access. Patients should be instructed to protect their veins, restricting blood sampling and intravenous cannulas to the dorsum of the hand whenever possible.

PRIMARY AUTOGENOUS VASCULAR ACCESS

Radiocephalic Arteriovenous Fistula

A well-functioning distal radiocephalic AVF in the nondominant arm is the ideal permanent access for HD. This usually gives adequate blood flow and a long length of superficial vein for needling. It also leaves proximal sites for further procedures in the event of failure. A distal radiocephalic AVF should be possible in a majority of incident patients but may be compromised if the cephalic and antecubital fossa veins are unusable because of thrombophlebitis and/or thrombosis from previous intravenous cannulas or venipunctures.

A radiocephalic AVF is usually created at the wrist but can be created more proximally in the forearm if distal vessels are inadequate (Fig. 91.1). On occasion, three or four radiocephalic AVFs can be created at progressively more proximal sites in the forearm before a brachiocephalic AVF is created. The radiocephalic AVF at the wrist was initially described as a side-to-side anastomosis, but an end-to-side configuration is preferred by most to reduce the risk for venous hypertension in the radial aspect of the hand.

The patency of radiocephalic fistulas varies from center to center, and reported primary failure rates vary from 5% to 41% and 1-year patency rates from 52% to 71% (Table 91.1).[2-7] Early thrombosis and nonmaturation of an AVF in the older comorbid population, who have poor upper limb vessels, are the major causes of these high primary failure and low patency rates. The patency of radiocephalic AVFs is

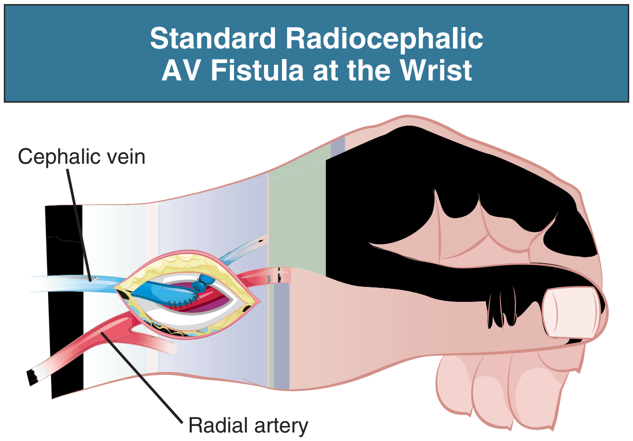


Fig. 91.1 **Standard radiocephalic arteriovenous fistula at the wrist.** Anastomosis of end of vein to side of artery.

TABLE 91.1 Early Failure and 1-Year Patency Rates of Radiocephalic Arteriovenous Fistulas

Author	Year	Number of Fistulas	Early Failure (%)	1-Year Patency (%)
Ravani et al[2]	2002	197	5	71
Rooijens et al[3]	2005	86	41	52
Korten et al[5]	2007	148	11	57
Biuckians et al[6]	2008	80	37	63
Goh et al[4]	2016	204	12	66
Wilmink et al[7]	2016	689	26	70

poorer in women, so a proximal elbow or upper arm AVF might be preferable if the forearm cephalic vein or radial artery is small.

Nonmaturation of Radiocephalic Arteriovenous Fistula

The autogenous radiocephalic AVF needs time to mature and for the vein to enlarge to a size at which it can be needled for dialysis. Usually 6 to 10 weeks for maturation is advised. Earlier cannulation can damage the thin veins. Nonmaturation rates vary from 25% to 33%. The essential components of a successful AVF are a sufficient vein diameter of 4 to 5 mm for needling and a high blood flow so that blood can be drawn from the fistula at 300 to 400 ml/min. This requires a fistula flow of at least 400 ml/min to prevent excessive recirculation and to permit adequate dialysis within the usual 4-hour time frame of HD treatment. Fistulas that fail immediately are the consequence of poor selection of vessels or poor technique. Regular duplex ultrasound investigation early after AVF formation, especially in fistulas that are not maturing, can detect poor flow, stenosis, and accessory branches, guiding the interventional radiologist and surgeon to the appropriate treatment. A randomized controlled trial (RCT) compared brachial plexus block (BPB) with local anaesthesia for AVF creation and showed superiority of BPB, with significant improvement in the primary outcome of patency at 3 months. Consideration should therefore be given to using BPB for all AVF creation.[8]

SECONDARY AUTOGENOUS VASCULAR ACCESS

Although a primary radiocephalic AVF is preferable, the first-choice procedure is increasingly an upper arm AVF with use of an autogenous superficially located arm vein, especially in the dialysis population with comorbidities such as diabetes mellitus, coronary heart disease, and peripheral arterial occlusive disease.[1]

The upper limb is preferred to the lower limb for vascular access because of the ease of cannulation, comfort for the patient, and considerably lower incidence of complications. Similarly, autogenous conduits are preferable to the use of prosthetic grafts because of better patency and lower risk for infection.

Forearm Cephalic and Basilic Vein Transposition and Elevation

Vein transposition or elevation increases the possibilities for creating a forearm fistula. The cephalic vein is preferred, but if it is unsuitable, the more deeply located basilic vein can be transposed from the ulnar to the radial side along a straight subcutaneous course from the elbow to the radial artery. Alternatively, an anastomosis from the basilic vein to the ulnar artery can be performed with additional volar transposition to facilitate needling for dialysis.

Different surgical techniques (with or without vein transposition) have been advocated according to the forearm artery and vein location. In one study,[9] 91% fistula maturation was achieved with a range of techniques; 15% were suitable for a straightforward AVF, 33% required vein transposition from dorsal to volar for anastomosis to the appropriate artery, and the remaining 52% required superficial transposition of a vein on the volar aspect of the forearm before arterial anastomosis. Primary patency rates were 84% at 1 year and 69% at 2 years.

Cannulation of fistulas may be difficult, particularly in obese patients. Vein elevation or transposition techniques can be applied in these patients with radio and/or brachiocephalic AVFs and cannulation difficulties; the primary failure rate is 15%, with a 1-year patency rate of 84%. Alternatively, surgical lipectomy or liposuction can be performed to facilitate cannulation of deeply located fistulas.[10]

Elbow and Upper Arm Cephalic Vein Arteriovenous Fistula

The brachiocephalic and antecubital configurations can be used for AV anastomoses in the elbow region. If possible, the anastomosis can be created between the cephalic, cubital, or perforating vein and the brachial artery 2 cm distal to the elbow, which optimizes opportunities for cannulation along the cephalic vein in the upper arm (Fig. 91.2). The outcome of the brachiocephalic AVF is usually good, with a high primary function rate and good long-term patency; studies show a 10% early failure rate caused by nonmaturation and an 80% 1-year patency rate.[11,12] Two-year primary, assisted primary, and secondary patency rates were 40%, 59%, and 67%, respectively. (Primary patency is functioning access without any intervention; assisted primary patency is functioning access after preemptive intervention for flow decline; secondary patency is functioning access after intervention for thrombosis.) Predictors of failure include diabetes mellitus and a history of contralateral forearm AV graft (AVG; indicating poor vessels). Therefore the primary patency of brachiocephalic fistulas is comparable to that of radiocephalic fistulas. The early failure and 1-year patency rates of brachiocephalic AVFs are shown in Table 91.2.[11-15]

Upper Arm Basilic Vein Arteriovenous Fistula

The upper arm basilic vein is usually inaccessible for dialysis cannulation because of its medial and deep position. Therefore the basilic vein needs to be superficialized and transposed to an anterolateral position. The original technique of brachiobasilic AVF construction is a two-step approach. First, a brachiobasilic anastomosis is constructed, and in the second operation, usually after 6 weeks, the arterialized vein is mobilized into a subcutaneous position, becoming accessible for needling

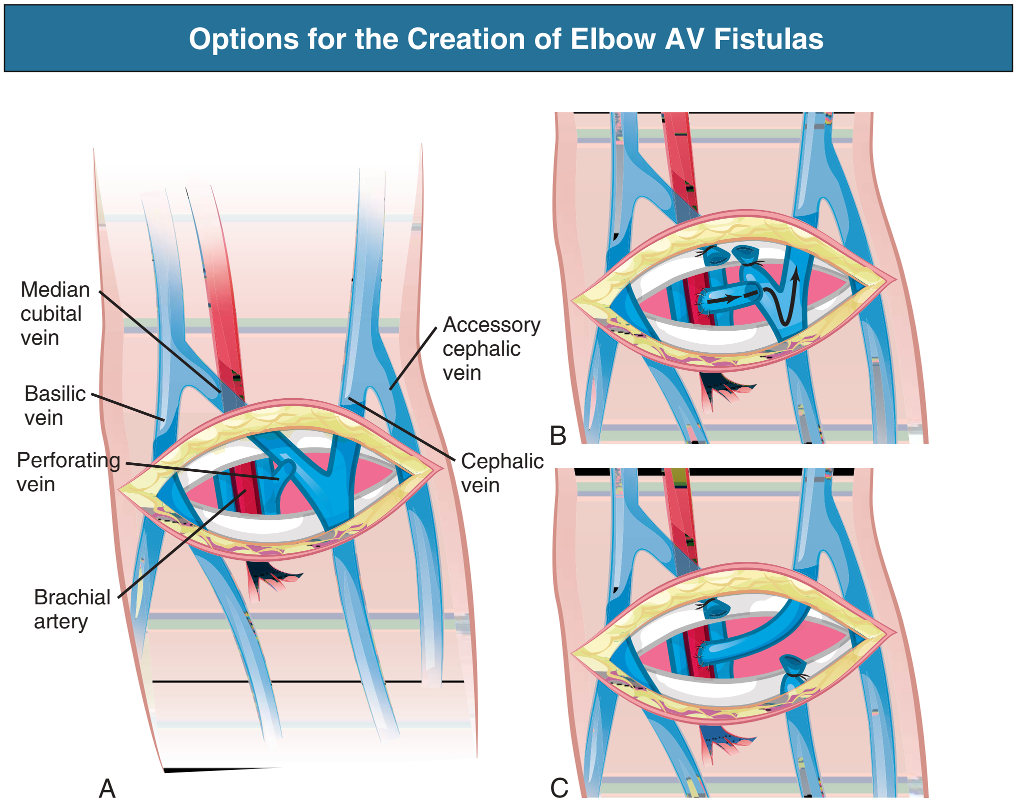


Fig. 91.2 Options for the creation of elbow arteriovenous fistulas (AVFs). (A) Anatomy of arterial and venous vessels in the elbow. (B) Brachio-perforating vein AVF with ligation of proximal cubital vein. (C) Brachiocephalic AVF.

TABLE 91.2 Early Failure and 1-Year Patency Rates of Brachiocephalic Arteriovenous Fistulas

Author	Year	Number of Fistulas	Early Failure (%)	1-Year Patency (%)
Zeebregts et al[12]	2005	100	11	79
Lok et al[11]	2005	186	9	78
Woo et al[14]	2007	71	12	66
Koksoy et al[13]	2009	50	10	87
Ayez et al [15]	2012	87	8	83

TABLE 91.3 Early Failure and 1-Year Patency Rates of Brachiobasilic Arteriovenous Fistulas

Author	Year	Number of Fistulas	Early Failure (%)	1-Year Patency (%)
Harper et al[18]	2008	168	23	66
Keuter et al[19]	2008	52	2	89
Koksoy et al[13]	2009	50	4	86
Field et al[20]	2011	140	26	69
Ayez et al[15]	2012	86	6	73
Syed et al[17]	2012	106	19	86

(Fig. 91.3). However, the brachiobasilic AVF creation may be performed as a one-stage surgical procedure, with elevation or transposition of the vein to a subcutaneous and anterolateral position at the time of creation of the AV anastomosis. A nonrandomized study comparing the different techniques of brachiobasilic AVF creation reported 86% to 90% 1-year patencies in all groups, with only 5% to 7% nonmaturation rates.[16] Primary failure rates are 2% to 26% with 1-year secondary patencies varying from 66% to 89% (Table 91.3).[13,15,17-20] In comparison with brachiocephalic fistulas, brachiobasilic AVFs are more likely to mature, although they are more susceptible to late thrombosis. However, studies showed similar patencies of brachiocephalic and brachiobasilic AV fistulas.[13,15]

The technique of subcutaneous placement of the basilic vein has several advantages over forearm or upper arm graft implantation, with less infection and thrombosis. A meta-analysis found that brachiobasilic AVFs have superior primary and secondary patency compared with prosthetic grafts, and the former should therefore be used preferentially in difficult access cases.[21]

NONAUTOGENOUS PROSTHETIC VASCULAR ACCESS

When autogenous AVF creation is impossible, graft implantation should be considered as a vascular access conduit. Xenografts such as the ovine sheep graft (Omniflow) are popular materials as an alternative access conduit, with acceptable patency and low infection rates. The most frequently used implants are prosthetic grafts made of either polyurethane (Vectra) or polytetrafluoroethylene (PTFE). These prosthetic

Transposed Brachiobasilic AV Fistula

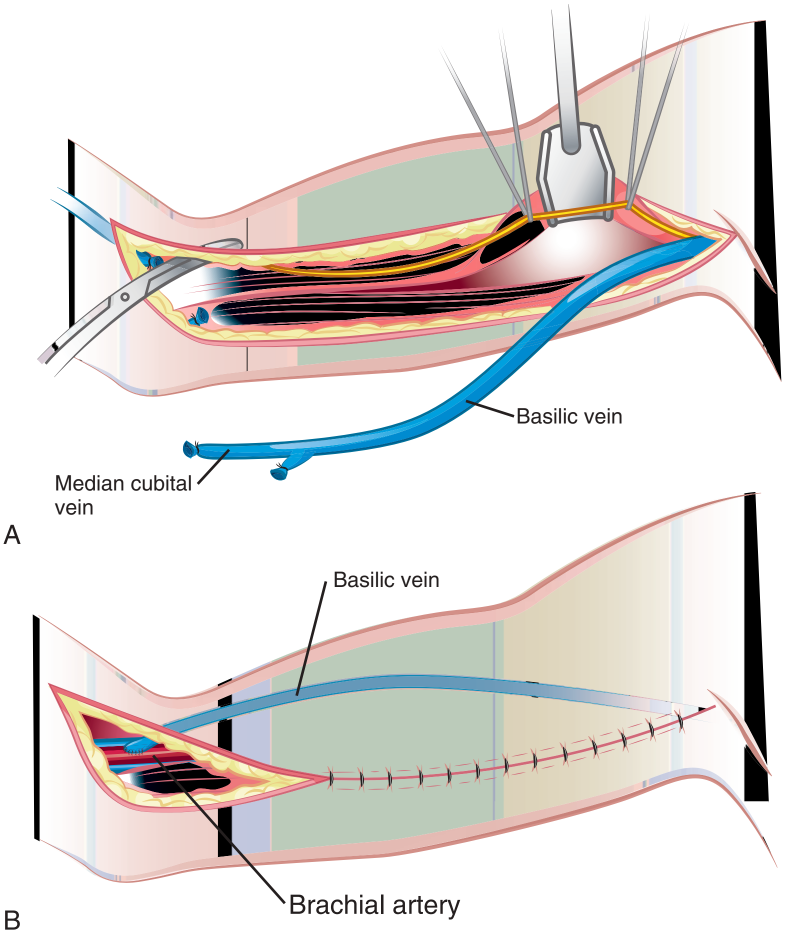


Fig. 91.3 Transposed brachiobasilic arteriovenous fistula (AVF). (A) Dissection of the basilic vein. (B) Anterolateral transposition and brachial artery anastomosis.

grafts can be implanted in a wide variety of locations and configurations in the upper limb (Fig. 91.4). At present, early cannulation of PTFE grafts (within 24 hours of surgery) is feasible because of newer graft compositions. Short-term functional patency is usually good, but stenosis (mostly at the graft-vein anastomosis) may lead to thrombotic occlusion within 12 to 24 months. The primary patency rates of prosthetic AVGs vary from 60% to 80% at 1 year and from 30% to 40% at 2 years of follow-up. Secondary patency ranges from 70% to 90% and from 50% to 70% at 1 and 2 years, respectively.[22-25] Intimal hyperplasia, with smooth muscle cell migration and proliferation and matrix deposition, is the major cause of stenosis formation and thrombosis. The cause of the intimal hyperplasia is uncertain, although the high wall shear stress, caused by the access flow, may denude the endothelial cell layer, resulting in platelet adhesion and initiation of a cascade of proteins that stimulate the smooth muscle cells to proliferate and to migrate.

Measures to Improve Graft Patency

Numerous studies have defined the influence of graft material and design on AVG patency. Modulating the geometry of the arterial inlet or venous outlet of the graft may have a beneficial effect on intimal hyperplasia. Clinical studies using tapered (at the arterial side of the graft) grafts did not improve patency rates, nor did cuff implantation at the venous anastomosis.[26,27] However, primary patency did improve with the use of a cuff-shaped prosthesis (Venaflo).[28] Grafts such as polyurethane, which are more distensible, could in principle influence intimal hyperplasia by the better matching of the stiff prosthesis with the compliant vein at the anastomotic site; however, in clinical studies, this feature was not of proven benefit.[29]

Because PTFE AVGs are prone to thrombosis, infection, and intimal hyperplasia at the venous anastomosis, tissue-engineered vascular grafts have been developed as a potential solution to these limitations in dialysis access. Preliminary results of human studies suggest these grafts provide safe and functional HD access and warrant further study in RCTs.[30]

PHARMACOLOGIC APPROACHES FOR ACCESS PATENCY

Meta-analysis of three studies suggests that ticlopidine as an adjuvant treatment may increase the patency of AVFs and AVGs, but the duration of follow-up was only 1 month. There was insufficient evidence to determine if there was a difference in graft patency between placebo and other treatments such as aspirin, fish oil, clopidogrel, dipyridamole, warfarin, and sulfinpyrazone. However, the quality of the evidence was low because of short follow-up periods, the small number of studies

Nonautogenous Prosthetic Graft Vascular Access

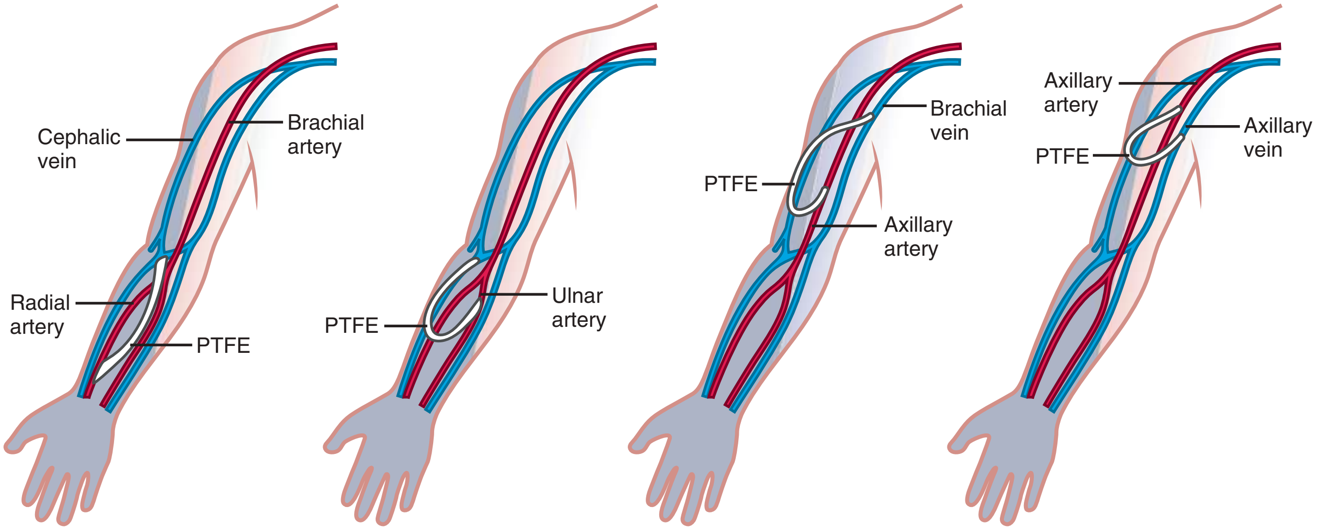


Fig. 91.4 **Nonautogenous prosthetic graft (polytetrafluoroethylene *[PTFE]*) vascular access.** Straight and loop configuration in upper limb.

for each comparison, heterogeneity among trials, and moderate methodologic quality of the studies as a result of incomplete reporting.[31] Warfarin reduces AVG thrombosis but increases the risk for hemorrhage and vascular calcification.[32] A large trial showed that dipyridamole plus aspirin had a significant but modest effect in reducing the risk for stenosis and improving the duration of primary unassisted patency of newly created AVGs.[33] In a large randomized study, clopidogrel improved primary radiocephalic fistula patency but not functional maturation.[34]

There have been suggestions that other drugs such as calcium channel blockers and angiotensin-converting enzyme inhibitors might be associated with improved AVF patency, but this requires confirmation with randomized studies.[35] Fish oil reduced AVG thrombosis in one randomized trial.[36] Clinical trials in patients undergoing AVF and AVG creation, who had perivascular biodegradable collagen wraps with sirolimus placed at the anastomosis, demonstrated safety and feasibility of the sirolimus wrap. An ongoing phase III RCT is assessing the safety, efficacy, and patency outcomes of a perivascular sirolimus-eluting implant placed at the AVF anastomosis in HD patients receiving new AVFs.[37]

LOWER LIMB VASCULAR ACCESS

Probably the only indication for lower limb vascular access is bilateral central venous or caval obstruction, which endangers the outflow of upper limb AVFs. Saphenous and superficial femoral vein transposition is a primary option for thigh AVFs, although this carries a relatively high risk for distal ischemia. If clinical evaluation indicates incipient ischemia, primary flow reduction by tapering of the anastomosis is indicated to prevent complications. Prosthetic graft implantation in the thigh bears a high risk for infection and septicemia.[38]

VASCULAR ACCESS COMPLICATIONS

Nonmaturation of Arteriovenous Fistulas

Fistulas that fail immediately do so as a consequence of poor selection of vessels, poor surgical technique, or postoperative hemodynamic instability. Vascular abnormalities, including stenoses, occlusions, and accessory veins, will be identified in virtually all early failures, and more than half of the stenoses are in the perianastomotic area of nonmatured fistulas. Arterial inflow stenoses of more than 50% vessel diameter reduction coupled with poor flows are seen in less than 10% of nonmaturing fistulas, but if identified, they should undergo angioplasty. Anastomotic and swing segment (in which the vein has been mobilized and swung over to the artery) stenosis may be treated percutaneously or surgically, depending on local expertise.

The diameter of the angioplasty balloon is chosen to correspond to the diameter of the vessel next to the stenotic or occlusive lesion and is usually not smaller than 5 mm for venous stenoses and not smaller than 4 mm for arterial or anastomotic stenoses. Ultra-high-pressure balloons inflatable up to 36 atm are used when necessary to abolish the waist of the stenosis on the balloon. Apart from local infection, contraindications to balloon angioplasty are anastomotic stenoses in fistulas less than 4 to 6 weeks after surgical construction, which increases the risk for anastomotic disruption at angioplasty. Percutaneous balloon angioplasty is further discussed in Chapter 92.

When a surgical approach is selected, matured fistulas that fail should be reconstructed, usually under regional or local anesthesia. The anastomosis is exposed and ligated; the vein then can be divided, mobilized proximally, and reanastomosed to the proximal radial artery. A prospective nonrandomized study of 64 patients showed that outcomes were similar with angioplasty or surgery.[39] Restenosis rates were significantly higher after angioplasty, but overall costs of treatment were similar.

Nonmatured fistulas are rescued by angioplasty of stenoses or occlusions, ligation of accessory veins, or both. Accessory veins can be obliterated through coil embolization, percutaneous ligation, or surgical ligation. The use of coils with a diameter of 1 mm in excess of the target vessel diameter will prevent coil dislocation. In predialysis patients the risk for renal function deterioration as a result of radiocontrast load can be overcome by performance of ultrasound-guided angioplasty of the nonmatured fistula.[40]

Stenosis and Thrombosis

Vessel stenosis in both autogenous AVFs and prosthetic AVGs is usually initiated by intimal hyperplasia caused by migrating and proliferating vessel smooth muscle cells, which form extracellular matrix. Progressive stenosis leads to access flow deterioration and subsequently thrombotic occlusion. Prophylactic repair of access stenoses may prevent thrombosis and prolong access patency.

Autogenous Fistula Stenosis or Thrombosis

AVF stenosis should be suspected if the vessel diameter is reduced by more than 50% and is accompanied by a reduction in access flow (25% flow decline between measurements or absolute flow below 500 ml/min) or in measured dialysis dose. Other indications for diagnostic testing are difficulties in cannulation and prolonged bleeding time after decannulation, indicating high intraaccess pressure caused by outflow vein stenosis. Venous pressure above 250 mm Hg with a blood flow of 200 ml/min is also suggestive of stenosis. In AVFs, 55% to 75% of the stenoses are close to the AV anastomosis, 25% in the venous outflow tract, and 15% in the arterial inflow. In brachiocephalic and brachiobasilic AVFs, the typical location for stenosis (other than the anastomosis) is at the junction of the cephalic with the subclavian vein (cephalic arch) and the basilic with the axillary vein (junctional stenosis). Initial evaluation of suspected access stenosis is by ultrasound; angiography is used subsequently when intervention is planned.

Endovascular treatment by percutaneous transluminal angioplasty (PTA) is the first option for arterial inflow and venous outflow stenoses and junctional stenoses, with the option of stent placement.[41] These techniques are discussed further in Chapter 92. Some stenoses may not be sufficiently dilated by conventional balloons (12 to 16 atm), and in these patients, cutting balloons or ultra-high-pressure balloons (up to 36 atm) may be applied. Drug-eluting balloons may prevent restenosis; however, outcome data for this approach are not yet available. Anastomotic stenoses in forearm and upper arm fistulas are primarily treated with PTA; however, surgical revision with a more proximal reanastomosis for swing segment stenosis is indicated after failed PTA of a radiocephalic AVF.

Fistula thrombosis should be treated as soon as possible because timely declotting allows immediate use of the access without the need for a CVC. Fistula salvage usually requires intervention within 6 hours (grafts may be salvaged up to 24 hours). The duration and site of AVF thrombosis, as well as the type of access, are important determinants of treatment outcome. Thrombi become progressively fixed to the vein wall, which makes surgical removal more difficult. When the clot is localized at the anastomosis in radiocephalic and brachiocephalic fistulas, the outflow vein may remain patent because of continuing flow in its tributaries, making it possible to create a new proximal anastomosis.[42]

Thrombolysis can be performed mechanically or pharmacomechanically. Whereas the immediate success rate is higher in AVGs than in autogenous AVFs (99% vs. 93% in forearm fistulas), the primary patency rate of the forearm AVF at 1 year is much higher (49% vs. 14%). One-year secondary patency rates are 80% in forearm and 50% in upper arm AVFs.[43]

Arteriovenous Graft Stenosis or Thrombosis

The most common cause of graft dysfunction and thrombosis is venous anastomotic stenosis. Because grafts should be implanted only in patients with exhausted peripheral veins, vein-saving procedures such as PTA or patch angioplasty are preferred to graft extensions to more central venous segments. When a stent or a patch fails, graft extension is still possible. Graft monitoring by access flow measurement is recommended; with preemptive endovascular treatment, this may diminish graft thrombosis but does not extend graft patency.

Intragraft (or midgraft) stenoses are found in the cannulation segment of grafts. They result from excessive ingrowth of fibrous tissue through puncture holes. These stenoses can be treated by PTA, graft curettage, or segmental graft replacement. When only a part of the cannulation segment is replaced, the access can be used immediately for HD without the need for a CVC. When restenosis occurs in a nonexchanged part of the graft, this can be replaced after healing of the new segment.

Prosthetic graft thrombosis can be treated with various percutaneous techniques and tools, including combinations of thromboaspiration, thrombolytic agents such as tPA, and mechanical thrombectomy. An initial success rate of 73% and primary patency rates of 32% and 26% at 1 and 3 months, respectively, are reported.[43] It is important to perform thrombolysis as soon as possible to avoid the need for a CVC and as an outpatient procedure to decrease costs, whenever possible. Postprocedural angiography to detect and correct inflow, intraaccess, or venous outflow stenosis is mandatory.

When endovascular treatment fails or is not possible, surgical thrombectomy may be performed with a Fogarty catheter after venotomy, with correction of the underlying obstruction. On-table angiography should be performed after completion of thrombectomy of both the arterial and venous limbs of the graft.

Central Venous Obstruction

In the majority of patients, central vein obstruction is a result of previously inserted CVCs or pacemaker wires. In 40% of patients with subclavian vein and 20% with jugular vein catheters, venous stenosis or occlusion will develop. Chronic swelling of the access arm is the most important sign, usually with prominent superficial collateral veins around the shoulder. The indications for intervention by PTA and stent placement are severe and disabling arm swelling, finger ulceration, and pain or inadequate HD. Contrast angiography of the access and complete venous outflow tract must be performed; ultrasound is not suitable for examining the central veins because of their retroclavicular location.

Endovascular Intervention

Endovascular intervention is the first treatment option for central venous obstruction. PTA alone results in patency rates of only 10% or less at 1 year, and numerous restenoses may develop. Primary or additional stent implantation gives a much better outcome, with 1-year patency rates up to 56% or higher.[44,45] Reinterventions are usually required to maintain patency and achieve long-term clinical success.

Stent placement should avoid overlapping the ostium of the internal jugular vein because this vein is essential for future placement of CVCs. Similarly, a stent placed in the innominate vein should not overlap the ostium of the contralateral vein; otherwise, contralateral stenosis may occur and preclude future use of the contralateral limb for access creation.

Surgical Intervention

When interventional treatment of central venous obstruction fails, surgical revision with bypass grafting is indicated. Surgical bypass to the ipsilateral jugular vein or contralateral subclavian or jugular vein is the first option in these patients. Alternative surgical approaches for upper limb vascular accesses with compromised venous outflow are axillary vein to femoral, saphenous, or popliteal vein and right atrial bypasses.[46] In case of bilateral obstruction of the mediastinal veins, including the superior vena cava, it will not be possible to sustain upper limb access and lower limb access will be required.

Ultimately, ligation of the upper limb access can be considered, which will relieve local symptoms but sacrifices a valuable dialysis access.

Vascular Access–Induced Ischemia

Vascular access–induced upper limb ischemia is a serious complication that without prompt intervention may lead to amputation. The incidence of symptomatic ischemia varies from 2% to 8% of the HD population.[47] Elderly patients, diabetics, patients with prior ipsilateral AV access, and those with peripheral or coronary arterial occlusive disease are most at risk for ischemia. Access-induced ischemia occurs more often with proximally located fistulas and high flow rates; such AVFs can induce a steal phenomenon with lowering of distal perfusion pressures, and when collateral circulation is inadequate, symptoms may occur. Pain during HD is a characteristic early symptom. A grade 1 to 4 classification for access-induced ischemia can be used to outline the severity of the disease; this ranges from minor symptoms to finger necrosis.[48]

- *Grade 1:* Pale and blue or cold hand without pain
- *Grade 2:* Pain during exercise or HD
- *Grade 3:* Ischemic pain at rest
- *Grade 4:* Ulceration, necrosis, and gangrene

For grades 1 and 2, conservative treatment of ischemia is advocated. With grades 3 and 4, interventional treatment is mandatory.

Diagnosis of Ischemia

Physical examination, including observation and palpation of peripheral vessels, may be inadequate and misleading for the diagnosis of symptomatic ischemia. Additional noninvasive testing with measurement of digital pressures and calculation of the digit-brachial index, transcutaneous oximetry ($TcPo_2$), ultrasound of forearm arteries, and access blood flow measurement are important steps in the diagnosis and decision making process.[49] Finally, contrast angiography with visualization of the upper extremity arterial tree from the proximal subclavian artery to the distal palmar arches with and without AVF compression to enhance distal flow is obligatory to outline the strategy for treatment and determine whether interventional or surgical options are preferred.

Endovascular and Surgical Management of Ischemia

The treatment strategy depends on the cause of the ischemia. Inflow arterial obstruction and distal arterial lesions are recanalized with small-caliber balloons or stent placement[50]; high-flow AVFs are suitable for flow-reducing procedures such as access banding and arterial inflow reduction by an interposition graft to a smaller forearm artery (revision using distal inflow) (Fig. 91.5).[51,52] Steal in itself may be cured by ligation of the artery distal to the AV anastomosis (distal radial artery ligation). In most patients, it is necessary to add a saphenous vein or prosthetic graft bypass to the forearm arteries to augment distal hand perfusion (distal revascularization–interval ligation [DRIL] procedure) (Fig. 91.6). The results of these procedures are usually good, with relief of symptoms and preservation of the access site (Table 91.4).[53-57] A simpler alternative to the DRIL procedure is the proximal AV anastomosis technique, in which the AV anastomosis at the elbow is disconnected and moved to the axilla, with anastomosis to the axillary artery by means of a graft interposition.[58] The minimally invasive limited ligation endoluminal-assisted revision procedure has been described; this procedure uses a minimally invasive percutaneous technique with banding of the access over a 4-mm balloon.[59]

Intraoperative digital pressure measurement (or $TcPo_2$) is mandatory to guarantee an adequate surgical intervention with acceptable outcome. A digital-brachial pressure index above 0.60 or $TcPo_2$ above 40 mm Hg is indicative of sufficient distal hand perfusion. In some patients, AVF ligation and transition to chronic catheter dialysis access

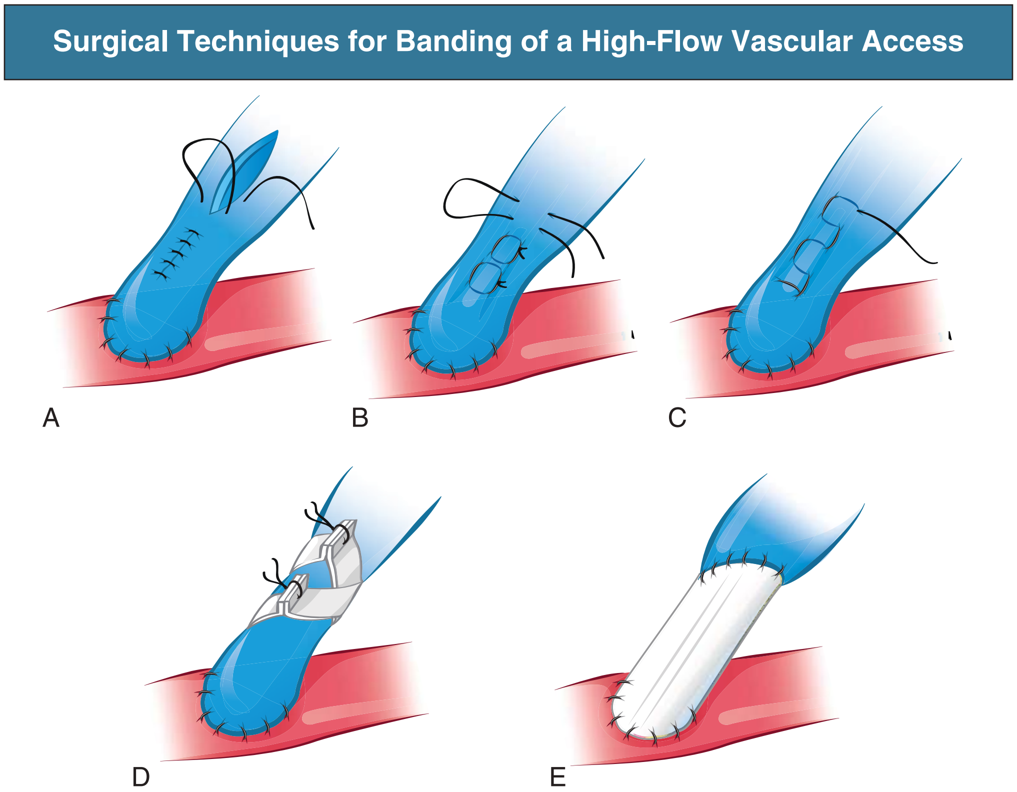

Surgical Techniques for Banding of a High-Flow Vascular Access
A
B
C
D
E

Fig. 91.5 Surgical techniques for banding of a high-flow vascular access. (A) Open venoplasty. (B) Interrupted mattress suturing. (C) Continuous mattress suturing. (D) Polytetrafluoroethylene (PTFE) banding. (E) PTFE interposition graft. The choice of technique is made by the surgeon on a case-by-case basis.

or a change in renal replacement modality to peritoneal dialysis may be the only solution.

CENTRAL VENOUS CATHETER ACCESS

CVCs are widely used as vascular access for HD despite practice guidelines to the contrary. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS)[60] indicate that 15% of HD patients in the United States are dialyzed with catheters; in other countries the use of catheters is even more common (Canada, 45%; Belgium, 38%; United Kingdom, 16%). CVCs are the preferred vascular access only for patients who present with acute kidney injury and patients with CKD without permanent AV access or with failed vascular access. Two types of catheters are used in practice: nontunneled catheters for short-term dialysis, with a limited use and high morbidity, and tunneled cuffed catheters, which can be used for up to several months with lower morbidity. The physical characteristics (i.e., design and geometry) not only influence the performance (blood flow rate, recirculation, and resistance) but also affect the overall efficiency of the HD therapy and morbidity risk (infection, thrombosis).

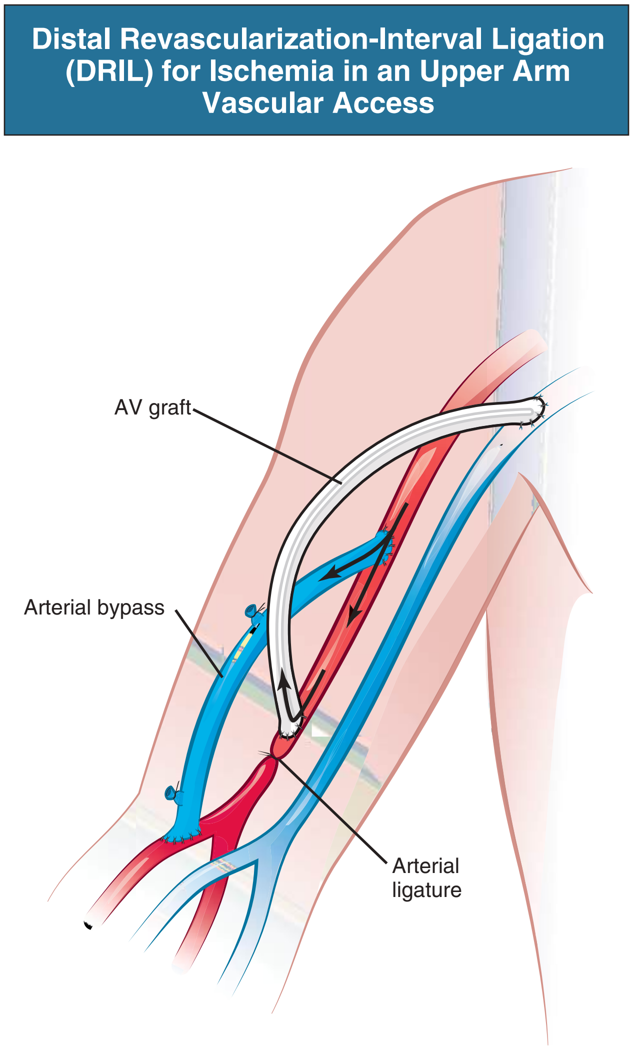

Distal Revascularization-Interval Ligation (DRIL) for Ischemia in an Upper Arm Vascular Access
AV graft
Arterial bypass
Arterial ligature

Fig. 91.6 Distal revascularization–interval ligation for ischemia in an upper arm vascular access. *AV,* Arteriovenous.

Nontunneled Catheters

Single- or double-lumen catheters are usually made of polymers (polyethylene, polyurethane), enabling a simple and direct implant possibility. The length of the catheter must be chosen in accordance with the insertion site. The femoral route requires catheters of 30 to 35 cm in length for the distal tip to be located in the inferior vena cava. The internal jugular vein route needs shorter catheters of 20 to 25 cm in length, with tip location at the inferior vena cava and right atrium junction. The subclavian vein should not be used because of the very high risk for subsequent venous stenosis. For sufficient blood flow rates to be achieved, the diameter of these catheters must be ideally 12 to 14 French. It is recommended that the use of nontunneled catheters not exceed 7 days.

Tunneled Catheters

Tunneled CVCs have two lumens, each having a length of 40 cm, 10 cm of which is tunneled under the skin; the cannulae are made of synthetic polymer with a large internal lumen and a Dacron cuff to ensure subcutaneous anchoring. The catheter characteristics rely on the type of polymer, design, and geometry (double-lumen catheters, dual catheters, split catheters). The use of tunneled CVCs is associated with reduced morbidity as well as better and constant performance compared with uncuffed catheters.[61]

Both tunneled and nontunneled catheters are inserted percutaneously by the Seldinger technique with ultrasound guidance. These techniques are described in Chapter 92. The internal jugular vein and femoral vein routes are preferred because of ease of implantation and low risk for complications, such as central vein stenosis (Fig. 91.7).

Catheter Infection

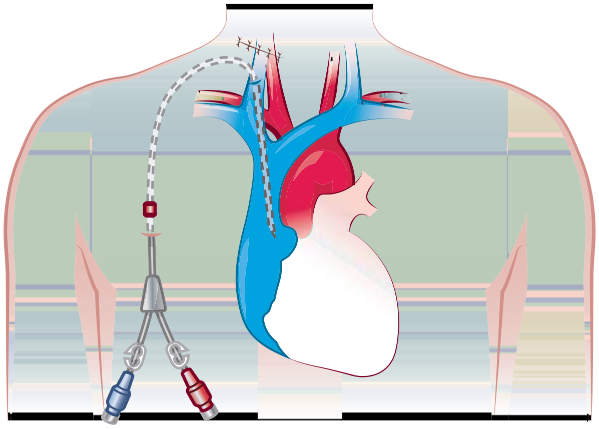
Catheter-related bloodstream infections are a significant cause of morbidity and mortality in HD patients. Results of the Hemodialysis (HEMO) study indicate that CVC use is associated with a relative risk for mortality

TABLE 91.4 Results of the Distal Revascularization–Interval Ligation Procedure for Vascular Access–Related Ischemia

Author	Year	Number of Fistulas	Ischemia Cured (%)	Ischemia Improved (%)	Ischemia Not Improved (%)	Access Patency (%)
Knox et al[53]	2002	55	66	25	9	86
Walz et al[54]	2007	36	100	—	—	54
Huber et al[55]	2008	64	78	NS	NS	68
Scali et al[56]	2013	134	82	—	18	85
Leake et al[57]	2014	56	98	NS	NS	100

NS, Not stated.

of 3.4 compared with patients with AVFs. Switching from CVCs to AVFs decreases the relative mortality risk to 1.4.[62] The most likely explanation for this increased mortality risk is infection and sepsis related to the CVC, including exit site infection. Typical infection rates are three episodes of infection per 1000 tunneled catheter–days and higher with nontunneled catheters.[63] These localized infections can progress to metastatic complications of osteomyelitis, septic arthritis, epidural abscess, and endocarditis. Various societies have issued recommendations for the management of catheter infections.[64] A recommended treatment algorithm is shown in Fig. 91.8.



Tunneled Cuffed Double-Lumen Central Venous Catheter Inserted in the Right Internal Jugular Vein

Fig. 91.7 Tunneled cuffed double-lumen central venous catheter inserted in the right internal jugular vein.

Infections Involving Temporary Catheters

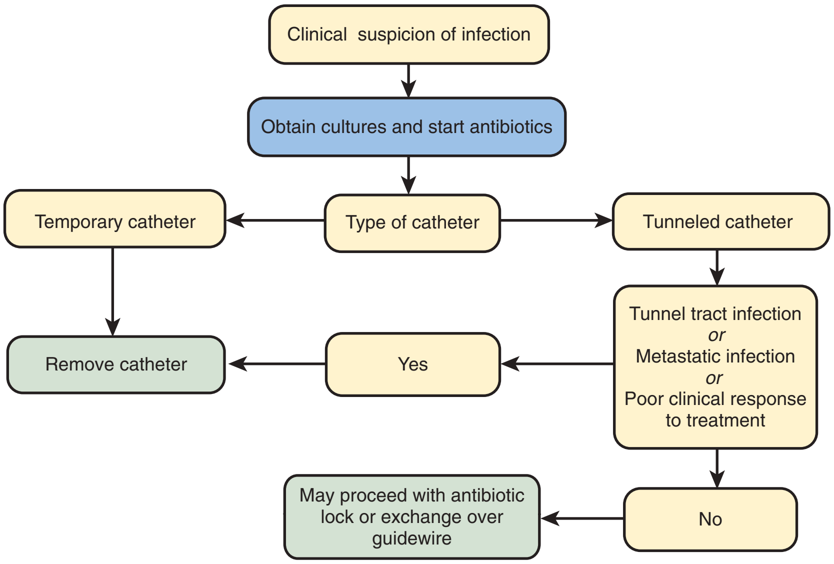
When a temporary dialysis catheter becomes infected, it should always be removed. There is no role for trying to salvage temporary catheters.[64]

Exit Site Versus Tunnel Tract Infections

An exit site infection is a localized cellulitis confined to the 1 to 2 cm where the catheter exits the skin. The majority of these infections respond well to systemic antibiotics and meticulous exit site care, and the removal of the catheter is generally not required.[64] However, exit site infections can progress to tunnel tract infections, which involve the potential space surrounding the catheter more than 2 cm from the exit site (Fig. 91.9). Patients with a tunnel tract infection sometimes but not always have an associated exit site infection; untreated, they can rapidly develop bacteremia. Patients with a tunnel tract infection present with fever as well as local signs of pain, swelling, fluctuance, and erythema along the tract of the catheter. Because tunnel tract infections involve a potential space, in an area with limited vascular supply, and an implanted synthetic material, they respond poorly to antibiotics alone and require catheter removal.[64]

Catheter-Associated Bacteremia

When a patient with a dialysis catheter has a fever, catheter infection always must be considered. If the patient does not have a clear and convincing alternative explanation for the fever, blood culture specimens should be obtained peripherally as well as through the catheter, and the patient should be started on antibiotic therapy, which is subsequently adjusted on the basis of culture results.[64] The most common organism is *Staphylococcus aureus,* although a wide range of gram-positive and gram-negative organisms have been reported (Table 91.5). The percentage of patients with methicillin-resistant *S. aureus* (MRSA) varies greatly across centers, with higher rates associated with greater antibiotic use. An aminoglycoside or a cephalosporin is a good choice for gram-negative coverage; however, local microbiologic epidemiology must be taken into consideration, especially with regard to antibiotic resistance.



Management of Central Venous Dialysis Catheter Infections

Clinical suspicion of infection
Obtain cultures and start antibiotics
Type of catheter
Temporary catheter
Tunneled catheter
Tunnel tract infection *or* Metastatic infection *or* Poor clinical response to treatment
Yes
Remove catheter
No
May proceed with antibiotic lock or exchange over guidewire

Fig. 91.8 Algorithm for the management of central venous dialysis catheter infections. (Modified with permission from reference 64.)

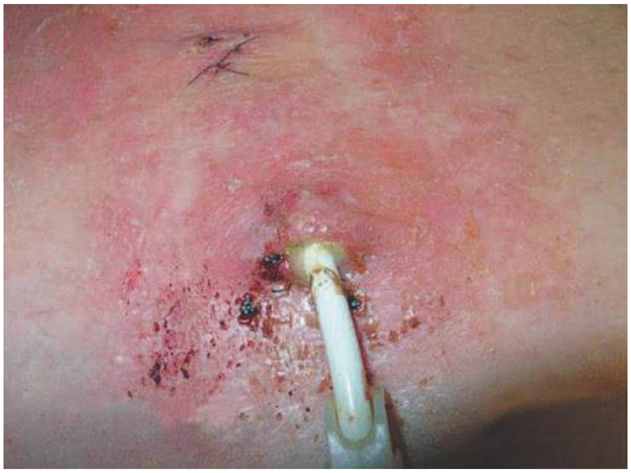


Fig. 91.9 Dialysis catheter tunnel infection. (Courtesy Dr. I. M. Leidig, University Hospital Erlangen, Germany.)

TABLE 91.5 Causative Organisms in Dialysis Catheter Infections

Infection	Organisms	Percent
Polymicrobial		16
Gram positive		89
	Staphylococcus aureus	30
	Staphylococcus epidermidis	37
	Enterococcus	17
	Corynebacterium	5
Gram negative		33
	Enterobacter	11
	Pseudomonas	7
	Acinetobacter	4
	Citrobacter	4
	Serratia	2
	Klebsiella	3
	Other gram-negative organisms	3
Mycobacteria		2

Modified with permission from reference 67.
Numbers do not add up to 100% because 16% of infections were polymicrobial.

Catheter Removal

The decision to remove a tunneled cuffed dialysis catheter because of an episode of catheter-associated bacteremia is not straightforward. The clinical condition of the patient and response to initial therapy, the presence of metastatic complications, the infecting organism, and the availability of other vascular access sites must be taken into consideration before a treatment plan is selected (see Fig. 91.8).

The conventional approach is to remove the catheter with interval replacement at a different site after the infection has resolved. Although this is effective, it leads to an additional temporary catheter if dialysis is needed before the catheter can be replaced. Attempts to salvage an infected catheter with systemic antibiotic therapy lead to resolution of infection in only about 30% of patients. Another treatment option is to combine systemic antibiotics with antibiotic “lock” solutions. Many different combinations of antibiotics mixed with either heparin or citrate have been tested; a popular regimen is vancomycin 2.5 mg/ml, gentamicin 1 mg/ml, and heparin 2500 U/ml. Infection clearance rates of 50% to 70% are reported with antibiotic locking.

Several studies have reported that exchange of the catheter over a guidewire after 48 hours of antibiotic treatment is more effective than treatment with antibiotics alone and is as effective as removal of the catheter and delayed replacement, with the advantages of only one invasive procedure and preservation of the venous access site.[65] There are no published randomized trials of antibiotic locking or catheter exchange over a guidewire.

Prevention of Infection

The most important measure to prevent catheter infection is meticulous handling of the catheter at all times. The catheter should be inserted with use of maximal sterile precautions. The dialysis nurses need procedures for accessing the catheters under strict sterile conditions, and it is of the utmost importance that these catheters never be accessed by untrained personnel. Compared with unfractionated heparin, citrate catheter locking solutions appear to reduce bleeding and may reduce bacteremia in patients undergoing HD with a CVC. However, it is unclear whether citrate alone has the same protective effect against systemic infection as it does when combined with other antimicrobial agents.[66] Topical application of mupirocin ointment to tunneled exit sites has been reported to reduce the incidence of catheter-associated bacteremia.

Catheter Obstruction

Catheter obstruction may be caused by endoluminal fibrin deposits, restricting the catheter lumen or obstructing catheter side holes at the tip, or external fibrin sleeves surrounding the catheter, resulting in inadequate flow and excessive extracorporeal blood pressure alarms during the dialysis session. Depending on the location of the fibrin clot (arterial or venous line), there may be high negative arterial pressure (obstruction at the arterial catheter line) or high positive venous pressure (obstruction at the venous catheter line).

Prevention of clot formation in the catheter tip during the interdialytic period is crucial. This is achieved by installing an antithrombotic lock solution (trisodium citrate 30%).[67] Catheter malfunction might be treated with regularly urokinase locking. A certain amount of the antithrombotic lock solution may leak into the circulation through side and central catheter holes, facilitating catheter clot formation while increasing risk for hemorrhage. Regular use of low-dose warfarin or antiplatelet agents has failed to improve catheter function in dialysis patients in randomized trials.

To correct catheter dysfunction, it is recommended that the catheter lumen be cleaned periodically by application of a fibrinolytic agent (urokinase) as a lock solution or by continuous infusion into both arterial and venous lines. Occluded catheters are reopened either by a mechanical method (brush) or pharmacologically (urokinase). Removal of the fibrin sleeve may be achieved by Lasso wire stripping or infusion of a fibrinolytic solution (urokinase) for 3 to 6 hours. Alternatively, the catheter may be exchanged over a guidewire.

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SELF-ASSESSMENT QUESTIONS

1. Arteriovenous fistulas (AVFs) are preferable to arteriovenous grafts (AVGs) because of:
   A. Lower early failure rate
   B. Improved ease of cannulation
   C. Better long-term patency
   D. Lower risk of ischemia
2. Ischemia in elbow fistulas with normal access flow (800 ml/min) is best treated by:
   A. Access banding
   B. Distal revascularization–interval ligation (DRIL) procedure
   C. Revision using distal inflow (RUDI) procedure
   D. Distal radial artery ligation
3. Tunneled cuffed central vein catheters are preferred over nontunneled catheters because of:
   A. Ease of insertion
   B. Lower occlusion rate
   C. Higher dialysis flows
   D. Lower infection rate
4. AVFs have a better long-term survival because of:
   A. Lower thrombosis rate
   B. Lower infection rate
   C. Higher access flow
   D. Less frequent aneurysm development
5. The primary treatment option for symptomatic central vein occlusion is:
   A. Percutaneous transluminal angioplasty
   B. Stent placement
   C. Surgical bypass
   D. Vascular access ligation

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Diagnostic and Interventional Nephrology

W. Charles O’Neill, Haimanot Wasse, Stephen R. Ash

A variety of procedures are essential to the care of nephrology patients and include ultrasound, renal biopsy, insertion of hemodialysis (HD) and peritoneal dialysis (PD) catheters, creation of arteriovenous fistulas (AVFs), and diagnostic and interventional procedures to maintain HD access function. These procedures have traditionally been performed by other specialists, but an increasing number of nephrologists perform these procedures. The field of diagnostic and interventional nephrology is most developed in the United States, where the American Society of Diagnostic and Interventional Nephrology (ASDIN) (www.asdin.org) has established training standards and certification procedures. This chapter covers ultrasound, insertion of dialysis catheters, and interventions in vascular access, focusing on the applications of these procedures and their performance by nephrologists. Renal biopsy is covered in Chapter 6, and placement of AVFs and arteriovenous grafts (AVGs) in Chapter 91.

ULTRASOUND

An important reason for nephrologists to be involved in ultrasound procedures is that many of the findings on ultrasound are not specific and require clinical correlation. The role and interpretation of ultrasound are further covered in Chapter 5.

Applications and Limitations of Ultrasound

Ultrasound is an excellent tool for examination of the kidneys and urinary tract. Under optimal conditions, both kidneys, the renal artery and vein, the proximal and distal ureter (when enlarged), and the bladder can be visualized. The ureter is usually apparent only when it is dilated. The middle portion of the ureter is usually obscured by overlying bowel but still may be visible when it is very dilated. In transplanted kidneys, the entire ureter can be visualized, even when it is not markedly dilated, because of the proximity to the probe and the lack of overlying bowel. In very ill patients who cannot be optimally positioned, cannot control their breathing, or have abdominal wounds or distention, views of the kidneys may be limited, but it is still usually possible to determine whether hydronephrosis is present.

Chronic Kidney Disease

Ultrasound is indicated in any patient with chronic kidney disease (CKD) to establish renal size and rule out polycystic kidney disease or urinary tract obstruction. Small, echogenic kidneys indicate severe irreversible disease, eliminating the need for a biopsy.[1]

Acute Kidney Injury

Although the diagnostic yield is very low in patients in whom the basis for renal failure is likely to be acute tubular necrosis or prerenal causes, ultrasound is still indicated in certain patients to rule out obstruction and identify preexisting CKD.[2]

Renal Transplantation

Ultrasound is indicated when there is an acute decline in renal transplant function, because urinary obstruction is common in this setting.[3] In the immediate post-transplantation period, Doppler evaluation of renal blood flow should also be performed to rule out thrombosis. Additional indications in transplant patients are pain, swelling, ipsilateral leg edema, and infection. Another important indication in both native and transplanted kidneys is guidance for percutaneous biopsy, nephrostomy, or drainage of fluid collections.

Renal Biopsy

Ultrasound is the method of choice to guide percutaneous renal biopsy.[4] Computed tomography usually offers no advantages over ultrasound[5] and results in unnecessary irradiation. This is discussed further in Chapter 5.

Urinary Bladder

Ultrasound is the procedure of choice for measurement of postvoid residual volume because it is simple, painless, and sufficiently accurate.[6] Additional indications include checking the location and patency of Foley catheters and examination of the distal ureters. Placement of the catheter in the proximal urethra is uncommon but not rare, and obstruction of catheters is frequent, so examination of the bladder always should be considered when urine output decreases. Prostatic hypertrophy, prostatitis, bladder carcinoma, mucosal edema, blood clots, stones, stents, and other foreign bodies can be recognized with ultrasound, but transabdominal ultrasound is not the appropriate test to rule out bladder cancer (which requires cystoscopy) or prostatic cancer (which requires transrectal ultrasound and biopsy).

Hemodialysis Access

Ultrasound is essential in the management of vascular access, including guidance of catheter insertion, evaluation of fistula dysfunction, preoperative vein mapping, and monitoring of access flow. Of these, the first two can be readily performed by nephrologists. Guidance of catheterization is best performed with a dedicated scanner but can be done with any scanner that has a vascular probe because Doppler imaging is not required. Examination of dysfunctional fistulas is also straightforward and does not necessarily require Doppler analysis. Vessel mapping and monitoring of access flow are both best performed by an experienced vascular technician. Sonography can be very useful in guiding cannulation of fistulas and grafts and in training patients for self-cannulation.[7]

Renovascular Ultrasound

Doppler ultrasound of renal arteries and veins is a difficult study requiring an experienced operator and is not usually practical for nephrologists. Tracings from segmental arteries are more easily obtained and can be useful in diagnosis of renal artery stenosis and vein thrombosis. However, measurement of resistive index can be unreliable and nonspecific because it is influenced by external factors such as systemic blood pressure and heart rate[8] and is of questionable usefulness in the evaluation of acute kidney injury either in native kidneys or transplanted kidneys. Doppler ultrasound is useful in distinguishing between cystic and vascular lesions and between renal vein and ureter.

Equipment

Important considerations in the choice of equipment are image quality, probe type and frequency, cost, size, portability, and output. Image quality is difficult to quantify and is related to the number of elements (crystals) in the probe and the number of channels that can be processed. Probes should be electronic and in the frequency range of 2.0 to 6.0 MHz (up to 7.5 MHz for pediatric use) for abdominal imaging. Preferably, these should be variable-frequency, curvilinear probes. Probes for vascular imaging are usually linear probes with a frequency of 10 to 12 MHz. For grayscale renal ultrasound, portable, lightweight scanners with good image quality are available; Doppler capability is increasingly being offered as a standard feature. Larger and more expensive scanners are difficult to maneuver and have additional features that are of little use to the nephrologist. Controls on the scanner allow adjustment of scanning depth, focal length, time-gain compensation, sound intensity, and grayscale. Although this seems a daunting number of variables, adjustment is usually straightforward and mostly empiric. Images can be printed directly or stored digitally.

Procedure

Description of the scanning procedures cannot substitute for hands-on training because scanning is an acquired skill that requires practice. Ideally, the patient should be fasting for abdominal scanning to minimize interference from intestinal gas, but this is not essential for examination of kidneys and is of no consequence for examination of the bladder or transplanted kidneys. There must be an airtight connection between the probe and the skin, which is accomplished by placing gel on the probe or skin and applying firm pressure against the skin. To avoid compression of the vessels, minimal pressure should be applied for vascular examinations, with the use of more gel. Gel specifically designed for ultrasound should be used because other gels, such as lubricating gel, give poorer image quality. Ambient light should be dimmed to optimize viewing of the monitor.

The patient should be flat in the supine or lateral decubitus position with imaging through the abdomen for examination of native kidneys. Initial attempts should be made with the patient in the supine position before resorting to the lateral decubitus position. Imaging through the back is not recommended for diagnostic imaging because of sound attenuation by muscle and fascia and limitations on angling of the probe. Placement of the ipsilateral arm over the head, removal of pillows from under the head, and deep inspiration aid in moving overlying ribs superiorly. Transplanted kidneys and the urinary bladder are examined with the patient in the supine position, but he or she need not be completely flat.

Initially, longitudinal images should be obtained to determine maximal kidney length. On the right side, this view should be obtained through the liver if possible (Fig. 92.1A). The probe should be oriented so the upper pole is toward the left side of the image. The probe should then be rotated 90 degrees counter-clockwise to obtain transverse views (see Fig. 92.1B), and the kidney is scanned from pole to pole to ensure visualization of the entire kidney. Examination of each kidney should include longitudinal images with adjacent liver or spleen if possible, as well as transverse images through the mid-kidney and each pole.[9] Measurements other than length are not clinically useful, and measurements of kidney volume are inaccurate and no better than length in judging kidney size.[10] Sagittal and transverse views of the urinary bladder are obtained with the probe just superior to the symphysis pubis and angled inferiorly (see Fig. 92.1C and D). Volume is obtained by multiplying the two transverse dimensions and the sagittal length by 0.523.[6] Although there is significant error in this measurement, it is rarely clinically significant. The technique for renal biopsy is discussed in Chapter 6.

Training and Certification

There are no data on what constitutes adequate training for renal ultrasound. Training is required for both performance and interpretation and should include didactic, hands-on, and supervised components. The last can vary considerably, depending on case volume and particularly type because any quantity of studies will be inadequate if the findings are all normal. Thus the number of studies required for competence is inversely related to the frequency of pathology. Minimal qualifications for physician-sonographers have been established by the American Institute of Ultrasound in Medicine[11] and the American College of Radiology,[6] but neither organization has developed guidelines for limited abdominal ultrasound. ASDIN (www.asdin.org) has established training standards for ultrasound limited to kidneys and bladder that specify 50 hours of training and 125 studies (at least 80 being supervised and the remaining having confirmatory follow-up).[11] Because renal ultrasound is not usually a formal component of nephrology training, a course for nephrologists has been established in the United States (http://medicine.emory.edu/renal-medicine/education/ultrasonography-nephrologists.html).[9] Training and certification are available in vascular ultrasound but are not limited to applications specific to nephrology. Such training is important for vascular studies of kidneys but is not necessary for examination of dysfunctional AVFs and AVGs (unless flow is measured) because this does not require Doppler analysis. There are currently no guidelines or training established for vascular ultrasound related to nephrology.

PERITONEAL DIALYSIS CATHETERS

Successful PD depends on proper catheter insertion and management. The feasibility, safety, and success of these procedures when they are performed by nephrologists have been well documented,[13-15] and this can facilitate use of PD. Tenckhoff catheters remain the most popular chronic peritoneal access devices, over 50 years since their description. These catheters are constructed of silicone rubber with a 5-mm external diameter and internal diameters of 2.6 to 3.5 mm and numerous intraperitoneal side-holes. The intraperitoneal portion can be straight, straight with perpendicular silicone disks, or curled have been Several, design modifications were developed to attempt to diminish outflow obstruction, including a version sold in Europe with a weighted tip. The subcutaneous portion is either straight or bent and has one or two extraperitoneal Dacron cuffs that prevent fluid leaks and bacterial migration around the catheter, although one catheter has a silicone ball and Dacron disc at the parietal peritoneal surface. The subcutaneous catheter shapes all provide a lateral or downward direction of the exit site. An upwardly directed exit site collects debris and fluid, increasing the risk for exit site infection. The method of catheter placement has more effect on the outcome than catheter choice does.

Catheter Insertion

The four techniques for PD catheter insertion are dissection (surgical), the Seldinger technique (blind or with fluoroscopy), peritoneoscopic,

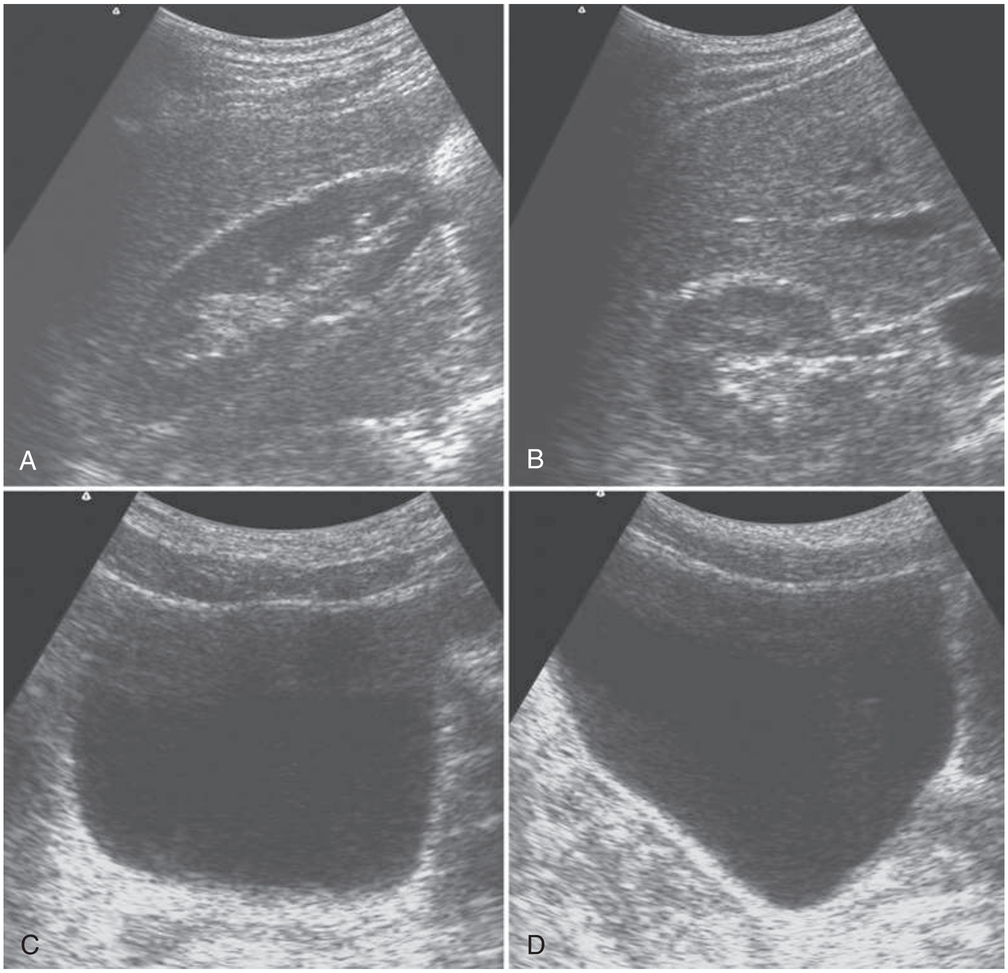

Fig. 92.1 Imaging planes for renal and bladder sonography. (A) Longitudinal image of right kidney. Upper pole should be on left side of the image. (B) Transverse image of right kidney through the renal hilum. (C) Transverse image of urinary bladder. Anteroposterior and mediolateral dimensions are obtained in this plane. (D) Sagittal image of the urinary bladder. Superior portion of the bladder is to the left. Superoinferior dimension is obtained in this plane.

and laparoscopic.[16] The Seldinger and peritoneoscopic techniques are most frequently used by nephrologists. Peritoneoscopic insertion is a single-puncture technique using a small (2.2-mm diameter) optical peritoneoscope for direct inspection of the peritoneal cavity and identification of a suitable site for the optimal intraperitoneal portion of the catheter. Peritoneoscopic placement is usually performed with local anesthesia (sometimes with conscious sedation) and manual infusion of about 1 liter of air. Laparoscopic techniques are performed with the patient under general anesthesia, with larger scopes, multiple insertion sites, and automated gas infusion. Both peritoneoscopic and laparoscopic techniques allow direct visualization of intraperitoneal structures.

The choice of technique must take into account the local experience with complications (pericatheter leakage, outflow failure, exit site and tunnel infection) and long-term catheter function associated with each technique, costs, ease and timely insertion of the catheter, and factors contributing to mortality risk (local vs. general anesthesia). Both randomized and nonrandomized studies have documented that the peritoneoscopic and fluoroscopic Seldinger techniques result in fewer catheter complications (infection, outflow failure, pericatheter leak) and improved catheter survival compared with surgical placement.[14,17] The superior results with peritoneoscopic placement may relate to direct visualization of the abdominal cavity, less tissue dissection, and avoidance of general anesthesia. Because tissue dissection for intermittent peritoneal dialysis is minimal, the catheter can be used immediately (after 36 hours), although a 2- to 3-week delay is recommended.[18]

For peritoneoscopic insertion (Fig. 92.2), a small skin incision (2 to 3 cm) is made and dissection is carried down only to the subcutaneous tissue.[19] The anterior rectus sheath is identified but not incised. A preassembled cannula with trocar and a spiral sheath is then inserted at a 40- to 50-degree angle into the abdominal cavity through the rectus muscle (see Figs. 92.2A and 92.3). The trocar is then removed and replaced by the peritoneoscope to confirm the intraabdominal position of the cannula (see Fig. 92.2B). Air is then infused (600 to 1000 ml) to separate visceral and parietal peritoneum. Alternatively, a Veress needle can be used.[20] Bowel loops, the dome of the bladder, and any intraabdominal adhesions are identified. The cannula and spiral sheath are advanced into the pelvis (see Fig. 92.2C). The cannula and the peritoneoscope are then removed, the spiral sheath is dilated to 6-mm diameter (see Fig. 92.2D), and the catheter is inserted through the sheath by a stylet (see Fig. 92.2E). The deep cuff is implanted into the rectus muscle with use of an implanter tool without dissection of the anterior rectus sheath or the muscle (see Fig. 92.2F). A tunnel and an exit site are created and the superficial cuff is implanted into the subcutaneous tissue. The subcutaneous tissue is sutured with absorbable material,

Steps for the Insertion of a Peritoneal Dialysis Catheter by Peritoneoscopy

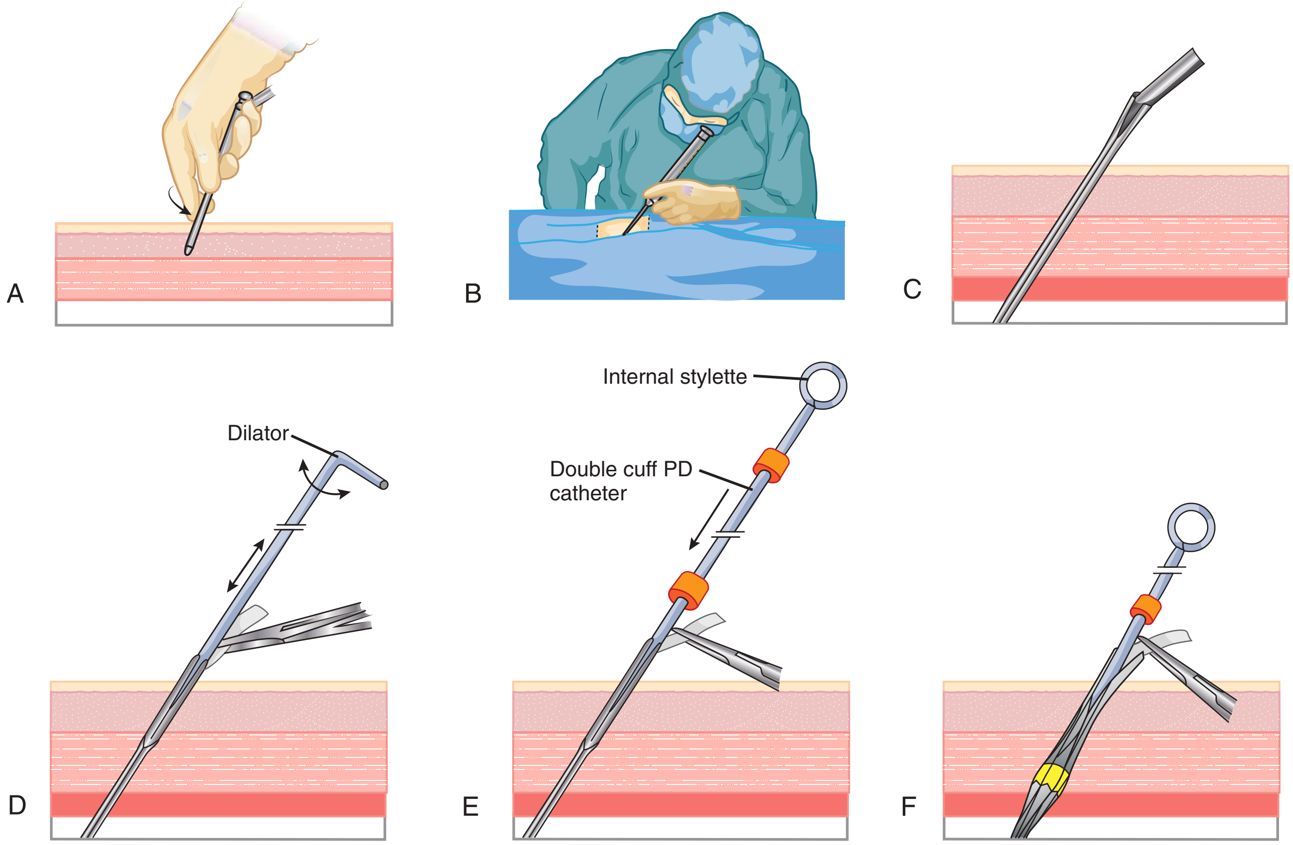

Fig. 92.2 Steps for the insertion of a peritoneal dialysis *(PD)* catheter by peritoneoscopy. (A) A trocar and cannula with a sheath are inserted into the abdominal cavity. (B) A peritoneoscope is passed through and locked into the cannula. (C) The sheath has been passed into the abdominal cavity and the peritoneoscope and cannula removed sequentially. (D) The sheath is secured with forceps while it is being dilated. (E) A PD catheter (with double cuff) is passed through the dilated sheath by use of an internal stylet. (F) The deep cuff is implanted into the rectus muscle. (Redrawn from Y-Tec Instructions: *Laparoscopic and Peritoneoscopic Placement of Peritoneal Dialysis Catheters.* Oswego, IL: Medigroup Inc. [division of Janin Group, Inc.]; 2004:1-5.)

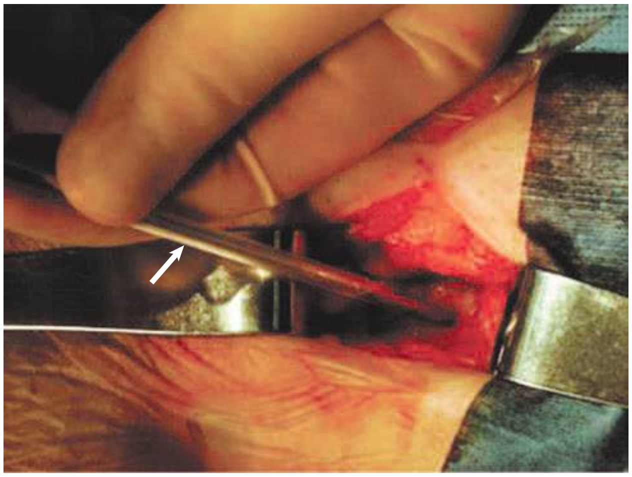

Fig. 92.3 Peritoneoscopic insertion of a peritoneal dialysis catheter. During peritoneoscopic insertion of a peritoneal dialysis catheter, a Quill guide trocar and cannula *(arrow),* with its wrapped spiral sheath, is being inserted through the rectus muscle under local anesthesia.

and the skin is closed with nylon. No sutures are placed on the external rectus sheath or at the skin exit site.

The Seldinger technique using fluoroscopy begins with blunt dissection down to the level of the lateral border of the rectus sheath. An 18-gauge needle with internal blunt stylet or a 22-gauge needle from a 5-French micropuncture set is inserted at an angle of 45 degrees, directed toward the lower pelvis into the peritoneum (ultrasound is helpful to identify thickness of the rectus muscle and presence of adhesions to the parietal peritoneum).[21] The location of the needle within the peritoneal cavity is confirmed by injecting 1 to 5 ml of contrast material, which forms a classic "spider web" appearance as dye moves into small spaces between bowel loops and parietal peritoneum (Fig. 92.4A).[21] If the tip of the needle is in the preperitoneal space, the dye collects around the tip of the needle, forms an outline of the parietal peritoneum, and appears static over a minute or so (Fig. 92.4B). Advancing the needle under fluoroscopic visualization allows the tip to penetrate the parietal peritoneal surface. If a micropuncture needle is used, an 0.018-inch wire is then inserted through the needle under fluoroscopy. Once the wire is in the lower pelvis, a 5-French catheter is placed over the wire. Contrast material can again be injected through the catheter

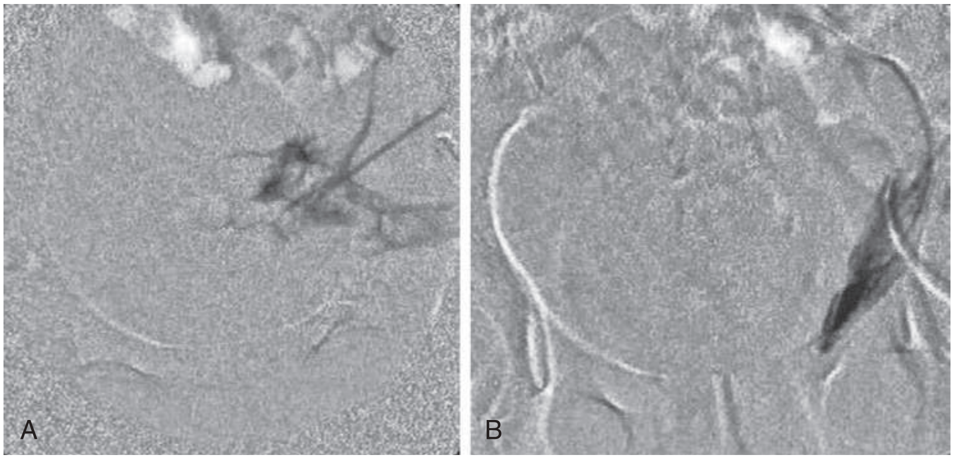

Fig. 92.4 (A) Fluoroscopic image after injecting a few milliliters of radiopaque dye through an 18-gauge needle after insertion through the rectus muscle and into the peritoneal space. Dye moves quickly away from the needle, and the image is not static. (B) Image after injecting a few milliliters of dye into an 18-gauge needle after insertion through the rectus muscle, with the tip of the needle in the preperitoneal space. Dye collects around the tip of the needle, at least one flat surface outlines the parietal peritoneum, and image changes very little with time. (With permission, from reference 21.)

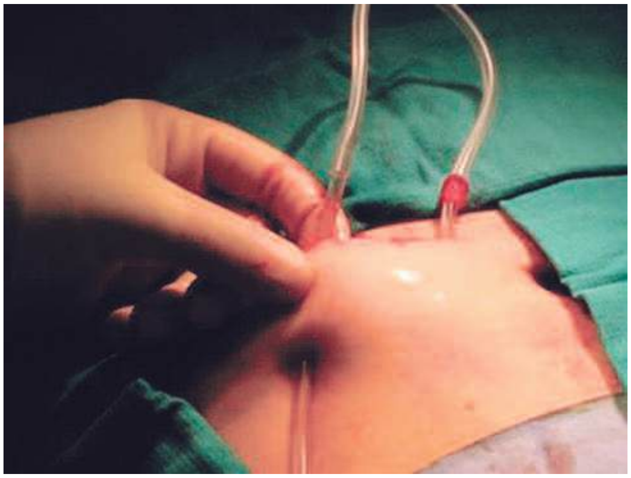

Fig. 92.5 Subcutaneous tunnel being created for a peritoneal dialysis catheter. With use of a disposable tool, a subcutaneous tunnel is created for the catheter. The superficial cuff shown will be implanted in the subcutaneous tunnel.

to confirm the position. If an 18-gauge needle is used, a 0.035-inch guidewire is passed directly through the needle and dilators are advanced sequentially up to the final 18-French dilator and peel-away sheath. The guidewire is removed, and the PD catheter is inserted over a metal stylet through the sheath, splitting the sheath as the deep Dacron cuff advances. This cuff is pushed into the rectus muscle while the sheath is in place, and the sheath is then removed around the cuff and catheter. The catheter is tunneled laterally with a tunneling tool (Fig. 92.5).[22,23]

Burying (Embedding) the Peritoneal Dialysis Catheter

If the catheter will not be used immediately, it can be embedded (buried) under the skin for weeks to months before it is tunneled to the outside and used. The catheter is placed in the usual manner, filled with dilute heparin solution in saline (100 U/ml), blocked with a plug, and tunneled through a small skin exit site. The tip is then directed into the exit site and tunneled through the subcutaneous space in a direction toward midline, caudal to the umbilicus. In some centers the catheter is tied off with silk suture and coiled into a pouch under the exit site. The primary incision and exit site are then closed over the catheter. Embedding the catheter allows ingrowth of tissue into the cuffs of the catheter with less chance of bacterial colonization and diminishes the incidence of early pericatheter infections and peritonitis.[24,25] Exteriorization of the catheter is done by making a small incision (1 cm) through the original exit site. Catheters buried in this fashion have been successfully exteriorized and used more than 1 year after insertion.[26] We recommend embedding the catheter when the catheter will not be used for at least a month.

Complications of Peritoneal Dialysis Catheter Insertion

Bowel perforation is the most feared complication of catheter insertion. The incidence is 1% to 1.4% with surgical insertion[14,15] but 0% to 0.8% with the peritoneoscopic insertion.[13,15] The diagnosis is established by direct peritoneoscopic visualization of bowel mucosa, bowel contents, or hard stool or return of fecal material or emanation of foul-smelling gas through the cannula. Whereas some investigators suggest this complication should be treated with surgical intervention,[27] successful conservative management of bowel perforation with bowel rest and intravenous antibiotics also has been reported.[22,28] To minimize the risk for perforation, a needle (such as a Veress needle) that is smaller and has a blunt, self-retracting end can be used instead of a trocar to gain access to the abdominal cavity.[20] Previous abdominal surgery is mentioned as a relative contraindication to PD because of intraperitoneal adhesions.[29,30] However, with careful ultrasound examination before needle placement an area free of adhesions can be identified. Peritoneoscopy is especially valuable for patients at high risk for adhesions. The scope can be used to identify intraperitoneal adhesions, assess their extent, and locate another site more suitable for catheter placement. With either fluoroscopic or peritoneoscopic techniques, the incidence of bowel perforation is no higher than during surgery, for patients with or without prior abdominal surgery, and the early success rate of catheters exceeds 95%.[11,13]

Catheter Repositioning

Migration of the PD catheter to the upper abdomen is a frequent cause of catheter failure. A variety of techniques have been used for repositioning, including guidewire or stylet insertion, Fogarty catheters, and laparoscopy, and many of the techniques are feasible for nephrologists.

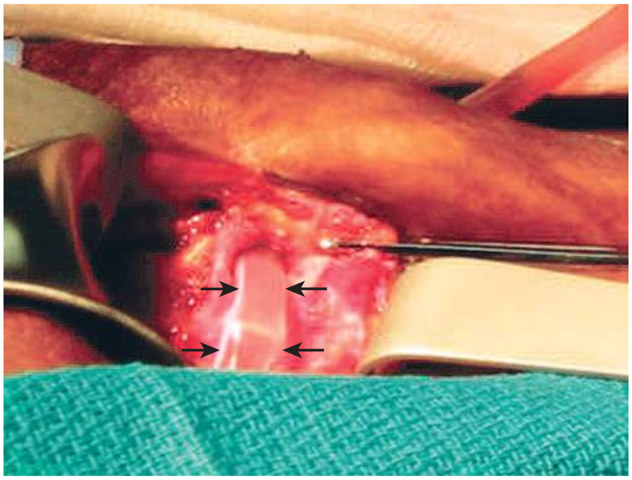

Fig. 92.6 Peritoneal dialysis catheter removal. The catheter (*arrows* show lateral margins of catheter) has been exposed by dissection of the subcutaneous tunnel.

The long-term success rate of repositioned catheters is only 27% to 48%,[31,32] probably because the migration of the catheter is the result of adhesion of omentum to the catheter. Thus insertion of a new catheter is required in many patients. Fogarty catheter manipulation is perhaps the most cost-effective, safe, and simple method for catheter reposition. A Fogarty catheter is advanced into the PD catheter, and the balloon is inflated. Manipulation is performed by tugging movements to reposition the catheter into the pelvic area. Infusion and drainage of dialysate and fluoroscopy are performed to determine patency and position of the PD catheter, respectively. Peritoneal catheters can be repositioned using stiff guidewires or stylets. Fluoroscopic images are very helpful in determining the degree of catheter entrapment and the progress of the repositioning procedure.[21]

Removal of Peritoneal Dialysis Catheters

A Tenckhoff curled or straight PD catheter can be safely removed without need for an operating room or general anesthesia.[18] Local anesthetic is infiltrated at the site of the original primary incision, and it is incised. Dissection is carried down to the subcutaneous portion of the catheter, which is elevated while the surrounding fibrous sheath is opened. The catheter is clamped with a hemostat, a nylon suture is placed in the catheter beyond the hemostat as a tag, and the catheter is cut between tag and hemostat. Dissection is continued toward the deep cuff by incising the fibrous tunnel adjacent to the catheter (Fig. 92.6). Additional anesthetic is infiltrated around the deep cuff. For catheters that have been in place for less than a month, blunt dissection is usually sufficient to free the deep cuff. Older catheters require sharp dissection. Exposure of the deep cuff and the anterior rectus sheath is required. Once the deep cuff is separated from the surrounding tissue, the intraperitoneal portion of the catheter is gently withdrawn from the peritoneal cavity and the defect in the rectus sheath closed with an absorbable purse-string suture. The nylon tag is then pulled to expose the remaining subcutaneous portion of catheter segment, and dissection is performed in the direction of the superficial cuff. Once the superficial cuff is free, this portion of the catheter is removed through the primary incision site or the exit site. Absorbable suture material in the dermis is used to close the skin incision subcutaneous tissue; and nylon sutures or sterile adhesive strips are applied to reinforce the skin closure. The exit site is not sutured.

Training and Certification

The ASDIN has established training guidelines and criteria for certification of physicians in the insertion of PD catheters (www.asdin.org).[12] In addition to appropriate didactic training, there should be two practice insertions (into models, animals, or human cadavers), observation of two insertions into patients, and then six successful insertions into patients as primary operator.

TUNNELED HEMODIALYSIS CATHETERS

Central venous catheters are used as a temporary HD access, as a bridge to AVF or AVG use, and when all other permanent access sites have been exhausted. Nontunneled catheters are used when a limited number of dialysis sessions is anticipated or there are contraindications to tunneled catheters (systemic infection, risk for bleeding) and are appropriate for use only in the inpatient setting. Tunneled catheters can be placed in both inpatient and outpatient settings, can be inserted at multiple vein locations, are relatively low in cost, and provide immediate access. However, there are significant disadvantages, including morbidity from infection and thrombosis and the risk for central vein stenosis or occlusion.[33,34] The role of the tunneled dialysis catheter in the provision of vascular access for HD is discussed further in Chapter 91.

Tunneled Catheter Insertion

The right internal jugular vein is the preferred catheter location compared with the left internal jugular and subclavian vein sites; it provides a straight route to the right atrium, thereby reducing the risk for central vein stenosis. Catheters also may be placed in the femoral veins.

Catheter insertion is performed in a sterile setting, ideally in an operating room environment with fluoroscopy available or at a minimum in a dedicated procedure room with cardiac monitoring. Before cannulation the vein should be located by ultrasound to detect anatomic variation or venous thrombosis. The patient's neck is then prepared and draped in sterile fashion; under ultrasound guidance, the vein is cannulated with a micropuncture needle (18 to 22 gauge), and a micropuncture guidewire is inserted and positioned in the superior vena cava. The needle is then removed, and the micropuncture dilator is inserted over the guidewire so it can be replaced with a standard guidewire. The use of the smaller needle rather than the standard 15-gauge needle minimizes trauma to the vein. A small subcutaneous incision is made adjacent to the dilator or guidewire, additional dilation is performed, and the catheter is placed over the guidewire, with care taken to hold the guidewire in place. If a tunneled catheter is to be placed, a catheter exit site is selected inferior to the clavicle and sufficiently lateral to the venotomy to avoid a kink in the catheter. A 1-cm superficial incision is made at this point, and a subcutaneous tract adjacent to the venotomy is infiltrated with lidocaine. A double-lumen catheter, generally 24 or 28 cm in length, is attached to the tunneling device and pulled through the subcutaneous tunnel in a curved path. A guidewire is passed through the dilator and into the inferior vena cava. The venotomy site is then serially dilated over the guidewire. The catheter can then be inserted over the guidewire through the venous port. When a split-tip catheter is used, the guidewire is passed in and out of the two venous ports and through an arterial port or through a hollow intracatheter stiffener. Alternatively, a peel-away sheath is placed over the guidewire and the catheter inserted through the sheath after the removal of the guidewire; however, this method has greater potential for blood loss and air embolism. Fluoroscopy is used to confirm tip placement at the level of the right atrium, with the arterial port facing away from the atrial wall, and to ensure there are no kinks in the catheter (Fig. 92.7). Each port of the catheter is then flushed with saline and locked with the appropriate amount of heparin based on catheter length and priming volume designation, followed by placement of the catheter hub caps.

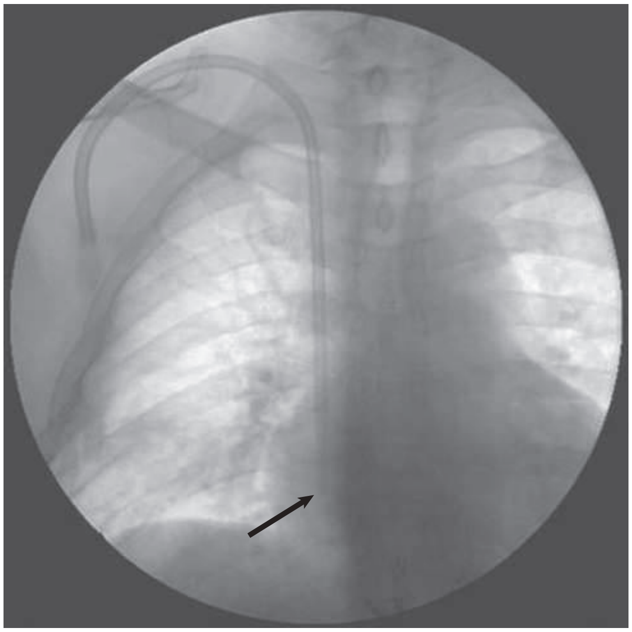

Fig. 92.7 **Insertion of a venous catheter for hemodialysis.** Chest radiograph confirming that the tip of the catheter *(arrow)* is at the junction of the superior vena cava and the right atrium.

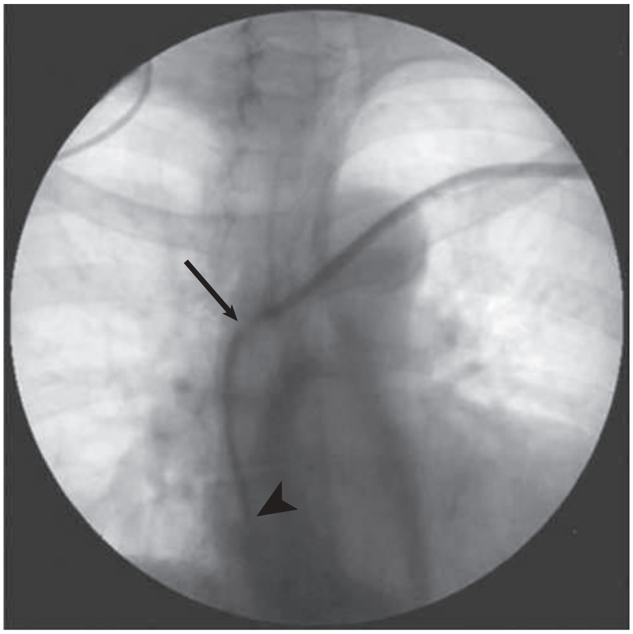

Fig. 92.8 **Fibrin sheath on a tunneled venous catheter.** Contrast material has been injected into a tunneled catheter after the tip *(arrow)* has been pulled back into the innominate vein. The contrast material fills a sheath that extends from the catheter tip as far as the *arrowhead.*

Catheter Dysfunction

Catheter dysfunction is defined as the failure to maintain a blood flow sufficient to perform HD without significantly extending treatment time; this is usually 300 ml/min or greater for conventional dialysis.[35] Causes of immediate dysfunction include a kink in the catheter, incorrect position or orientation (e.g., arterial port against the vessel wall), and errant venous cannulation. These problems should be ascertained and corrected at the time of catheter placement. Catheter thrombosis is the most common cause of late dysfunction. Extrinsic thrombosis is less common than intrinsic thrombosis and is caused by central vein, mural, or right atrial thrombosis. Intrinsic obstruction results from thrombus within the catheter lumen or tip or most commonly from a fibrin sheath. Fibrin sheaths typically develop weeks to months after catheter insertion and result when a sleeve of connective tissue forms at the venotomy site and extends and encases the catheter tip, creating a flap-valve. First-line treatment of catheter thrombosis includes forceful flush of the catheter with saline. If flow is not restored, a fibrinolytic agent should be instilled. Tissue plasminogen activator (tPA) is commonly used and appears more effective than urokinase in restoring patency and adequate flow.[36,37] Typically, 2 mg of tPA is instilled per occluded catheter lumen with 0.9% sodium chloride without preservative to fill the internal volume of each lumen and is allowed to dwell 30 minutes. If this fails, the catheter should be exchanged. Strategies to minimize dialysis catheter thrombosis are discussed in Chapter 91.

Catheter Exchange and Fibrin Sheath Removal

Catheter exchange over a guidewire is useful in the setting of catheter thrombosis or bacteremia and allows the preservation of the venotomy, tunnel, and exit sites. The tunnel and exit sites must appear free of infection if the same sites are to be used. Catheter exchange should take place within 72 hours of the initiation of antibiotic therapy.[35] Under sterile conditions, the exit site is anesthetized and the cuff is freed. Once the catheter is pulled back 8 to 10 cm, contrast material is injected through the catheter under fluoroscopy to check for a fibrin sheath (Fig. 92.8). To obliterate a sheath, a guidewire is passed down the venous port of the catheter and into the inferior vena cava. The catheter is then removed, and a balloon catheter is inserted over the guidewire to the sheath location and inflated to disrupt the sheath. A new catheter is then inserted over the guidewire. When the catheter tip is beyond the venotomy site, near the superior vena cava, contrast material can be injected again to check for sheath removal before proceeding with catheter insertion.

Training and Certification

The American Society of Diagnostic and Interventional Nephrology guidelines for HD vascular access procedure certification specify formal didactic training in central venous anatomy, sonographic examination of central veins, fluoroscopy, and catheter design and complications. In addition, practical training for certification includes satisfactory insertion of 25 tunneled long-term catheters. More information may be obtained at www.asdin.org.

PROCEDURES ON ARTERIOVENOUS FISTULAS AND GRAFTS

The most common indications for intervention are inadequate flow during dialysis, thrombosis, and failure of AVFs to mature. Specific interventions include angiography, thrombectomy, angioplasty, and stenting. All of these procedures require a dedicated facility, either inpatient or outpatient, with fluoroscopy, monitoring equipment, and staff to assist with the procedures and deliver conscious sedation. There are many different techniques for AV access procedures and few data to indicate superiority of one method over the other, so the choice is generally one of personal preference and cost. However, the first step always should include careful physical and ultrasound examination of the access. An examination will generally identify the problem and allow detection of access infection, an absolute contraindication to intervention. Appropriate intervention then can be planned. Monitoring and management of vascular access to minimize stenosis, thrombosis, and failure are discussed further in Chapter 91.

Percutaneous Balloon Angioplasty

Stenosis in AVGs and AGFs is routinely managed by percutaneous balloon angioplasty, which causes minimal discomfort and allows immediate use of the access. Not all stenotic lesions are responsive, however, and some require repeated treatment. In fistulas, the stenosis is most commonly located at the "swing point," including the portion of the native vein mobilized during creation of the AV anastomosis (Fig. 92.9), or during vein transposition, or at the cephalic arch; in grafts, the venous anastomosis is the most common site of stenosis.[38-42] Angioplasty is indicated if the stenosis is 50% or more and is associated with clinical or physiologic abnormalities.[35] Treatment of stenosis increases access blood flow and longevity and reduces access thrombosis and access-related hospitalization.[42,43,44] A relative contraindication to angioplasty is a newly created access (<4 to 6 weeks old).

The access is cannulated with an introducer needle, a sheath is inserted, and initial angiography is performed. This should include views of the access, draining veins (peripheral and central), and arterial anastomosis and is used to confirm the location and degree of stenosis. Unless contraindicated, short-acting sedation and analgesia are given once a lesion has been identified on initial angiography, because angioplasty is painful.

A guidewire is passed through the sheath and across the stenosis. An angioplasty balloon catheter is passed over the guidewire, positioned at the stenotic site, and inflated with a syringe or inflation device (Fig. 92.10). A variety of sheaths, guidewires, balloon sizes, and maximum pressures are available. The guidewire is left in place, and angiography is repeated to identify residual stenosis or any complications. Angioplasty is repeated for residual stenosis or when multiple lesions are present and may require a second cannulation of the access in the opposite direction for inflow stenoses. After removal of all devices, hemostasis at the cannulation site is achieved by manual pressure or suture placement. There is no evidence to support the use of antiplatelet agents or anticoagulation after intervention. According to Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, a successful angioplasty is achieved when there is no more than 30% residual stenosis and physical indicators of stenosis have resolved.[35]

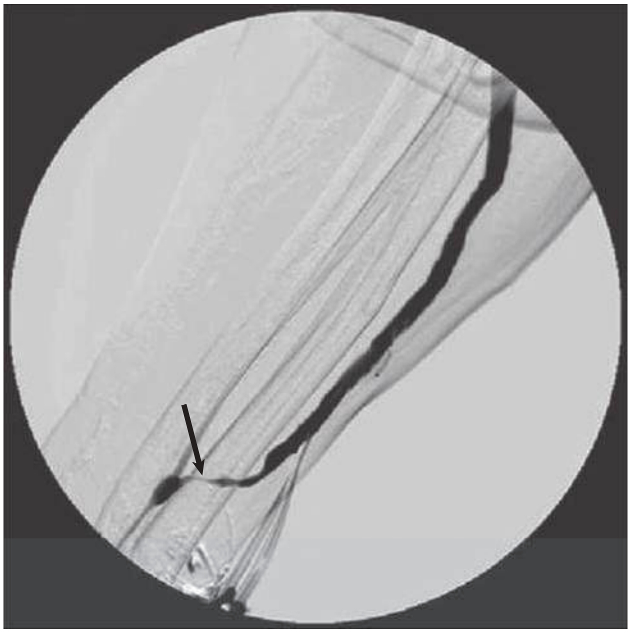

Fig. 92.9 **Juxtaanastomotic stenosis in a radiocephalic arteriovenous fistula.** Contrast material was injected at the arterial anastomosis *(bottom left of image)* and demonstrates a narrowing in the initial portion of the fistula *(arrow).*

Percutaneous Thrombectomy

A variety of techniques are used for thrombus removal. In thromboaspiration—the least costly method, and as effective and efficient as mechanical and pharmacomechanical thrombolysis—low-dose tPA is instilled into the thrombosed access, the clot is manually macerated, flow returns, and angioplasty is used to dilate access stenoses.[45] Thrombectomy by thromboaspiration combines angiography with balloon angioplasty and thrombectomy by clot aspiration. Absolute contraindications to thromboaspiration include access infection and known right-to-left cardiac shunt; relative contraindications include a large clot burden and long-standing access occlusion.

The access is cannulated in an antegrade direction, and a guidewire is passed to the level of the central veins. A straight catheter is inserted over the wire to the central veins, and angiography is performed to confirm central venous patency. Anticoagulation and short-acting sedative and analgesic medications are administered in the central circulation. An angiogram is then obtained as the catheter is pulled back to identify the location of stenosis. The guidewire is then inserted beyond the stenotic lesion, followed by an angioplasty balloon catheter. The balloon catheter is insufflated by hand with a syringe or inflation device, and the stenotic lesion is dilated. The access is then cannulated in the retrograde direction, a sheath is inserted, and a Fogarty catheter is passed across the arterial anastomosis, inflated, and pulled back through the entire length of the access while clot fragments are aspirated. On return of flow through the access, angiography is performed to evaluate the inflow and the arterial anastomosis, and angioplasty is repeated if necessary. Hemostasis is achieved by manual pressure or a suture at the cannulation sites.

Stents

Stents are considered in the setting of failed balloon angioplasty (an elastic lesion), when there are few remaining access sites, if the patient is not a surgical candidate for a new access, or when an outflow vein ruptures after balloon angioplasty (Figs. 92.11 and 92.12).[50,51] Results of randomized studies designed to demonstrate stent graft noninferiority to conventional angioplasty for AVG venous anastomotic stenosis show

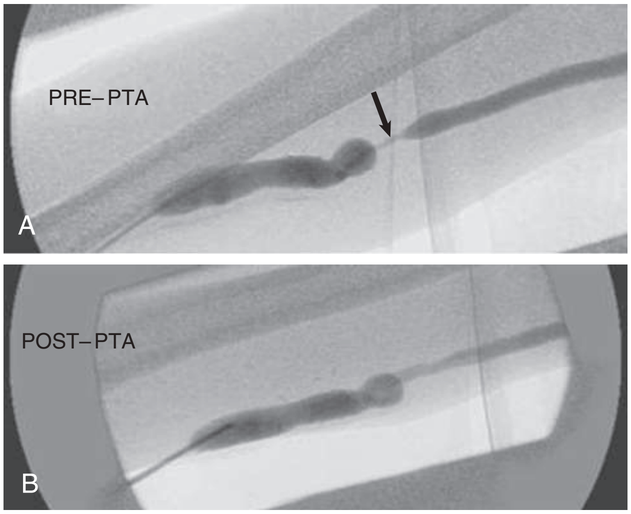

Fig. 92.10 **Arteriovenous graft stenosis.** (A) Stenosis in the outflow vein of an upper arm arteriovenous graft *(arrow).* (B) Angiogram performed immediately after percutaneous angioplasty. *PTA,* Percutaneous transluminal angioplasty.

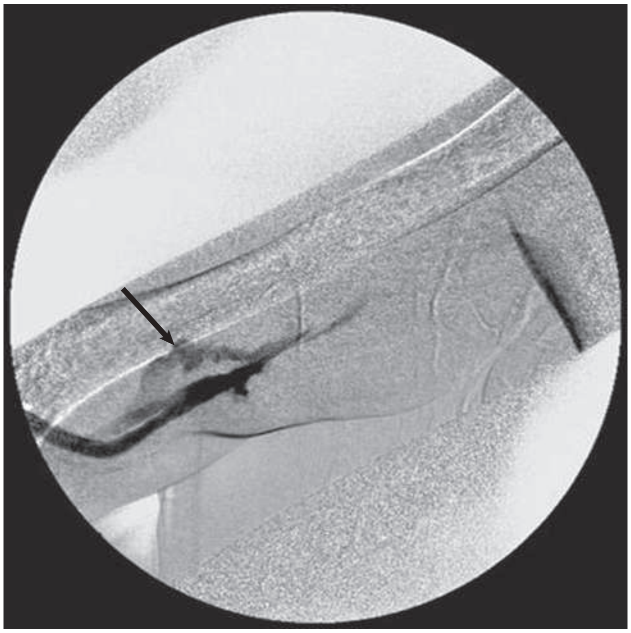

Fig. 92.11 Vein rupture. Postangioplasty angiogram of an arteriovenous fistula showing extravasation of dye *(arrow),* indicative of a vein rupture. (Courtesy Dr. G. Beathard, Austin, Tex.)

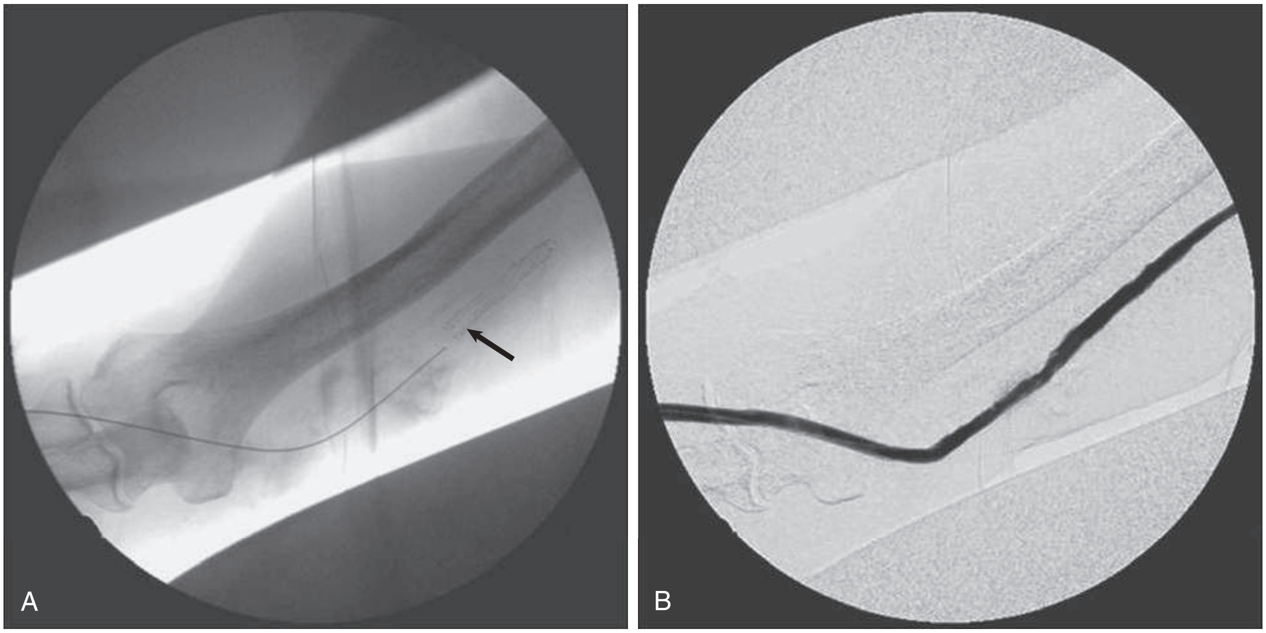

Fig. 92.12 Treatment of vein rupture with an intraluminal stent. (A) Placement of the stent *(arrow).* (B) An angiogram obtained after stent placement showing that venous outflow has been reestablished. (Courtesy Dr. G. Beathard, Austin, Texas.)

an increased primary patency for stent grafts.[52-54] Further, data suggests improved patency with stent grafts used to treat outflow vein re-stenosis in AVG, AVF and central veins. Remove work 'bare-metal'.[46-49,55] Finally, a stent may be useful in the setting of an expanding pseudoaneurysm.[56,57]

Despite these encouraging findings, stents should be used judiciously, particularly when surgical options may provide greater enduring patency. Stents should be avoided in situations in which their use will not extend the life of the access.

Training and Certification

The ASDIN guidelines for HD vascular access procedure certification specify didactic training in venous anatomy, fluoroscopy, procedural equipment, and sedation and analgesia. Requirements for practical training include 125 procedures in both fistulas and grafts of each of the following: angiography, angioplasty, and thrombectomy as primary operator (refer to www.asdin.org for more information). In general, several hundred procedures as secondary operator will be required before one can become a primary operator.

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SELF-ASSESSMENT QUESTIONS

1. Tissue plasminogen activator (tPA) is generally effective in treating poor blood flow in tunneled central venous catheters resulting from fibrin sheath formation.
   A. True
   B. False
2. A 57-year-old male patient with end-stage renal disease with a mature, left brachiocephalic arteriovenous fistula (AVF) is referred for evaluation of prolonged bleeding from his AVF on removal of the dialysis needles. His AVF is pulsatile on examination and does not collapse when the left arm is raised above the heart. An angiogram identifies a 75% stenosis at the cephalic arch, and an angioplasty is performed. According to National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, what defines a successful percutaneous angioplasty of an AV access?
   A. Less than 10% residual stenosis at the angioplasty site
   B. Ability to receive eight uncomplicated, consecutive dialysis sessions after the procedure
   C. Less than 30% residual stenosis and resolution of physical indicators of stenosis
   D. A and B
   E. B and C
3. Embedding (or burying) a newly placed peritoneal dialysis (PD) catheter under the skin:
   A. Allows ingrowth of tissue into the cuffs of the catheter without an opportunity for bacterial colonization
   B. Diminishes the incidence of early pericatheter infections
   C. Results in better catheter function in the future
   D. A and B
   E. Is of no benefit other than cosmetic
4. Which of the following statements about ultrasound of the renal and urinary tract is *false?*
   A. For examination of the kidneys a renal ultrasound is always indicated in the workup of chronic kidney disease.
   B. A renal ultrasound is not indicated in every patient with acute kidney injury.
   C. Ultrasound is not useful in the diagnosis of bladder outlet obstruction.
   D. The ureters are usually visible only when dilated.
5. Which of the following are commonly used techniques for insertion of PD catheters?
   A. Laparoscopy
   B. Surgical dissection
   C. Peritoneoscopy
   D. The guidewire (Seldinger) technique
   E. All of the above

93

Hemodialysis

Principles and Techniques

Peter Kotanko, Martin K. Kuhlmann, Christopher Chan, Nathan W. Levin

Hemodialysis (HD) has existed for more than 50 years and has extended the lives of millions of patients with renal failure worldwide. Although the basic principles of HD are still being applied today, dialysis technology has improved markedly.

DIALYSIS SYSTEM

The aim of the HD system is to deliver blood in a fail-safe manner from the patient to the dialyzer, enable the efficient removal of uremic toxins and excess fluid, and deliver the cleared blood back to the patient. The main components of the dialysis system are the extracorporeal blood circuit, the dialyzer, the dialysis machine, and the water purification system.[1]

HD has conventionally been delivered in three treatment sessions per week. This developed as a practical compromise between the physiologic benefits of replacing renal function by HD and the practicalities of delivering HD. Treatment times of 3 to 5 hours per session are now typical (for a detailed discussion of outcomes related to treatment time and frequency see Chapter 94).

DIALYZER DESIGNS AND MEMBRANES

The dialyzer provides countercurrent transfer of solutes and fluid across a semipermeable membrane. The semipermeable dialysis membrane separates the blood compartment from the dialysate compartment (Table 93.1). The original membrane material was cellulose. In cellulose acetate, most hydroxyl groups are replaced by acetate radicals. Synthetic tertiary amino compounds are added to form cellulosynthetic membranes. The current generation of membranes is made of entirely synthetic materials that are considered more biocompatible, such as polyacrylonitrite, polysulfone, polycarbonate, polyamide, and polymethylmethacrylate.

Transport of molecules across the dialysis membrane is due to (1) the concentration gradient (diffusive transport) and (2) the hydrostatic pressure gradient across the membrane (convective transport) and depends on membrane pore size. Dialyzer efficiency increases with surface area (usually 0.8 to 2.1 m^2). The dialyzer mass transfer area coefficient (KoA) for urea is a measure of the theoretically maximal possible urea clearance (milliliters per minute). Dialyzer efficiency can be categorized based on KoA for urea as low (<500 ml/min), moderate (500 to 700 ml/min), and high (>700 ml/min). High-flux dialyzers have pores large enough to allow the passage of larger molecules such as β_2-microglobulin (molecular weight 11,800 d). Water permeability is defined by the ultrafiltration coefficient (Kuf) that describes the transmembrane ultrafiltration volume per hour and unit of hydrostatic transmembrane pressure in millimeters of mercury. In high-flux dialyzers Kuf can be as high as 80 ml/h/mm Hg. During high-flux HD, backfiltration of dialysate into the blood as a result of higher hydrostatic pressure on the dialysate side occurs at the distal end of the dialyzer blood compartment and may result in a transfer of 5 to 10 liters of dialysate into the blood during a treatment; it is compensated for by an increased blood water removal at the proximal part of the dialyzer. Therefore water quality is of paramount importance when high-flux dialyzers are used (see later). The ultrafiltration rate is controlled precisely by a volumetric control system.

SAFETY MONITORS

Safety monitors are integral parts of the dialysis machine.

Pressure monitors are in most machines integrated to monitor the system pressure in critical positions (Fig. 93.1)[1]:

- Between the arterial side and the blood pump (prepump arterial pressure) to assess the suction pressure; overly negative values may signal reduced arterial inflow and access problems.
- Between the blood pump and the dialyzer inlet (postpump) to assess the dialyzer inflow pressure; a high pressure may signal dialyzer clotting.
- Between the dialyzer outlet and the air trap (venous pressure) to control the return pressure; a high pressure may point toward an obstruction in the venous limb; it is important to realize that in the event of venous needle displacement, with external bleeding, the venous pressure will remain positive because of the needle's flow resistance and a pressure alarm may not occur.

A *venous air detector* and *air trap* are located downstream of the venous pressure monitor. A positive signal at the air detector automatically clamps the venous line and stops the blood pump.

A *blood leak detector* is placed in the dialysate outflow line. Dialysate temperature is constantly monitored. Dialysate is produced by a proportioning system that mixes acid and bicarbonate concentrates with highly purified water. The osmolality of the dialysate translates into conductivity, which is measured by the dialysis conductivity monitor.

ANTICOAGULATION

Either unfractionated or low molecular weight heparin (LMWH) is used to prevent blood clotting in the extracorporeal circuit. Constant infusion of heparin, repeated boluses of heparin, or a single bolus of LMWH is used. Alternatives are available for patients at high risk for bleeding or who have contraindications to heparin, such as saline flushes, regional citrate anticoagulation, prostacyclin, danaparoid, argatroban (direct thrombin inhibitor), and lepirudin (recombinant hirudin).

TABLE 93.1 **Dialysis Membrane Properties**

Membrane	Membrane Name (Example)	High or Low Flux	Biocompatibility
Cellulose	Cuprophane	Low	Low
Semisynthetic cellulose			
Cellulose diacetate	Cellulose acetate	High and low	Intermediate
Cellulose triacetate	Cellulose triacetate	High	Good
Diethylaminoethyl-substituted cellulose	Hemophane	High	Intermediate
Synthetic polymers			
Polymethylmethacrylate	PMMA	High	Good
Polyacrylonitrile methacrylate copolymer	PAN	High	Good
Polyacrylonitrile methallyl sulfonate copolymer	PAN/AN-69	High	Good
Polyamide	Polyflux	High and low	Good
Polycarbonate-polyether	Gambrane	High	Good
Ethylene vinyl alcohol copolymer	EVAL	High	Good
Polysulfone	Polysulfone	High and low	Good

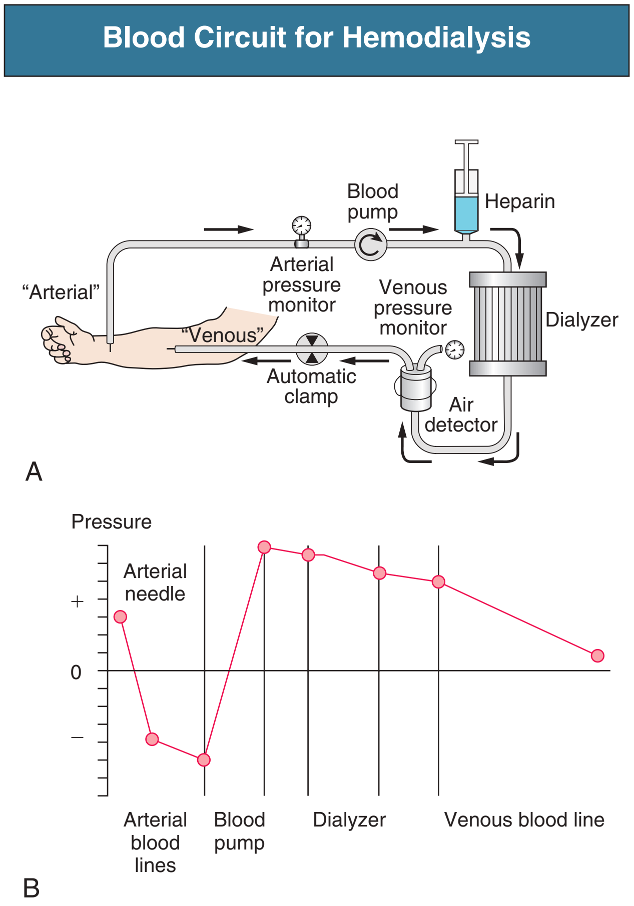

Fig. 93.1 Blood circuit for hemodialysis. (A) The blood circuit. (B) The pressure profile in the blood circuit with an arteriovenous fistula as the vascular access.

Lepirudin has the disadvantage of a very prolonged half-life in dialysis patients. In some institutions, regional citrate anticoagulation is used routinely, especially in patients with recent surgery, coagulopathies, thrombocytopenia, active bleeding, pericarditis, or heparin-associated side effects (heparin-induced thrombocytopenia type 2, pruritus, rapidly progressive osteoporosis, alopecia). Heparin requirements may be reduced with the use of citrate-containing dialysate.[2]

A typical routine prescription of constant infusion heparin is to administer an initial bolus of 2000 IU followed by a heparin infusion (800 to 1200 IU/h) which is stopped 30 to 60 minutes before the end of the session. Applying the repeated-bolus method, an initial heparin bolus (e.g., 4000 IU) is followed by a second bolus (e.g., 1000 to 2000 IU) after 2 hours. LMWH has become the anticoagulant of choice in many centers, usually given as a bolus at the beginning of the session. Routine monitoring of whole-blood partial thromboplastin time, activated clotting time, or factor Xa is usually not necessary.

DIALYSATE FLUID

Water and Water Treatment

A standard 4-hour HD session exposes the patient to 120 to 160 liters of water. Therefore water quality is of paramount importance to the patient's well-being. A typical water purification plant is shown in Fig. 93.2. Water from municipal sources is filtered to remove particulate matter. Activated carbon adsorbs substances such as endotoxins, chlorine, and chloramines. Downstream water softeners use a resin coated with sodium ions, which are exchanged for calcium and magnesium ions before the water enters the reverse osmosis (RO) system. During RO, water is pumped at high pressure (15 to 20 bar) through a tight membrane. The small pore size of these membranes (0.5 to 0.5 nm) provides an absolute barrier for molecules larger than 100 to 300 d. This process rejects over 99% of all bacteria, viruses, pyrogens, and organic materials. Optional ultraviolet irradiation upstream of a filter is used to further protect against contamination with bacteria.

Standards for chemical quality of water are widely accepted, but there is less consensus regarding acceptable levels of bacterial and endotoxin contamination. The microbiologic standards for HD water, dialysis fluid, and substitution fluid vary across countries (Table 93.2).[3] Endotoxin concentrations below 0.25 endotoxin units (EU)/ml are suggested, and many support the use of 0.06 EU/ml or lower. Municipal water supplies may contain a variety of contaminants that are toxic to HD patients. Substances added to the water supply such as aluminum and chloramines cause significant morbidity. Aluminum accumulation may result in a severe neurologic disorder, bone disease, and erythropoietin-resistant anemia. Is it recommended to measure plasma aluminum concentration regularly in situations in which aluminum exposure of the patient is likely to occur. Levels should be below 1 μmol/l, and levels above 2 μmol/l should prompt the search for excessive exposure. Chloramines have been associated with hemolysis

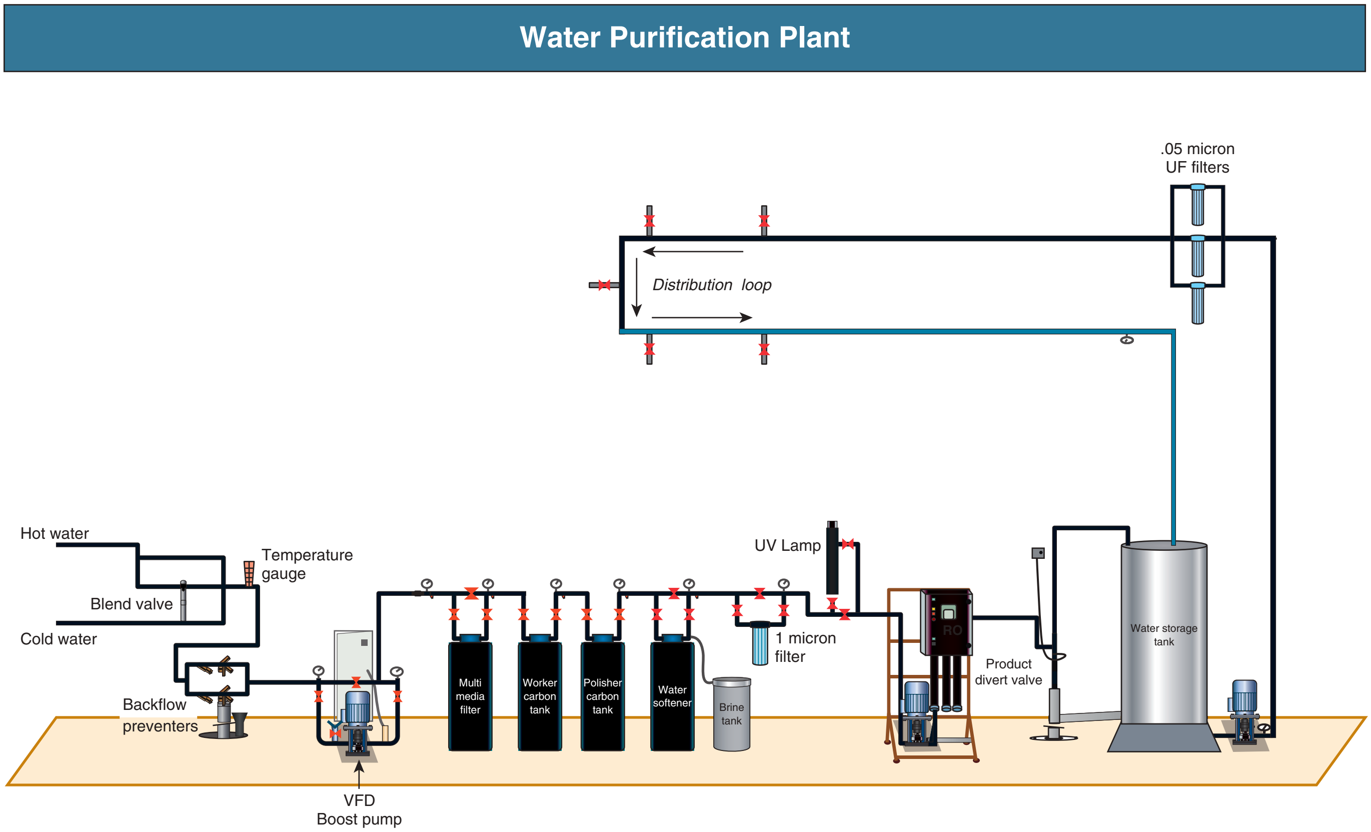

Fig. 93.2 Water purification plant. The four main functional domains are water supply, water pretreatment, primary purification, and delivery to the loop. A series of filters and water softeners are the key technical pretreatment components, whereas reverse osmosis is the main component of the primary purification. Note that several features are optional, for example, the water storage tank. *UF,* Ultrafiltration; *UV,* ultraviolet light; *VFD,* variable frequency drive. (Original artwork courtesy of Rob Levin and Randy Hux, New York, NY.)

and methemoglobinemia. Copper and zinc may leach from plumbing components and may cause hemolysis. Lead has been associated with abdominal pain and muscle weakness. Nitrate and nitrite may cause nausea and seizures. High concentrations of calcium may cause the hard water syndrome, characterized by acute hypercalcemia and hypomagnesemia, hemodynamic instability, nausea, vomiting, muscle weakness, and somnolence.

Gram-negative bacteria produce endotoxins, and fragments of these endotoxins may be responsible for some dialysis-related symptoms. Exposure to bacteria and endotoxin is associated with rigors, hypotension, and fever. Low levels of microbiologic contaminants may be a major cause of chronic inflammation in HD patients. Use of a polysulfone or polyamide filter in the dialysate line may be adequate to remove endotoxins, but smaller molecules, including bacterial DNA fragments, may pass through the dialyzer and stimulate immune cells. In the absence of routine hot water disinfection of the machine and the connections to the water loop, the only way endotoxin concentration can be kept low is by frequent measurement and disinfection of the entire system when concentration exceeds accepted standards. Liquid bicarbonate dialysis fluid concentrate distributed in a central distribution system may be a source of bacterial growth and should be replaced daily; acid concentrates in canisters and bicarbonate powder represent no bacterial growth risk.

Ultrapure water is recommended by international guidelines for use with high-flux dialyzers. Water used for online hemodiafiltration (HDF) has to be virtually sterile and nonpyrogenic, thus fulfilling the criteria for ultrapure water. To ensure chemical and microbial purity, water is treated by microfiltration and activated charcoal followed by two RO modules in series. Ultrapure water is delivered to dialysis machines for the production of ultrapure dialysate, which undergoes cold sterilization using additional sterilizing ultrafilters. A sterile and nonpyrogenic replacement fluid is generated online by filtering dialysis fluid through bacteria- and endotoxin-retentive filters before it is infused into the patient.

Dialysate Solution

Dialysis fluid can be considered as a drug to be adjusted to the individual patients' needs (Table 93.3). Dialysate is made by mixing two components, which may be provided as liquid or dry (powder) concentrates. The *base concentrate* contains sodium bicarbonate and sodium chloride. The *acid concentrate* typically contains chloride salts of sodium, calcium, magnesium, and potassium, glucose monohydrate, and an organic acid, the latter in the form of acetic acid, citric acid, or lactic acid. The acid concentrate may contain the salt of an organic acid, such as sodium acetate. The purpose of the acid is to lower the dialysate pH to below 7.3 so that calcium and magnesium do not precipitate when bicarbonate is added. Base and acid components are mixed simultaneously with purified water to make the dialysate. Dialysate proportioning pumps ensure proper mixing. One typical mixing relationship is 1 : 1.72 : 42.28 (acid concentrate:base concentrate:water; also known as *45X preparation*). The relative amounts of water, bicarbonate, and acid component define the final dialysate composition. It is important to note that some dry acid concentrates contain sodium diacetate (8 mmol/l), which is made up of equal parts of acetic acid and sodium acetate. After mixing

TABLE 93.2 Microbiologic Standards for Water, Concentrates, and Dialysis Fluids

National and International Standards	Year Issued	Microorganisms (CFU/ml)	Endotoxins (EU/ml)
Water			
EDTA-ERA	2001	<100	<0.25
USA (AAMI RD 52)	2004	200 (alert 50)	2 (alert 1)
ISO/DIS 13959 (draft)	2009	100	0.25
Concentrates (Acid and Basic)			
USA (AAMI RD 52)	2004	200 (alert 50)	2 (alert 1)
Ph Eur, 5th ed	2005	—	<0.5*
Dialysis Fluid			
EDTA-ERA	2001	<100	<0.25
USA (AAMI RD 52)	2004	200 (alert 50)	2 (alert 1)
ISO/DIS 11663 (draft)	2009	100 (alert 50)	0.5
Ultrapure Dialysis Fluid Before Last Filter for Hemodiafiltration On-line			
EDTA-ERA	2001	<0.1	<0.03
USA (AAMI RD 52)	2004	0.1	0.03
ISO/DIS 11663	2009	<0.1	<0.03
Substitution Fluid On-line			
EDTA-ERA	2001	$<10^{-6}$	<0.25
USA (AAMI RD 52)	2004	$<10^{-6}$	<0.03
ISO/DIS 11663	2009	Sterile	Nonpyrogenic

*Diluted to user concentration.
AAMI, Association for the Advancement of Medical Instrumentation; *EDTA-ERA,* European Dialysis and Transplant Association- European Renal Association; *ISO/DIS,* International Organization for Standardization/Draft International Standard; *Ph Eur,* European Pharmacopoeia; *RD,* renal disease.

TABLE 93.3 Composition of Dialysates for Bicarbonate Dialysis

	CONCENTRATION	
Component	**Range**	**Typical**
Electrolytes (mmol/l)		
Sodium	135-145	138
Potassium	1.0-4.0	2.0
Calcium	1.0-1.75	1.25
Magnesium	0.5-1.0	0.75
Chloride	87-124	105
Buffers (mmol/l)		
Acetate	2-4	3
Bicarbonate	20-40	35
pH	7.1-7.3	7.2
P_{CO_2} (mm Hg)	40-100	
Glucose	0-11 (0-200 mg/dl)	5.5 (100 mg/dl)

with bicarbonate, the final dialysate contains 8 mmol/l sodium acetate.[4] Dialysate composition can be modified by small changes in the mixing ratio and adding salt solutions; potential advantages and disadvantages of dialysate modifications are shown in Table 93.4

BIOCOMPATIBILITY

The contact of blood with some lines and membranes triggers an inflammatory response. Although many components of the dialysis procedure contribute to the degree of biocompatibility, it is the membrane itself that is most important. Biocompatibility is especially important when cellulose membranes are used, whereas synthetic and reused membranes activate complement to a much lesser extent (Fig. 93.3). Activation of complement peaks at 15 minutes after the start of dialysis and lasts up to 90 minutes.

HEMOFILTRATION AND HEMODIAFILTRATION

Hemofiltration (HF) and HDF involve the removal of large fluid volumes from the patient, with the removed fluid replaced by substitution fluid. It is the use of substitution fluid that sets these techniques apart from simple ultrafiltration.

Hemofiltration (HF; Fig. 93.4) is a convective elimination technique by which water and solutes from the blood compartment are driven solely by positive hydrostatic pressure across the dialyzer membrane into the filtrate compartment without the use of dialysate. As a result of solvent drag effects, small and larger solutes are eliminated at a rate depending on membrane characteristics.

Hemodiafiltration (HDF; Fig. 93.5) combines diffusive (HD) and convective (HF) solute transport using a high-flux membrane. Fluid is removed by ultrafiltration, and the volume of filtered fluid exceeding the volume to achieve target weight loss is replaced by ultrapure, nonpyrogenic infusion solution. *Online* HDF refers to the online production by the dialysis machine of nearly unlimited amounts of ultrapure, nonpyrogenic dialysate, which is also used as infusion solution. *High-volume* HDF refers to an effective convection volume of at least 20% of the total blood volume processed.

Modes of Hemofiltration and Hemodiafiltration

Modes of HDF are differentiated depending on the site in relation to the dialyzer, with through which replacement fluid is infused into the patient's blood.

Postdilution Hemodiafiltration

Ultrafiltration is enforced on the undiluted blood with the replacement fluid being infused to the patient downstream of the dialyzer. Filtration is limited by hemoconcentration. Postdilution HDF is most efficient in terms of increasing solute removal.

Predilution Hemodiafiltration

Replacement fluid is added upstream of the dialyzer, which results in dilution of the patient's blood. Although filtration rates up to 100% of blood flow rate are possible, the efficiency of this mode is lower than postdilution HDF because of dilution of solute blood concentrations and thus the transmembrane gradient.

Mixed Dilution Hemodiafiltration

Replacement fluid is infused both upstream and downstream of the dialyzer. The ratio of upstream and downstream infusion rates can be varied to achieve the optimal compromise between maximizing clearance and avoiding the consequences of a high transmembrane pressure and hemoconcentration.

TABLE 93.4 Advantages and Disadvantages of Modifications in the Dialysate Composition

Component	Advantage	Disadvantage
Sodium		
Increased	Hemodynamic stability	Postdialytic thirst; increased postdialytic serum sodium levels; increased intradialytic weight gain; high blood pressure
Decreased	Reduced osmotic stress in the presence of predialytic hyponatremia	Intradialytic hemodynamic instability
Potassium		
Increased	Fewer arrhythmias in digoxin intoxication with hypokalemia; may improve hemodynamic stability	Hyperkalemia
Decreased	Increased dietary potassium intake	Arrhythmias; risk for sudden death
Calcium		
Increased	Suppresses PTH, increased hemodynamic stability	Hypercalcemia, vascular calcification, adynamic bone disease resulting from PTH suppression
Decreased	Permits more liberal use of calcium-containing phosphate binders	Stimulation of PTH, reduced hemodynamic stability
Bicarbonate		
Increased	Acidosis control improved	Postdialytic alkalosis; increased mortality
Decreased	No postdialytic alkalosis	Promotes acidosis; increased mortality
Magnesium		
Increased	Hemodynamic stability, fewer arrhythmias, suppresses PTH	Altered nerve conduction, pruritus, renal bone disease
Decreased	Permits use of magnesium-containing phosphate binders; improved bone mineralization; less bone pain	Arrhythmias, muscle weakness and cramps, elevated PTH
Glucose		
Decreased	Avoidance of intradialytic hyperglycemia and hyperinsulinemia	Increased risk for disequilibrium (rare), hypoglycemia
Increased	Lower risk for disequilibrium	Intradialytic hyperglycemia and hyperinsulinism
Citrate	Heparin-sparing effect	High blood citrate levels in liver failure

PTH, Parathyroid hormone.

Middilution Hemodiafiltration

Replacement fluid is infused within specifically designed dialyzers partway down the blood pathway so that the first part of the blood circuit is operated in postdilution and the second part in predilution mode.

UREMIC TOXINS AND THEIR REMOVAL BY HEMODIALYSIS

Uremic toxins have been traditionally categorized based on their molecular weight and binding properties (Table 93.5). The list of uremic toxins is steadily growing.[5] Recent research has identified the gut, in particular the colon, as an important source of uremic toxins and their precursors. These colon-derived toxins are products of bacterial metabolisms, such as phenols, indoles, and amines.[6]

Low molecular weight compounds not bound to protein: These include urea, and guanidines such as asymmetric dimethylarginine (ADMA), which are structural metabolites of arginine, purines, pyrimidines, oxalate, phosphorus, and uric acid. Modern dialysis membranes achieve maximal removal of these compounds. However, clearances are usually lower than that of urea, which is explained by their higher molecular weights (within the 500 d limit) and multicompartmental distribution increasing transfer time.

Low molecular weight compounds bound to protein: To varying degrees, these include major uremic toxins indoxyl and cresyl compounds, advanced glycation end-products, tumor necrosis factor-α, and phenolic compounds. Clearances of the unbound fraction may be increased by use of HDF, especially postdilutional modes. "Leaky" dialysis membranes increase the clearance of such substances bound to plasma proteins decreasing with total molecular weight of the bound substance in relationship to the pore size of the membrane.

Middle molecule compounds: Traditionally, middle molecules encompass substances with a molecular weight between 5 and 32 kDa. Their removal by low-flux dialyzers is poor. The diffusive removal of these compounds can be improved by the use of high-flux dialyzers, and their convective removal is further improved by high-volume HDF.[7] The potential advantages in increasing the removal of specific middle molecule toxins have not been evaluated yet in appropriate clinical trials.

ADDITIONAL DEVICES AND TECHNOLOGIES

Relative Blood Volume Monitoring

Blood volume monitors provide continuous noninvasive monitoring of relative changes in blood volume by continuous measurement of plasma protein concentration by ultrasound or hematocrit by optical scattering. A decline in relative blood volume occurs when the ultrafiltration rate exceeds the plasma refilling rate. A sharp decline in relative blood volume may precede intradialytic hypotension. In the randomized controlled Crit-Line Intradialytic Monitoring Benefit (CLIMB) study, mortality was higher in patients using relative blood volume monitoring compared with conventional monitoring. However, because of an atypically low mortality rate in the conventional monitoring group, the authors pointed out that these findings should be generalized to the U.S. HD population with caution.[8] In some dialysis machines the rate of blood volume change is used to automatically adjust ultrafiltration rates and dialysate sodium concentration (feedback control). This

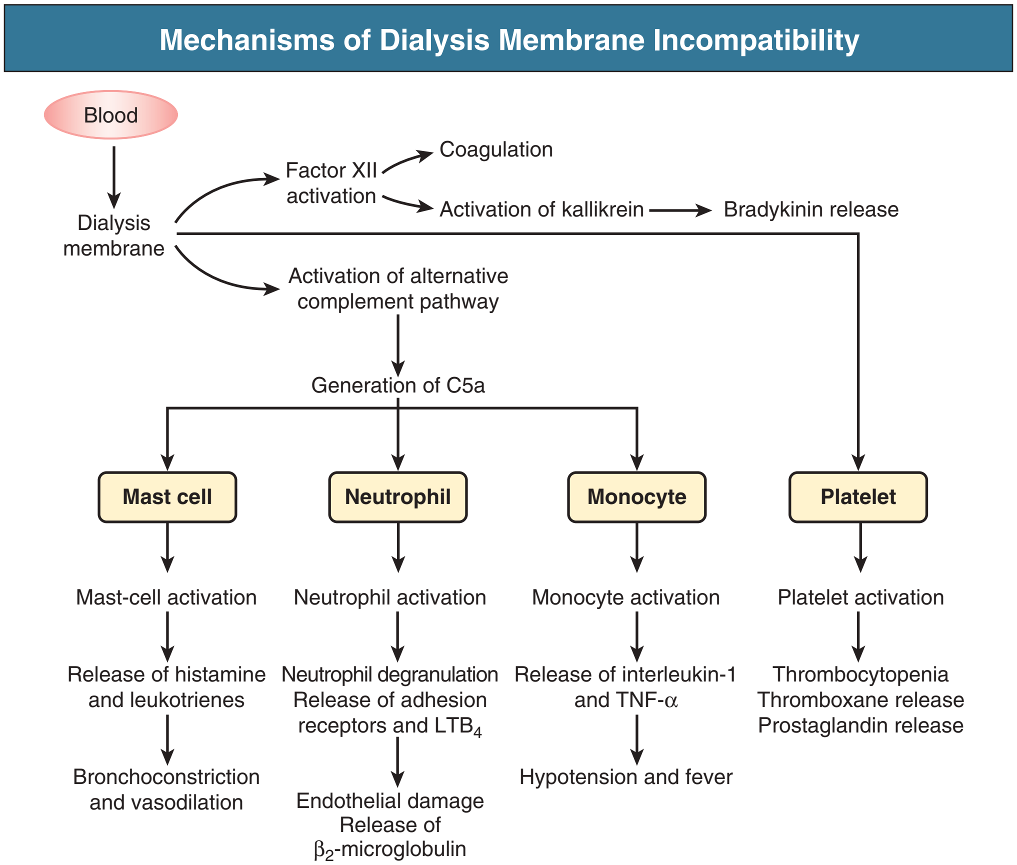
Mechanisms of Dialysis Membrane Incompatibility
Blood
Dialysis membrane
Factor XII activation
Coagulation
Activation of kallikrein
Bradykinin release
Activation of alternative complement pathway
Generation of C5a
Mast cell
Neutrophil
Monocyte
Platelet
Mast-cell activation
Neutrophil activation
Monocyte activation
Platelet activation
Release of histamine and leukotrienes
Neutrophil degranulation Release of adhesion receptors and LTB4
Release of interleukin-1 and TNF-α
Thrombocytopenia Thromboxane release Prostaglandin release
Bronchoconstriction and vasodilation
Endothelial damage Release of β2-microglobulin
Hypotension and fever

Fig. 93.3 **Mechanisms of dialysis membrane incompatibility.** Pathways involved in the body's response to dialysis membranes. *LTB 4,* Leukotriene B_4; TNF-α tumor necrosis factor-α.

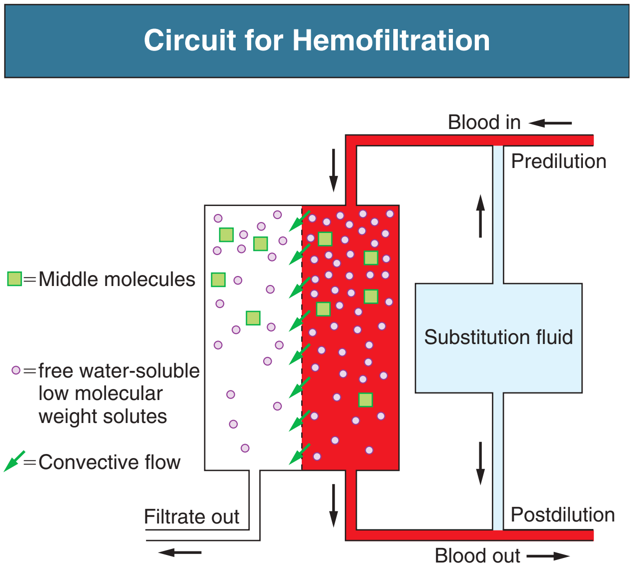
Circuit for Hemofiltration
Blood in
Predilution
🟩=Middle molecules
○=free water-soluble low molecular weight solutes
=Convective flow
Substitution fluid
Filtrate out
Postdilution
Blood out

Fig. 93.4 Circuit for hemofiltration.

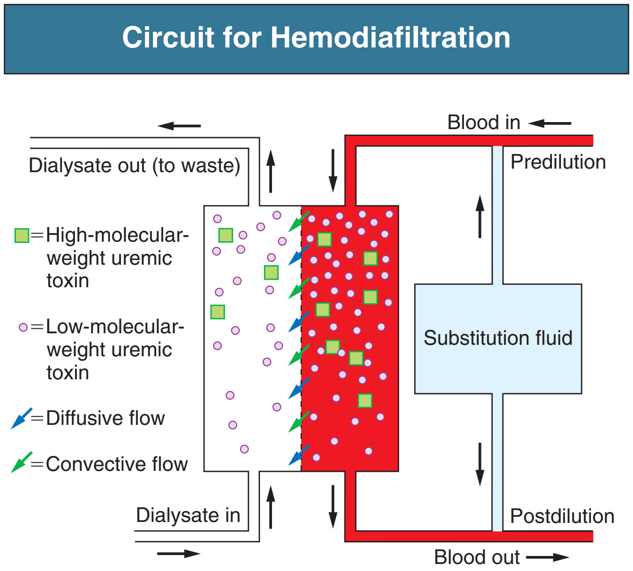
Circuit for Hemodiafiltration
Blood in
Dialysate out (to waste)
Predilution
🟩=High-molecular-weight uremic toxin
○=Low-molecular-weight uremic toxin
=Diffusive flow
=Convective flow
Substitution fluid
Dialysate in
Postdilution
Blood out

Fig. 93.5 Circuit for hemofiltration.

approach has been shown to reduce the frequency of symptomatic intradialytic hypotension.[9,10]

Ultrafiltration Profiling

The ultrafiltration rate is usually kept constant, but can be changed during the dialysis session in a preprogrammed manner (ultrafiltration profiling). It may be advantageous to remove a large proportion, for example, two thirds of the prescribed total ultrafiltration volume in the first half of the HD session. Because of a high initial plasma refilling rate, severely fluid-overloaded patients may tolerate a higher ultrafiltration rate in the early stages and normal fluid status may be reached more easily. The clinical benefits of ultrafiltration profiling are under debate.

TABLE 93.5 **Organic Uremic Solutes**

Free Water-Soluble Low Molecular Weight Solutes	MW	Protein-Bound Solutes	MW	Middle Molecules	MW
Guanidines		**AGEs**		**Cytokines**	
ADMA	202	3-Deoxyglucosone	162	Interleukin-1β	32,000
Argininic acid	175	Fructoselysine	308	Interleukin-6	24,500
Creatinine	113	Glyoxal	58	Tumor necrosis factor-α	26,000
Guanidine	59	Pentosidine	342	**Peptides**	
Methylguanidine	73	**Hippurate**		Adrenomedullin	5,729
Peptide		Hippuric acid	179	ANP	3,080
β-Lipotropin	461	**Indoles**		β_2-Microglobulin	11,818
Polyols		Indoxyl sulfate	251	β-Endorphin	3,465
Erythritol	122	Melatonin	126	Cholecystokinin	3,866
Myoinositol	180	Quinolinic acid	167	Cystatin C	13,300
Sorbitol	182	**Phenols**		Delta sleep-inducing peptide	848
Threitol	122	Hydroquinone	110	Hyaluronic acid	25,000
Purines		*p*-Cresol	108	Leptin	16,000
Cytidine	234	Phenol	94	Neuropeptide Y	4,572
Hypoxanthine	136	**Polyamines**		PTH	9,225
Uracil	112	Putrescine	88	Retinol-binding protein	21,200
Uric acid	168	Spermidine	145	**Other**	
Xanthine	152	Spermine	202	Complement factor D	23,750
Pyrimidines		**Other**			
Orotic acid	174	Homocysteine	135		
Thymine	126				
Uridine	244				
Ribonucleosides					
1-Methyladenosine	281				
Pseudouridine	244				
Xanthosine	284				
Others					
Malondialdehyde	71				
Oxalate	90				
Urea	60				

ADMA, Asymmetric dimethylarginine; *AGEs,* advanced glycation end products; *ANP,* atrial natriuretic peptide; *PTH,* parathyroid hormone.

Sodium Profiling

Normally, the dialysate sodium concentration is kept constant throughout the dialysis treatment. The variable sodium option allows dynamic changes of the dialysate sodium concentration during the treatment (sodium profiling). Some patients with hemodynamic instability may benefit from this option in which the initial sodium concentration is kept high and then slowly reduced to avoid sodium loading. In a recent meta-analysis, stepwise profiling was shown to be effective in reducing intradialytic hypotensive episodes.[11] Care is needed to ensure a significant amount of sodium is not added to the circulation.

Online Clearance Monitoring

Sodium and urea clearances are identical for practical purposes. The conductivity of the dialysate is largely a function of the dialysate sodium concentration, and online clearance monitors can use this feature to compute the urea clearance (K) of a dialyzer during a dialysis treatment. The conductivity clearance is equivalent to urea clearance, and Kt is easily calculated. Together with estimates of V (total body water), Kt/V can be determined during each treatment.

Blood Temperature Monitoring and Dialysate Cooling

In most patients, HD exerts a net positive thermal balance that may affect hemodynamic stability. "Cool" dialysate has been shown to improve vascular stability during dialysis. The core temperature can be controlled by blood temperature monitoring, which adapts the dialysate temperature according to the desired core temperature. A meta-analysis of 22 studies concluded that intradialytic hypotension occurred 7.1 times less frequently with cool dialysis[12] without reduction in urea clearance. A recent prospective randomized trial showed cardiac and brain white matter protection with individualized cooling at 0.5°C below body temperature.[13,14]

Intradialytic Oxygen Measurement

Blood coming from a functioning arteriovenous access resembles arterial blood. Some devices and dialysis machines measure predialyzer

TABLE 93.6 Home Hemodialysis Prescription and Practices

	Conventional	Short Daily	Nocturnal	Low Dialysate Flow Systems
Treatments per week	3	6	5-6	6
Treatment time (hours)	4	2-3	6-8	2.5-3.5
Blood flow rate (ml/min)	400	400	200	400
Dialysate flow rate (ml/min)	500	800	300	130

blood oxygen saturation. There is some indication that hypoxemia is associated with episodes of intradialytic hypotension. In an observational study, patients with prolonged intradialytic hypoxemia showed greater morbidity and mortality.[15]

Bioimpedance

Bioimpedance devices are increasingly used to determine fluid status in HD patients. In a prospective randomized trial the use of whole-body bioimpedance resulted in a reduction of fluid overload by 2 liters in fluid-overloaded patients without increasing the occurrence of intradialytic adverse events. This reduction of fluid overload was associated with reduction in systolic blood pressure and antihypertensive medication.[16]

HOME HEMODIALYSIS

Home HD (HHD) offers several clinical benefits compared with conventional renal replacement therapies, such as better survival, enhanced blood pressure control and left-ventricular geometry, normalization of phosphate balance, augmentation of kidney-specific quality of life scores, and improved fertility.[16] HHD also provides greater patient autonomy in a cost-effective manner.[17] There are variations in HHD prescription and practices (see Table 93.6). Additionally, conventional HD platforms and low dialysate flow systems may be used in the home.

Several considerations should be addressed before commencing patients on HHD. Routinely, a home visit should be conducted before starting home dialysis to assess for feasibility and potential renovations and modifications.

DIALYSIS MACHINE CHOICE AND OTHER EQUIPMENT

The choice of machine should be tailored to the patient's individual requirements and preference, and it will also determine the ease of dialysis fluid preparation. Additionally, the availability of appropriate water, electrical supply, and space may influence the choice of HD machine. Conventional HD platforms will require water filtration systems, whereas others (i.e., low-dialysate flow systems) may use prepackaged dialysate or generate online dialysis solutions. Premixed bags are available with bicarbonate-buffered or lactate-buffered dialysate. All types of vascular accesses may be used for HHD. Registry data suggest that permanent vascular access has superior outcomes compared with tunneled HD catheters. Moreover, the use of buttonhole cannulation (compared with stepladder technique) is associated with higher infectious complications.

WATER PREPARATION, STANDARDS, AND PLUMBING

As for in-center HD, prevailing standards for water quality should be adhered to (see previous discussion). Depending on the local water conditions and regulations, water softener, backflow preventers, and blending devices may be necessary in the home. In certain circumstances, feeder tanks may be necessary to provide the water pressure necessary for the RO unit and dialysis machine to function properly.

SAFETY

All dialysis machines are equipped with monitors, as described earlier. Leak and moisture detectors should be placed around vascular access cannulation sites, under the dialysis machine, and at the water treatment system. For central venous catheters, special connectors or catheter safety lock boxes can be used. Telemonitoring systems have been employed for HHD, though they are not a prerequisite. Practically, most HHD users continue to rely on an "on-call" system for troubleshooting. Typically, arterial and venous pressure alarms are the most common type of alarms. The average number of alarms per night decreased significantly over time as patients gained experience with HHD (from a maximum of 1.98 ± 3.31 alarms/night to a low of 0.74 ± 1.63 alarms/night) according to the London Ontario experience.[18]

WEARABLE ARTIFICIAL KIDNEY

Wearable artificial kidneys (WAKs) have been successfully tested in clinical trials, proving the concept that this technology is safe and a potential future form of renal replacement therapy.[19] The WAK is light, small, and ergonomic enough to be worn as a belt, allowing patients to ambulate and perform activities of daily life while the WAK delivers sufficient rates of fluids and solutes removal. The dialysate is recirculated through a series of sorbent cartridges containing urease, zirconium resins, and charcoal. These purify and regenerate the dialysate so it can be recirculated back into the dialyzer continuously. As a result, the WAK requires only 400 ml of dialysate. At their current stage, though, WAKs are not yet suitable for routine use, facing formidable challenges such as anticoagulation, toxin clearance, and fluid removal.

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SELF-ASSESSMENT QUESTIONS

1. Which statement is correct?
   - **A.** Bacterial endotoxin in the hemodialysis (HD) fluid cannot pass through the dialysis membrane.
   - **B.** An increase in HD fluid sodium concentration will always raise the serum sodium level.
   - **C.** HD fluid buffers include anions such as bicarbonate diacetate, chloride, and citrate.
   - **D.** HD fluid potassium concentrations of 1 mEq/l are safer than 3 mEq/l.
2. Which statement is correct?
   - **A.** A high-protein diet will eventually reduce the level of uremic toxins in the blood.
   - **B.** Urea is considered a powerful uremic toxin.
   - **C.** Some uremic toxins are synthesized in the colon and absorbed into the bloodstream.
   - **D.** Hemodiafiltration (HDF) is highly efficient in removing protein-bound uremic toxins.
3. Which statement is correct?
   - **A.** Heparin should not be used as an anticoagulant when dialyzing patients with autoimmune diseases.
   - **B.** Thanks to biocompatible dialysis membranes, aluminum intoxication is no longer a concern.
   - **C.** Predilution HDF is most efficient in terms of increasing solute removal.
   - **D.** Dialysate cooling is an effective means to increase hemodynamic stability.
4. Which statement is correct?
   - **A.** Intradialytic hypoxemia is associated with poor outcomes.
   - **B.** Sodium profiling is a preferred way to treat patients with intradialytic hypertension.
   - **C.** In patients with predialysis serum potassium levels above 6.2 mEq/l, a dialysate potassium concentration of 0 mEq/l is warranted.
   - **D.** Home HD is not advised in patients with diabetes mellitus.
5. Which statement is correct?
   - **A.** A positive venous pressure is a reliable indicator of correct needle placement.
   - **B.** Water treatment is key to the preparation of adequate dialysis fluid.
   - **C.** Intradialytic hypoxemia is associated with poor outcomes.
   - **D.** Modern dialyzer membranes combine polysulfone with cellulose.

94

Hemodialysis: Dialysis Prescription and Adequacy

Martin K. Kuhlmann, Peter Kotanko, Nathan W. Levin

From an idealistic perspective an adequately treated hemodialysis (HD) patient is physically active, well nourished, euvolemic, and normotensive with a maintained good quality of life and a life expectancy comparable to that of similarly aged persons with normal kidney function. The HD treatment retains a core position among the many different aspects of the multifactorial management necessary to achieve these goals. Adequacy of HD treatment today encompasses more than just the replacement of excretory kidney function (dialysis dose) and extends to the prevention of intradialytic and interdialytic complications, particularly the maintenance of hemodynamic stability and organ perfusion. Elderly patients, the largest group of prevalent and incident dialysis patients worldwide, because of their compromised vascular status and multiple comorbid diseases, are especially vulnerable to hemodynamic effects of the dialysis treatment and therefore require a special approach in dialysis prescription.

ASSESSMENT OF DIALYSIS DOSE

Markers of Uremic Toxin Removal by Renal Replacement Therapy

Urea Removal

Among all potential uremic toxins, only urea, a 60-d small water-soluble compound, is established as a marker of uremic solute retention and removal. Urea, which itself shows little toxicity, is a metabolite of amino acid metabolism; urea generation therefore depends on protein intake and the balance between protein anabolism and catabolism. Urea removal was originally considered to be representative of the removal of other water-soluble solutes with a higher pathogenic impact, but it is now clear that urea removal does not closely parallel that of other small water-soluble compounds, protein-bound solutes, or middle molecules. Urea is most easily transferred across cell membranes by diffusion or specific urea transporters, thus allowing rapid equilibration of urea concentration within whole-body water after dialytic removal of urea from the blood compartment. For almost all other small and middle molecular weight uremic toxins, many of which are highly protein bound, the intercompartmental transfer rate is much slower, leading to protracted equilibration between the various compartments. Nevertheless, knowledge of urea kinetics is essential for the general understanding of the physics and basic principles of solute accumulation and of removal during dialysis.[1]

Similarly to native kidney function, the delivered dose of dialysis is conventionally assessed by the rate of removal of selected uremic toxins from the patient's body. For more than two decades urea removal from the body has been expressed either by the urea reduction ratio (URR), or by the treatment index *Kt*/*V*. The urea clearance of the dialyzer itself is a marker of dialyzer efficiency but not of dialysis dose. Although urea has shortcomings as a marker of dialysis adequacy, its removal is still the standard measure to quantify dialysis treatment. The dialysis dose ideally should be evaluated in conjunction with residual renal function (RRF) measurement using the same uremic toxin.

Intradialytic Urea Kinetics

Dialyzers are highly efficient at removing urea from the blood, reducing plasma urea concentration during one dialyzer passage by more than 90%. Intradialytic plasma urea kinetics is satisfactorily described by a two-compartment model in which the intravascular blood compartment is replenished with urea through redistribution from extravascular body water compartments. Because intercompartmental redistribution is not immediate, the intradialytic urea concentration in the blood compartment is always lower than in the extravascular compartments and postdialysis blood urea concentration rebound occurs within 30 to 60 minutes after the end of the dialysis treatment until full equilibration between all compartments is reached. The dynamics of urea redistribution depend on the urea concentration gradient between blood water and extravascular water, but also on blood flow in the various tissue regions. Accordingly, intradialytic urea kinetics are best described by "equilibrated" models that consider the various compartments (Fig. 94.1, *solid line*). In contrast, the classic single-compartment (single-pool) urea kinetic model (UKM) assumes that full equilibration between blood and tissue compartments occurs immediately. In such idealized models, the change in serum urea follows first-order kinetics, with a linear decline and no urea rebound (see Fig. 94.1, *dashed line*).

Current methods for assessment of dialysis dose are based on the predialysis and postdialysis difference in serum urea and include URR, single-pool *Kt*/*V* (*spKt*/*V*), equilibrated double-pool *Kt*/*V* (*eKt*/*V*), and weekly standard *Kt*/*V* (*d-Kt*/*V*).

Urea Reduction Ratio

URR refers to the treatment-related reduction of serum urea concentration and is computed as:

$$\mathrm{URR}\,(\%) = (1 - C_t/C_0) \times 100\%$$

where C_t is postdialysis and C_0 is predialysis serum urea concentration.

URR is a simple but rather imprecise way to quantify dialysis dose because it does not take into account intradialytic urea generation and convective urea removal by ultrafiltration and is a single-pool measurement. Despite these limitations, URR correlates well with dialysis outcome and is an accepted method for assessment of dialysis dose. A minimum URR of 65% to 70% can be considered an adequate dialysis dose.

Single-Pool Kt/V (spKt/V) and Equilibrated Double-Pool Kt/V (eKt/V)

The treatment index *Kt/V* is the most widely used parameter to assess dialysis dose. *Kt/V* is a dimensionless number representing the total plasma volume cleared (*K*×*t*, in liters) in relation to the individual volume of distribution (*V*, in liters). The concept of *Kt/V* may be applied to any substance but in clinical practice is almost exclusively used for urea, where *K* is the dialyzer blood water urea clearance (liters per hour), *t* is dialysis session length (hours), and *V* is the distribution volume of urea (liters), which equates closely to total body water. A delivered *Kt/V* of 1.0 implies that the volume of plasma cleared of urea (*K*×*t*) during a dialysis session is equal to urea distribution volume (*V*). However, because of the multicompartment kinetics of urea equilibration, and its constant formation, clearing a plasma volume equivalent to 1 unit of total body water (V) does not mean that all urea has been removed from body water.

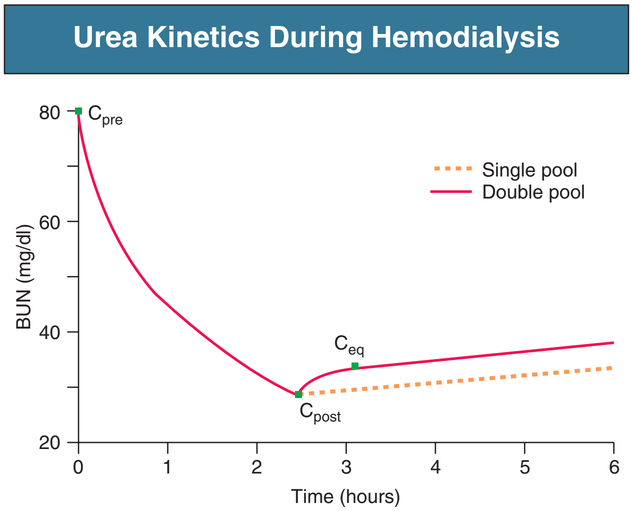


Fig. 94.1 Urea kinetics during hemodialysis. Urea kinetics is determined by the difference between predialysis (C_{pre}) and postdialysis (C_{post}) blood urea nitrogen *(BUN).* The single-pool Kt/V model assumes no relevant change in BUN concentration after termination of dialysis except for a slow constant increase as a result of BUN generation *(yellow dashed line).* The double-pool Kt/V model *(red line)* more accurately describes the in vivo situation, in which intercompartmental urea redistribution leads to a urea rebound until full equilibration between blood and tissue compartments is reached. Equilibrated postdialysis BUN concentration (C_{eq}) can be mathematically predicted from postdialysis BUN (C_{post}).

In daily clinical practice and in the absence of availability of formal UKM, single-pool Kt/V (spKt/V) is computed from the Daugirdas equation, which is based on URR but also accounts for intradialytic urea generation and ultrafiltration volume.[2] The Daugirdas equation is validated for a *Kt/V* range between 0.8 and 2.0 and is widely used because of its simplicity and accuracy.

$$spKt/V = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times UF/W$$

where *ln* is the natural logarithm, *R* is the postdialysis/predialysis serum urea ratio, *t* is treatment time (hours), *UF* is ultrafiltration volume (liters), and *W* is the patient's postdialysis body weight (kilograms).

Single-pool Kt/V regularly overestimates the delivered dialysis dose because nonequilibrated post-HD urea concentration is used for computation. A more accurate estimate of delivered dialysis dose is achieved by using the equilibrated post-HD urea concentrations. The difference between equilibrated and nonequilibrated urea concentration depends on the intensity of dialysis; the shorter and more intense a treatment, the higher is the rebound. The more accurate equilibrated double-pool Kt/V is directly computed from spKt/V and improves the accuracy of dialysis dose assessment. Because equilibrated post-HD serum urea concentrations are higher than nonequilibrated concentrations, *eKt/V* is lower than *spKt/V* for any treatment. By applying these equations the volume of distribution does not need to be measured separately (Table 94.1).

Correct assessment of *Kt/V* requires accurate timing of blood collections. Predialysis blood samples must be collected right at the start of the treatment and postdialysis samples immediately before termination of treatment after slowing the blood flow rate to reduce any potential effect of recirculation. Blood sampling procedures should be standardized (for recommendations see reference 3). URR, sp*Kt/V,* or *eKt/V* should be assessed monthly, and the dialysis prescription adjusted accordingly. In large observational studies, mortality was higher at *spKt/V* of less than 1.2, and a target *spKt/V* of 1.4 is recommended for conventional thrice-weekly dialysis schedules.[3]

A very accurate form for prescribing dialysis dose is a software-based formal UKM, in which spKt/V is modeled from prescribed dialyzer clearance (K), blood and dialysate flow rates, ultrafiltration volume, treatment time, and initial assumed urea distribution volume. By comparing modeled Kt/V to delivered Kt/V, problems in the delivery of dialysis dose (such as vascular access recirculation) can be readily identified. Besides dialysis dose, the mathematical models integrated in UKM allow the estimation of protein catabolic rate (PCR) or protein equivalent of nitrogen appearance (PNA), a measure of the balance between protein catabolism and protein synthesis, including dietary protein intake. Most modern HD machines provide the option to monitor urea clearance

TABLE 94.1 Computation of Dialysis Dose*

Results Derived From Different Model Equations

Formula	Result	Comment
$URR = (1 - C_t/C_0) \times 100\%$	67%	Urea rebound, urea generation, and ultrafiltration not taken into account
$Kt/V = \ln(C_0/C_t)$	1.10	Urea rebound, urea generation, and ultrafiltration not taken into account
$spKt/V = -\ln(R - 0.008 \times t) + (4 - 3.5\,R) \times UF/W$	1.33	Single-pool model; urea rebound not taken into account
$eKt/V = spKt/V - 0.6 \times spKt/V/t + 0.03$	1.16	Double-pool model for arteriovenous access, including urea rebound
$eKt/V = spKt/V - 0.47 \times spKt/V/t + 0.02$	1.20	Double-pool model for central venous access, including urea rebound

*Calculations based on dialysis duration *(t)* = 4 hours.
Predialysis blood urea nitrogen (BUN) (C_0) = 90 mg/dl; nonequilibrated postdialysis BUN (C_t) = 30 mg/dl; ultrafiltration volume *(UF)* = 3 liters; postdialysis body weight *(W)* = 72 kg; $R = C_t/C_0$.
URR, Urea reduction ratio.

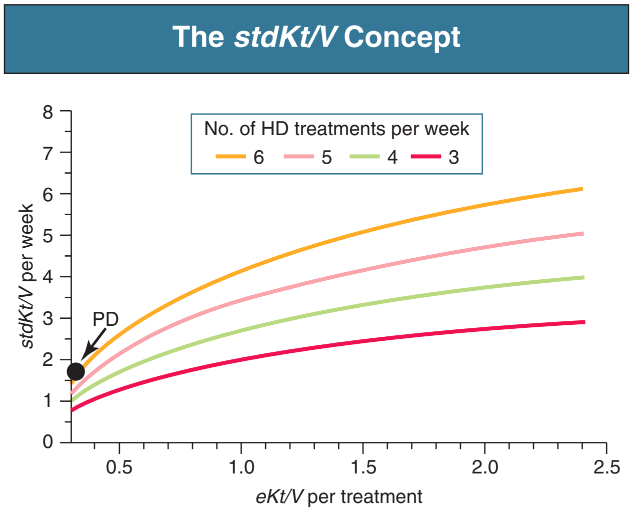


Fig. 94.2 **The weekly *std-Kt/V* concept.** The weekly *std-Kt/V* for any hemodialysis *(HD)* frequency is derived by plotting *eKt/V* of a representative dialysis session onto the respective frequency curve. *PD,* Peritoneal dialysis.

online during dialysis and assess sp*Kt/V* during each single dialysis session without the need for blood sampling. However, a weakness of the online method lies in the inability to measure the volume of urea distribution directly.

Weekly Dialysis Dose and Weekly Standard: *Kt/V* (*stdKt/V*)

A useful way to compare native kidney function with dialysis dose across a wide variety of dialysis modes and frequencies is by looking at an average clearance (in milliliters per minute) of any given solute achieved over a unifying period, such as 1 week. The established parameter developed for this comparison is the weekly standard Kt/V for urea (weekly stdKt/V). With this concept, a thrice-weekly *intermittently* provided dialysis urea clearance (e.g., 250 ml/min for 4 hours thrice weekly and 0 ml/min for the remaining 6.5 days per week) is converted to an equivalent *continuous* extracorporeal urea clearance (in milliliters per minute) related to urea distribution volume *V* (ml).[4] The resulting dimensionless *stdKt/V* value is directly compatible with the continuous native residual renal clearance (GFR or renal Kt/V) and peritoneal clearance (*weekly peritoneal Kt/V).* The principle of *weekly stdKt/V* is visualized in Fig. 94.2, in which on the x-axis the *eKt/V* of a representative dialysis session is plotted onto a curve representing the prescribed treatment frequency, and the resulting stdKt/V is then derived from the intercept with the y-axis. The frequency curves are not linear because the decreasing transmembrane urea gradient over time results in decline of the efficiency in dialysis urea mass removal. A maximum *stdKt/V* of 3.0/week can be achieved with conventional thrice-weekly dialysis independent of treatment time. To further increase weekly dialysis dose, treatment frequency needs to be modified. Continuous RRF, expressed as *renal Kt/V,* is added directly to dialysis *std-Kt/V*. Independent of the treatment schedule, a minimum target *stdKt/V* of 2.3/week with a minimum delivered stdKt/V of 2.1 including *renal Kt/V* is recommended for all patients.[5] In anuric patients this is achieved with a standard thrice-weekly schedule and delivered dialysis dose of *spKt/V* of 1.2 per treatment.

MIDDLE MOLECULE REMOVAL

It is widely held that retention solutes of middle molecular size may play an important role in the pathogenesis of uremia and contribute significantly to the high mortality of dialysis patients. Because of higher membrane porosity, high-flux dialyzers can remove larger amounts of middle molecules than low-flux dialyzers, and this may be further increased by the use of convective dialysis strategies, such as hemodiafiltration (HDF). Because of slower intercompartmental equilibration rates, middle molecule removal is limited during conventional 4-hour dialysis sessions. Serum β_2-microglobulin, a surrogate for uremic middle molecules, can be effectively removed only by high-flux dialysis. Predialysis β_2-microglobulin levels were found to be related to mortality in patients treated randomly with high-flux or low-flux dialyzers.[5] Certain subgroups of dialysis patients, such as diabetics, and incident patients with serum albumin levels below 40 g/l, may benefit most from high-flux dialysis.[6,7] The European Best Practice Guidelines recommend the use of synthetic high-flux membranes to reduce cardiovascular risk and improve control of hyperphosphatemia and anemia.[8]

High-volume online HDF has the potential to provide the largest removal of the widest range of low and middle molecular size solutes. Diffusive and convective solute elimination are maximized to the benefit of the removal of larger molecular size solutes. Because diffusive urea clearance during standard HD treatment is already high and does not increase by more than 10% when convective clearance is added, urea removal is not an adequate marker of treatment dose in convective dialysis modes. In HDF, mass removal of middle molecules is directly related to ultrafiltration volume, which is also referred to as *convection volume* (CV) (see Chapter 93). The *effective* CV is used as key quantifier for HDF dosing, where the term *effective* principally relates to the undiluted blood water volume removed by filtration. Thus, in postdilution mode, the *effective* CV is identical to total CV whereas in predilution or mixed-dilution mode, the *effective* CV is considerably lower than total CV.

Three randomized controlled studies (CONTRAST Study, the Turkish HDF Study, and the ESHOL trial)[9-11] failed to demonstrate convincingly that survival with postdilution high-volume HDF is superior to conventional low-flux or high-flux HD. However, in each trial, patients receiving the highest CV had a significantly lower mortality risk compared with those receiving a lower HDF dose. An individual patient data analysis of these online HDF trials demonstrated a significantly reduced risk for mortality for patients receiving more than 23 liters of effective CV normalized to a body surface area of 1.73 m^2 in postdilution HDF mode.[12] Adjustment of target HDF dose to some measure of body size makes sense in view of the fact that both generation rate and distribution volume of uremic toxins are related to body mass.

Phosphate Removal

Hyperphosphatemia is a major problem in HD (see Chapter 85).[13] Management of hyperphosphatemia is based on phosphate removal by dialysis, dietary phosphate restriction, and intestinal phosphate binding with use of phosphate binder medication. Despite its low molecular weight, the effective molecular size of phosphate (as a result of rather stable coating with several water moieties) is much bigger than that of other low molecular weight solutes, which impairs intercompartmental and transmembrane phosphate transport during dialysis. Intradialytic phosphate kinetics resembles much more those of middle molecules, with serum phosphate levels steeply falling during the first 90 to 120 minutes into dialysis as a result of removal primarily from plasma and extracellular volumes and stabilizing thereafter (Fig. 94.3). This intradialytic plateau is explained by phosphate mobilization from various compartments at a rate similar to that of dialyzer phosphate removal. Phosphate removal can be improved by high-flux HD and HDF, by the use of larger dialyzer surface area, and, most dramatically, by longer or higher frequency dialysis schedules, such as short daily or daily nocturnal HD. Long, frequent dialysis schedules may even result in

Management of Low *Kt*/*V*

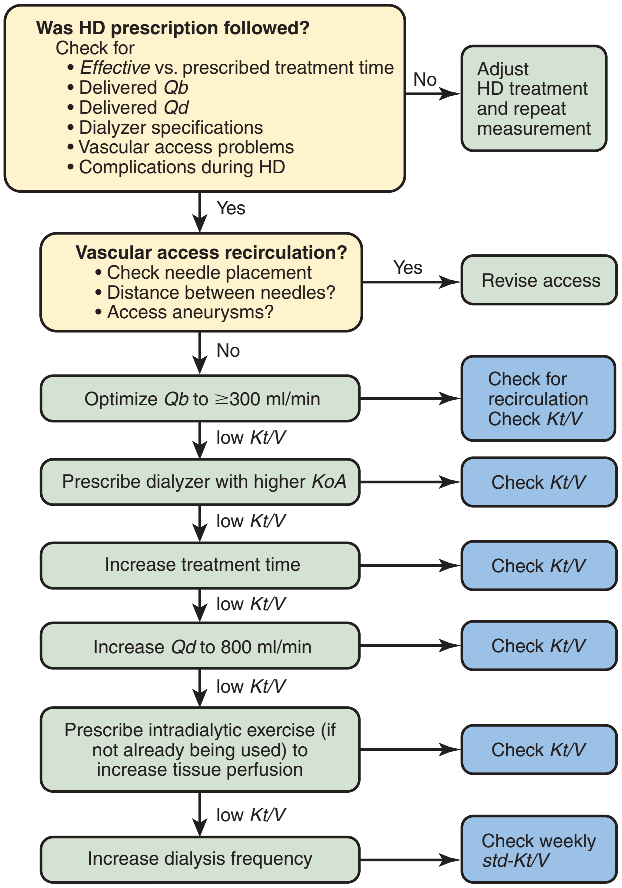

Was HD prescription followed?
Check for
• Effective vs. prescribed treatment time
• Delivered Qb
• Delivered Qd
• Dialyzer specifications
• Vascular access problems
• Complications during HD
No
Adjust HD treatment and repeat measurement
Yes
Vascular access recirculation?
• Check needle placement
• Distance between needles?
• Access aneurysms?
Yes
Revise access
No
Optimize Qb to ≥300 ml/min
Check for recirculation Check Kt/V
low Kt/V
Prescribe dialyzer with higher KoA
Check Kt/V
low Kt/V
Increase treatment time
Check Kt/V
low Kt/V
Increase Qd to 800 ml/min
Check Kt/V
low Kt/V
Prescribe intradialytic exercise (if not already being used) to increase tissue perfusion
Check Kt/V
low Kt/V
Increase dialysis frequency
Check weekly std-Kt/V

Fig. 94.3 Management of low and inadequate *Kt/V*. *HD,* Hemodialysis; *KoA,* the dialyzer urea mass transfer area coefficient; *Qb,* blood flow rate; *Qd,* dialysate flow rate.

hypophosphatemia so that phosphate has to be added to the dialysate. In all patients, predialysis serum phosphate levels should be lowered toward the normal range.

PRESCRIPTION OF HEMODIALYSIS

Hemodialysis Dose

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend a target spKt/V of 1.4 per HD session for patients treated thrice weekly, with a minimum delivered spKt/V of 1.2. In patients with significant residual native kidney function, the dose of HD may be reduced provided RRF is measured periodically to avoid inadequate dialysis. For HD schedules other than thrice weekly, a target stdKt/V of 2.3 volumes per week is provided with a minimum delivered dose of 2.1 using a method of calculation that includes the contributions of ultrafiltration and residual kidney function.[3]

Delivered dialysis dose depends on dialyzer efficiency (Kd), effective treatment time (t), and distribution volume (V). Dialyzer clearance Kd depends on the flow rates within the blood and dialysate compartments (Qb and Qd), dialyzer KoA, effective membrane surface area, hematocrit, and anticoagulation. Effective treatment time t is essential for reaching the Kt/V target and can be substantially shorter than prescribed treatment time because of intermittent pump stops or patient demand. Distribution volume V does not substantially change during a single HD session but may change over time. Therefore the dialysis dose needs to be adjusted when lean body mass, which closely correlates with V, increases. On the contrary, if there is a loss in muscle mass, which is associated with a decrease in V, Kt/V should not be reduced but rather based on a higher (ideal) patient V to support gains in body mass.[3]

Intradialytic Kinetics of Phosphate Removal and Mobilization

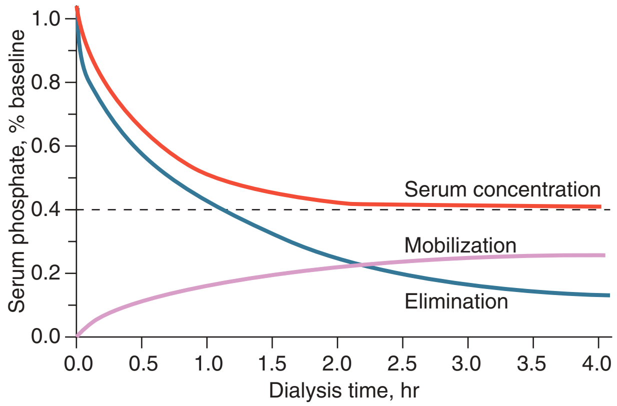


Fig. 94.4 Intradialytic kinetics of phosphate removal and mobilization.

A standard dialysis prescription should consist of a high-flux dialyzer, a minimum treatment time of 4 hours, a blood flow rate of at least 250 ml/min, and a dialysate flow rate of 500 to 800 ml/min. The prescription is then adjusted to meet the target *spKt/V* of 1.4. In severe and long-standing uremia, the target dose is approached slowly over the course of several sessions to avoid the dialysis disequilibrium syndrome. Confronted with an inadequate URR or *Kt/V*, it is sensible to check whether the studied session was representative of the average session, because unusual problems may have occurred (e.g., shortened time, vascular access recirculation, single-needle HD). Frequent causes of inadequately low delivered dialysis dose with recirculation are vascular access problems particularly of arterial supply. Blood sampling errors also should be considered because delayed post-HD blood sampling results in falsely low *Kt/V* results. If a low *Kt/V* remains unexplained, treatment time should be increased and a more efficient dialyzer and higher blood and dialysate flow rates should be considered (Fig. 94.4). Active or passive muscle stimulation before or during dialysis improves *Kt/V* by increasing blood supply to poorly perfused muscle tissue and facilitates urea and phosphate removal.[14] In selected patients, physical exercise before or during HD treatment will be a way to improve dialysis dose. Delivered *Kt/V* should be checked whenever the dialysis prescription has been modified substantially.

Hemodiafiltration Dose

The two major aims governing the prescription of high-volume online-HDF dose are adequate delivery of the target effective CV and the prevention of excess hemoconcentration. High-flux membranes offering high hydraulic permeability as well as high middle-molecule clearance are required for adequate HDF. Hydraulic permeability is reflected by the membrane ultrafiltration coefficient, whereas membrane permeability is defined by the sieving coefficients for selected middle molecules. For high-volume HDF a high-flux membrane with an ultrafiltration coefficient greater than 20 ml/h/mm Hg/m^2 and a sieving coefficient for β_2-microglobulin of 0.6 is recommended.[15]

The major determinants of achieving a prescribed target CV in postdilution HDF are blood flow rate (Qb), ultrafiltration rate (UFR), and treatment time (T). Because ultrafiltration is applied to undiluted blood, hemoconcentration necessarily occurs together with a lowering of blood flow rate within the dialyzer. Under certain circumstances this leads to the deposition of plasma proteins on the membrane surface, clogging of membrane pores, and occlusion of dialyzer capillaries. To prevent excessive hemoconcentration, UFR and Qb need to be individually adjusted so that the filtration fraction (FF), which is defined as the ratio of UFR to Qb, does not exceed 25%. Higher FF up to 30% can be safely achieved only with modern HD machines designed to optimize filtration rate based on constant assessment and optimization of transmembrane pressure. Effective treatment time in high-volume HDF with a fixed target CV will thus always depend on achievable Qb and UFR.

Treatment Time and Frequency

The European best practice guidelines recommend that dialysis should be delivered at least 3 times per week and the total duration should be at least 12 h per week, unless supported by significant residual RRF.[8]

Conventional thrice-weekly dialysis remains the standard of care in most countries, where treatment time is typically governed by dialysis dose *(*Kt/V*)*, with the consequence of longer dialysis in patients with higher urea distribution volumes. Acknowledging the difficulties in removing adequate amounts of fluid and low and middle molecular size uremic solutes during short dialysis sessions, a minimum treatment time of 4 hours per HD session is recommended in various countries. The argument that longer treatment time improves survival is confounded by factors such as body size, (smaller patients having higher mortality), lack of compliance, differences in sodium intake and therefore in interdialytic weight gain (IDWG), and frequently lack of successful postdialytic weight reduction.[16] More frequent in-center dialysis and longer dialysis hours delivered by in-center or home HD are increasingly used alternatives to conventional thrice-weekly treatment. Both modalities offer the opportunity for improved solute clearance and complete removal of IDWG with fewer intradialytic problems, particularly hypotension.

Several retrospective epidemiologic studies in larger patient populations suggest a survival advantage for patients treated with extended time and/or frequency dialysis schedules, such as daily nocturnal or thrice-weekly nocturnal HD, over conventional HD.[17-19] The randomized controlled Frequent Hemodialysis Network (FHN) Study[20] demonstrated that short daily in-center HD yielded favorable effects on the coprimary composite outcomes of death, change in left ventricular mass and death, or change in self-reported physical health. Analysis of patient survival over a median of 3.6 years after randomization suggested that short daily in-center HD reduced long-term mortality. Of note, a post-trial observational study of the FHN nocturnal trial with a median follow-up of 3.7 years, for reasons unknown thus far, indicated a higher mortality rate in patients randomly assigned to nocturnal HD compared with those randomly assigned to conventional dialysis.[21,22] In summary, current data suggest that short daily dialysis appears the most favorable for survival followed by thrice-weekly nocturnal and thrice-weekly HD.

Dialysate Composition

During a standard HD treatment session, a patient's blood is exposed to 120 to 200 liters of dialysate. The several ingredients of dialysate composition should therefore be prescribed with great care. Generation of near sterile dialysate and prescription of dialysate temperature are addressed in Chapter 93.

Sodium

A positive sodium balance is a typical feature of end-stage renal disease (ESRD) and an important factor in the pathogenesis of hypertension and fluid overload in HD patients. Judicious control of sodium balance is effective in normalizing blood pressure (BP), and dietary sodium intake should be restricted to approximately 6 g salt (2300 mg or 100 mmol sodium) per day. Sodium is mainly removed through ultrafiltration; but depending on the ratio of dialysate to plasma water sodium concentration, it will be additionally removed from or delivered to the patient by diffusion. To avoid a positive diffusive sodium balance, dialysate and serum sodium concentrations should be aligned or care should be taken that dialysate sodium does not exceed the patient's average predialysis serum sodium concentration by more than 2 to 3 mmol/l. There is clear indication that a positive sodium gradient— a dialysate sodium concentration exceeding the patient's serum sodium level—is associated with higher ultrafiltration volumes and possibly higher BP. The associations between serum and dialysate sodium levels, morbidity, and mortality are controversial.[23]

Nonosmotic tissue sodium storage has been documented in HD patients, and HD has the ability to clear some of the tissue sodium. More recently in patients with chronic kidney disease an association between left ventricular hypertrophy and tissue sodium has been demonstrated.[24,25]

Potassium

Potassium removal during dialysis ideally should be equal to the amount accumulated during the interdialytic period. The dialysate potassium concentration has to be set at a level that avoids pre-HD hyperkalemia as well as intradialytic hypokalemia, which may provoke dialysis-induced arrhythmia. The typical dialysate potassium concentration is set between 2.0 and 4.0 mmol/l. Prescription of potassium dialysate concentrations less than 2.0 mmol/l has been associated with an increased risk for tachyarrhythmia and sudden cardiac death and should therefore be avoided.[26]

Calcium

In light of accelerated vascular calcification in ESRD, intradialytic calcium delivery to the patient should be avoided. In patients using calcium salts as phosphate binders, a negative intradialytic calcium mass balance is desirable.[27] A standard dialysate calcium concentration of 1.25 to 1.50 mmol/l is recommended by Kidney Disease: Improving Global Outcomes (KDIGO), but some patients will be in positive balance even at 1.25 mmol/l.[28] These and higher dialysate calcium concentrations may be associated with tissue calcium accumulation, whereas lower dialysate calcium will stimulate parathyroid hormone (PTH) secretion. In most patients a dialysate calcium concentration of 1.25 mmol/l is now used.

Bicarbonate

Chronic metabolic acidosis is associated with decreased protein synthesis and increased protein catabolism and contributes to mineral and bone disorders. Normalized pre-HD bicarbonate levels in the range of 20 to 23 mmol/l are associated with improved survival. Dialysate bicarbonate concentration is typically set between 35 and 40 mmol/l to generate a transmembrane concentration gradient favoring bicarbonate delivery to the patient. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicate that both high (>27 mmol/l) and low (<17 mmol/l) predialysis serum bicarbonate levels are associated with increased risk for mortality and hospitalization.[29]

Magnesium

In the past, dialysate magnesium levels of 1.5 mmol/l were used frequently. Current recommended levels are between 0.5 and 1.0 mmol/l. Two recent observational studies in Japanese and U.S. HD patients showed an inverse association between serum magnesium levels and mortality.[30] It is unclear to what extent dialysate magnesium levels have a sustained effect on serum levels.

Fluid Status and Ultrafiltration Rate

Fluid overload is an established risk factor for the development of left ventricular hypertrophy and cardiovascular mortality. Adequate HD aims to normalize body water homeostasis and extracellular volume to a level comparable with that of patients of similar age and normal renal function. This ideal postdialysis body weight, which is representative of normal fluid status, is frequently termed *dry weight,* which often differs substantially from the target weight prescribed by the physician. Because of the difficulties in detecting fluid overload of 2 to 3 liters clinically, technical methods, such as bioimpedance, relative blood volume monitoring, and imaging (ultrasound, chest x-ray) for assessing volume status should be applied regularly.[31] UFRs above 10 ml/kg/h are associated with higher odds of intradialytic hypotension and a greater risk for mortality.[32]

With exception of habitual overdrinkers, salt intake governs water intake from thirst. Dietary salt restriction to 6 g salt per day is recommended to prevent high IDWG and the development of arterial hypertension and congestive heart failure. This often requires constant education including the family. A successful approach used has been the gradual and small reduction in postdialysis weight until BP is in the normal range.[33] Predialysis extracellular fluid depletion as determined by bioimpedance is associated with increased mortality.[34] It is important to realize that IDWG and fluid overload are not synonymous and that fluid depletion can result in high IDWG.[35]

DIALYSIS ADEQUACY

Dialysis adequacy used to be defined as prescribing and delivering a dialysis dose that is associated with the best long-term outcome. However, after many decades of intense international research it has become evident that not only mortality but also morbidity and quality of life of HD patients cannot be influenced by single measures but depend on a multitude of factors. Therefore dialysis adequacy in modern terms along with dialysis dose and dialysis prescription also includes several other measures, including prevention of intradialytic and interdialytic complications, particularly the maintenance of hemodynamic stability and organ perfusion during HD treatment.

Prevention of Intradialytic Hypotension

Intradialytic hypotension occurs in 20% to 30% of treatments and is associated with well-proven damage to the brain, gut, heart, and kidney and poor outcome. Intradialytic hypotension is often due to high rates of ultrafiltration occasioned by the necessity to remove large IDWGs in an often arbitrarily defined short dialysis time.[36] In addition, an individual inability to preserve organ perfusion in the face of dialysis-related hypotension or intravascular hypovolemia (e.g., secondary to uremic and/or diabetic autonomic dysfunction) may lead to short-term changes such as intradialytic cardiac stunning and long-term consequences, such as heart failure and cardiac mortality outcomes.[37] Prevention of high IDWG through dietary counseling in regard to sodium intake as well as lengthening of dialysis duration, dialysate cooling, use of α-sympathetic agonists such as midodrine, and avoidance of food during dialysis may be useful. In addition, prevention and management of postural hypotension immediately after dialysis is essential to prevent falls. Intradialytic hypotension is also discussed in Chapter 96.

Preservation of Residual Renal Function

Most patients starting dialysis still have considerable RRF, but by the end of the first year, the majority have lost RRF completely. Only 10% to 20% of patients still have RRF after more than 3 years of dialysis. RRF of urea clearance of 2 to 3 ml/min contributes significantly to the elimination of uremic toxins.[38] For a patient with an estimated total body water of 40 liters, a residual urea clearance of 2 to 3 ml/min is equivalent to a *stdKt/V* of 0.5 to 0.75/week. This translates into lower serum β_2-microglobulin, phosphate, potassium, urea, creatinine, and uric acid levels, as well as maintained endocrine, metabolic, and antioxidative stress functions; higher hemoglobin concentration; enhanced nutritional status; better quality of life scores; and a reduced need for dietary and fluid restrictions. Loss of RRF, in contrast, is associated with left ventricular hypertrophy. Risk factors for the loss of RRF include activation of the immune system by cellulose-based membranes and dialysate water impurities; intradialytic hypotension and renal hypoperfusion; use of angiotensin-converting enzyme inhibitors or nephrotoxic agents, such as radiocontrast media, aminoglycosides, and nonsteroidal antiinflammatory drugs; and hypercalcemia. Loss of RRF may be delayed by adequate target post-HD weight prescription and prevention of intradialytic hypotensive episodes.

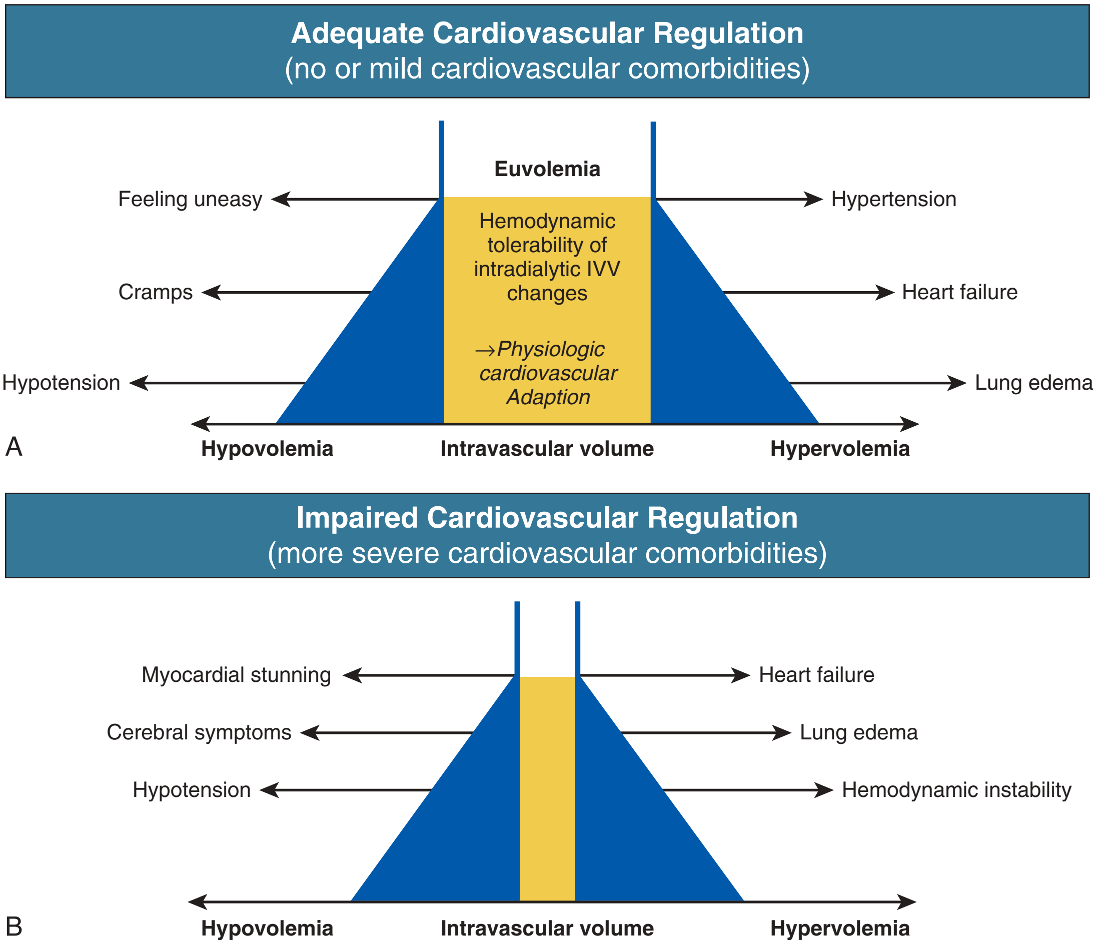
Maintenance or Improvement of Nutritional Status

HD patients are at risk for malnutrition secondary to protein-energy wasting, decreased appetite, infection, intercurrent illnesses, hospital admissions, and missed meals after dialysis.[39] The recommended daily intake of 1.2 g protein per kilogram of ideal body weight and 30 to 35 kcal per kilogram of ideal body weight are often not met. The nutritional status of dialysis patients should be assessed regularly by clinical and biochemical means, including measurement of PCR (or PNA), and technical means such as bioimpedance. Observational data indicate a beneficial effect of monitored intradialytic oral nutritional supplements in patients with albumin levels of 3.5 g/dl or greater.[40] Vitamin intake should be according to needs. Nutrition in HD patients is also discussed in Chapter 86.

Dialysis Adequacy in the Elderly

Patients older than 75 years of age represent the largest incident and fastest growing prevalent patient population in HD worldwide, and the unique medical and social needs of these patients requires consideration. Studies in this elderly patient population show that not the classic parameters of HD dose such as Kt/V and treatment time but other factors, such as cardiovascular comorbidity, nutritional status, functional capacity, and falls, are predictive of outcome.[41] Therefore the focus of dialysis adequacy in elderly patients should shift from assessment of dialysis dose to the use of a more multidimensional measure.[42]

Elderly dialysis patients with multiple comorbidities tolerate HD treatments less well than younger patients. Typical complications, such as intradialytic hypotension, cramps, trial fibrillation, and postdialysis fatigue contribute to the rapid loss of independence occurring in this vulnerable patient population. The underlying etiology is reduced tolerance to intravascular volume reduction during dialysis, which is at least partially caused by impaired cardiovascular hemodynamic responses in combination with uremic and/or diabetic autonomic neuropathy (Fig. 94.5). Significant reductions in organ perfusion occurring in the gut, liver, kidneys, heart, and brain contribute to the development of inflammation, malnutrition, heart failure, loss of RRF, frailty, depression, and dementia.[43] To protect vulnerable elderly patients from the dramatic short- and long-term consequences of intradialytic tissue hypoxia, the HD prescription can be individually adjusted. The following list provides some interventions that may help make HD treatments more tolerable in elderly patients, with the goal to reduce cardiovascular complications, sustain nutritional status, and slow the development of frailty.



Adequate Cardiovascular Regulation (no or mild cardiovascular comorbidities)

Impaired Cardiovascular Regulation (more severe cardiovascular comorbidities)

A
Euvolemia
Feeling uneasy
Hypertension
Hemodynamic tolerability of intradialytic IVV changes
Cramps
Heart failure
→Physiologic cardiovascular Adaption
Hypotension
Lung edema
Hypovolemia
Intravascular volume
Hypervolemia
B
Myocardial stunning
Heart failure
Cerebral symptoms
Lung edema
Hypotension
Hemodynamic instability
Hypovolemia
Intravascular volume
Hypervolemia

Fig. 94.5 Intradialytic vulnerability. The occurrence of complications *(arrows)* in response to intradialytic changes in intravascular volume *(IVV)* (x-axis) depends on the functionality of physiologic cardiovascular (CV) adaptation mechanisms, such as an increase in heart rate and constriction of arterioles and venous capacity vessels. The individual hemodynamic tolerability of intradialytic IVV changes *(yellow field)* is higher in patients on hemodialysis (HD) with no or mild CV comorbidities and intact CV responses (A) than in typically older and multimorbid HD patients with impaired cardiovascular regulation (e.g., secondary to diabetic autonomous neuropathy) (B). (Modified from reference 44.)

- Carefully evaluate individual susceptibility to intradialytic hypotension in relation to UFR.
- Assess vascular refilling capacity by monitoring intradialytic changes in blood volume.
- Individualize maximum UFR (ideally <10 ml/kg body weight/h).
- Consider ultrafiltration profiling and/or the use of dialysis machines with biofeedback control of UFR.
- Lower dialysate temperature to prevent the intradialytic increase in body core temperature associated with an increased risk for intradialytic hypotension.
- Reduce IDWG (dietary counseling regarding salt intake, prescribe adequately dosed diuretics).
- Avoid intradialytic positive sodium balance (individualize dialysate composition).
- Increase dialysis frequency in case the patient does not tolerate a long interdialytic interval.
- Reduce β-blocker medication to allow cardiac compensation for changes in intravascular volume.
- Reduce or pause antihypertensive medication before dialysis in hypotension-prone patients.
- Assess the effect of food intake during dialysis on hemodynamic stability.
- Regularly adjust postdialysis target weight (bioimpedance).
- If hypertensive, gradually reduce postdialysis weight, avoiding intradialytic hypotensive episodes.
- Consider supine position during dialysis.
- Consider online HDF.
- Consider peritoneal dialysis in patients with otherwise intractable intradialytic hypotension (IDH).
- Treat intradialytic hypoxia by intradialytic oxygen application.
- Ensure three meals per day, including the dialysis day.
- Prescribe oral nutritional supplements during and between dialysis treatments.
- Prevent immobilization by early rehabilitation and physical therapy.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following factors related to the hemodialysis prescription in a patient without much residual renal function is likely to result in the *worst* outcome?
   A. *Kt/V* of 1.15 over months
   B. Use of low-flux dialysers
   C. 3-Hour dialysis times
   D. Dialysate potassium of 2 mEq/l
2. Hypertension is very common in dialysis patients. Which factor alone is *least* likely to reduce blood pressure (BP)?
   A. Use of antihypertensive drugs
   B. Longer dialysis times with fluid removal
   C. Postdialysis weight reduction
   D. Dietary sodium restriction
3. Which action is *not* useful when the BP falls frequently during dialysis?
   A. Decrease dialysate temperature
   B. Apply abdominal pressure
   C. Reduce the ultrafiltration rate
   D. Increase postdialysis target weight
4. The recommended target convective volume in online hemodiafiltration (HDF) is 23 l/1.73 m^2/treatment. Which of the following actions is *not* useful to increase the convective volume?
   A. Increase ultrafiltration rate (UFR)
   B. Increase filtration fraction (FF)
   C. Increase blood flow rate (Qb)
   D. Increase dialysate flow rate (Qd)
   E. Increase treatment time (T)
5. In patients with residual kidney function, an intrinsic urea clearance of 3 ml/min is approximately equivalent to a weekly standard *KtV* of:
   A. 0.10
   B. 0.25
   C. 0.75
   D. 1.05
   E. 1.50

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Acute Complications During Hemodialysis

Kevan R. Polkinghorne, Peter G. Kerr

Although technical advances in hemodialysis (HD) have made the procedure increasingly safe and well tolerated, there are still important acute complications that will be encountered by physicians responsible for patients receiving HD in both acute and chronic clinical settings. These complications with their causes and management are discussed in this chapter.

CARDIOVASCULAR COMPLICATIONS

Intradialytic Hypotension

Intradialytic hypotension occurs in 10% to 30% of treatments, and ranges from asymptomatic episodes to marked compromise of organ perfusion resulting in myocardial ischemia, cardiac arrhythmias, vascular thrombosis, loss of consciousness, seizures, or death.[1] Furthermore, in patients with acute kidney injury, intradialytic hypotension may induce more renal ischemia and retard recovery of renal function. Recurrent HD-induced ischemic cardiac injury (myocardial stunning) is a prominent cause of intradialytic hypotension and is more common at higher ultrafiltration rates and less frequent with longer and more frequent dialysis treatments.[2] Like intradialytic hypotension and postdialysis orthostatic hypotension, myocardial stunning is an independent risk factor for mortality.[3] The pathogenesis of intradialytic hypotension is complex and is summarized in Fig. 95.1. Most commonly, however, intradialytic hypotension results from the need to deal with excessive fluid weight gain between dialysis treatments. The subsequent rate of fluid removal required exceeds the achievable rate of intravascular filling, resulting in relative intravascular volume depletion. Recent data demonstrate an increased risk for death as the ultrafiltration rate increases, regardless of the threshold used.[4]

The immediate treatment for intradialytic hypotension is to restore the circulating blood volume by placing the patient in the Trendelenburg position, reducing or stopping ultrafiltration, and infusing boluses of 0.9% isotonic saline (≥100 ml, as necessary). Salt-poor albumin and other hypertonic solutions offer no advantage over isotonic saline and are more expensive. Blood flow rate should not be routinely reduced to manage hypotension, because this has not been shown to be beneficial and will compromise solute clearance. Of course, in the setting of excessive weight gain, the administration of boluses of saline or cessation of ultrafiltration, makes achieving the target dry weight more difficult. Because cardiac factors can precipitate intradialytic hypotension, the clinician should maintain a high index of suspicion for cardiac ischemia, especially if hypotension is accompanied by chest pain or dyspnea, and an electrocardiogram and serum troponin values should be obtained. Similarly, recurrent and unexplained episodes of hypotension might warrant echocardiography to rule out pericarditis or pericardial effusion.

Preventive strategies include correction of anemia and hypoalbuminemia and treatment of congestive heart failure or arrhythmias, avoidance of antihypertensive drugs before dialysis, and avoidance of food before and during dialysis. Patients should be counseled to avoid excessive interdialytic weight gain because this is the predominant cause of intradialytic hypotension, and accurate assessment of the patient's dry weight is required. Particular attention should be given to ensuring minimal salt intake. Midodrine, an oral selective α_1-agonist, 5 to 10 mg before dialysis, can be a useful preventive therapy.

Preventive strategies through modification of the dialysis procedure include in the first instance use of bicarbonate dialysate, volumetric control of ultrafiltration, and sodium modeling. Subsequently, reducing the ultrafiltration rate by increasing either treatment time or the frequency of dialysis can be tried.[5] Online blood volume monitoring and biofeedback techniques have been developed in an attempt to improve intradialytic cardiovascular (CV) stability.[6] Although online blood volume devices decrease the incidence of intradialytic hypotension in an at-risk population, there is limited evidence that blood volume monitoring can predict intradialytic hypotension in individual patients or produce a long-term morbidity and mortality benefit, especially in the wider HD population.[6] Cooling of dialysate to 35.5° to 36° C (95.9° to 96.8° F), a measure that induces release of catecholamines, resulting in vasoconstriction or at least preventing vasodilation, may lessen hypotension. Modulation of dialysate temperature is achieved by measuring the blood temperature in the arterial and venous circuits and feeding back the information to the arterial and venous thermostats in the dialysis machine. The machine can be programmed to allow a constant body temperature and a negative overall energy transfer, so-called *isothermic* or *thermoneutral* HD, which aims to prevent energy transfer between the dialysate and extracorporeal blood. A recent systematic review of the randomized controlled trials using biofeedback-modulating dialysate temperature demonstrated significant reductions in the incidence of intradialytic hypotension compared with conventional dialysis.[7] However, large multicenter, randomized trials are needed to determine whether reduced temperature dialysis reduces CV events and patient death.

Across Europe and many other countries, hemodiafiltration (HDF) has become a common mode of dialytic therapy. Although claims of improved mortality with this modality remain a matter of debate, most accept that HDF is associated with improved intradialytic CV stability and less frequent hypotension, although this is also disputed by some.[8]

Intradialytic Hypertension

Intradialytic hypertension occurs in 8% to 30% of treatments.[9] Hypertension during or immediately after HD constitutes an important risk factor for CV mortality. Moreover, an intradialytic increase in systolic blood pressure (BP) is associated with an increased risk for hospitalization or death.[10]

In most circumstances, an intradialytic elevation of BP indicates significant volume overload. However, in a number of patients, BP remains elevated despite fluid removal, a syndrome called *dialysis-refractory*

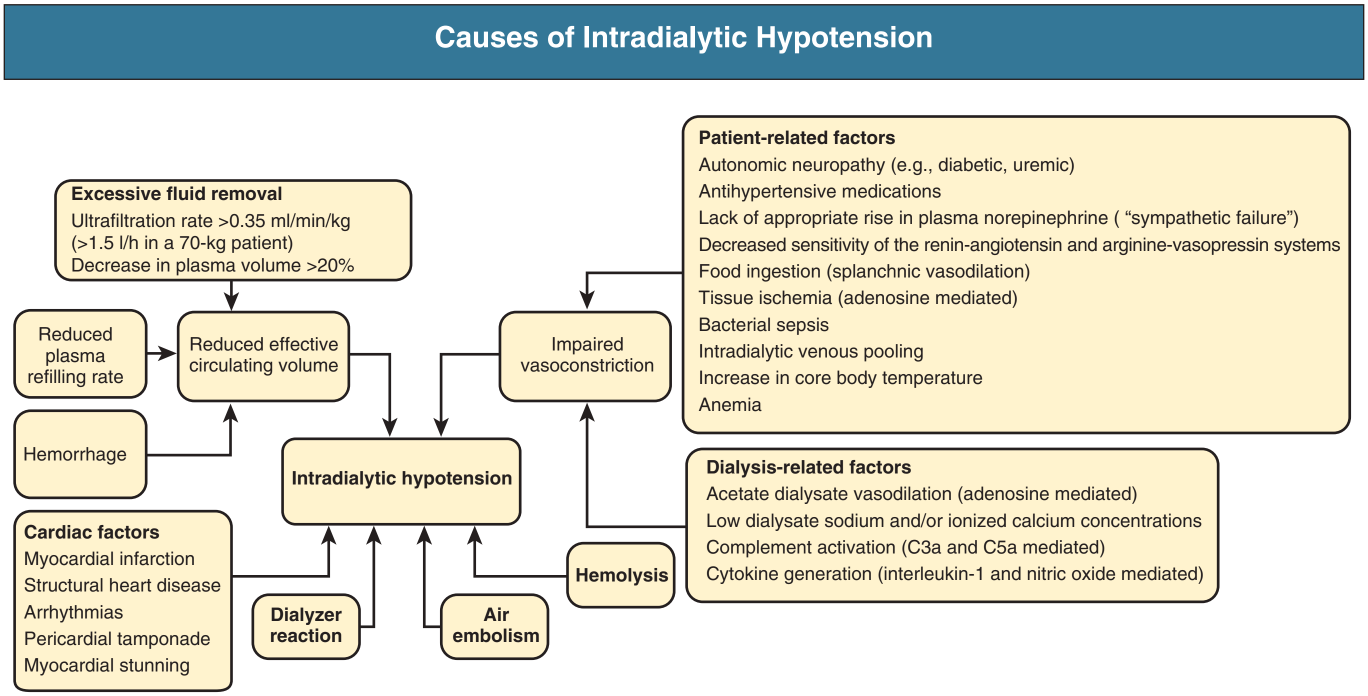
Causes of Intradialytic Hypotension
Excessive fluid removal
Ultrafiltration rate >0.35 ml/min/kg
(>1.5 l/h in a 70-kg patient)
Decrease in plasma volume >20%
Reduced plasma refilling rate
Reduced effective circulating volume
Hemorrhage
Patient-related factors
Autonomic neuropathy (e.g., diabetic, uremic)
Antihypertensive medications
Lack of appropriate rise in plasma norepinephrine ("sympathetic failure")
Decreased sensitivity of the renin-angiotensin and arginine-vasopressin systems
Food ingestion (splanchnic vasodilation)
Tissue ischemia (adenosine mediated)
Bacterial sepsis
Intradialytic venous pooling
Increase in core body temperature
Anemia
Impaired vasoconstriction
Intradialytic hypotension
Dialysis-related factors
Acetate dialysate vasodilation (adenosine mediated)
Low dialysate sodium and/or ionized calcium concentrations
Complement activation (C3a and C5a mediated)
Cytokine generation (interleukin-1 and nitric oxide mediated)
Cardiac factors
Myocardial infarction
Structural heart disease
Arrhythmias
Pericardial tamponade
Myocardial stunning
Dialyzer reaction
Air embolism
Hemolysis

Fig. 95.1 Pathogenesis and causes of intradialytic hypotension.

hypertension. These patients are usually young, with preexisting hypertension, and have excessive interdialytic weight gain and a hyperactive renin-angiotensin system in response to fluid removal.[11] In these patients the hypertension is still mediated by the previous volume expansion, but there is often a lag of days to 2 or more weeks before the BP becomes normal after reduction of the dry target weight (known as the dialysis "lag phenomenon"). Often patients can discontinue most of their antihypertensive agents once this occurs.

Erythropoietin (EPO) and other erythropoiesis-stimulating agents have been associated with a 20% to 30% incidence of new-onset or exacerbation of hypertension. Furthermore, among patients receiving intravenous (not subcutaneous) EPO, elevated levels of endothelin-1 (a potent vasoconstrictor) have been shown to correlate with increased BP. Predominantly, such EPO-induced rises in BP are associated with a rapid rise in hemoglobin and can be avoided by a more conservative approach to correcting the hemoglobin.

Intradialytic hypertension can be precipitated by the use of high-sodium dialysate, which is intended to mitigate the intradialytic decrease in serum osmolality that occurs with the diffusive removal of urea and sodium.[12] Although this approach stabilizes BP during dialysis by improving intravascular filling, high-sodium dialysate results in a positive intradialytic sodium balance and is associated with increased postdialysis thirst, resulting in significant weight gain in the interdialytic period. To circumvent these problems, sodium modeling has been adopted as an approach that uses variable sodium concentrations in the dialysate, generally with sodium reduced in a continuous or stepwise manner from an initial level of 150 to 154 mmol/l to 138 to 142 mmol/l. Although sodium modeling has been widely promoted, results from both randomized and nonrandomized cross-over studies do not suggest any definitive benefit.[13] Other hypothesized mechanisms of intradialytic hypertension include hyperactivity of the sympathetic nervous system[14] and increased cardiac output resulting from fluid removal, particularly in patients with cardiomyopathy.[15] Clinicians also should be aware of possible dialytic removal of certain antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers.

Increasing hypertension during a dialysis session requires intervention if systolic BP is greater than 180 mm Hg. This is best treated with a centrally acting agent such as clonidine or a short-acting ACE inhibitor such as captopril. Successful treatment of hypertension for a longer period requires an accurate determination of the patient's dry weight and its achievement by gradual ultrafiltration over several weeks of dialysis. Once dry weight is achieved, optimization of antihypertensive drug therapy is warranted, potentially including the use of minimally dialyzable or nondialyzable medications such as angiotensin receptor blockers, calcium channel blockers, clonidine, and carvedilol. However, use of antihypertensive agents may make achievement of dry weight difficult because of induced intradialytic hypotension. Evidence from the Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial[16] suggests that optimal control of BP in HD patients is via control of extracellular fluid volume (salt and water) not the use of antihypertensive agents. One common error in management is to treat dialysis hypertension with increasing BP medications as opposed to opting to achieve dry weight. The use of vasodilator drugs (hydralazine, minoxidil) can lead to increased fluid retention that worsens volume overload. Minoxidil also can cause pleural and pericardial effusions and should be avoided in dialysis patients if at all possible.

Cardiac Arrhythmias

Intradialytic arrhythmias are common and are often multifactorial in origin.[17,18] Left ventricular hypertrophy, congestive cardiomyopathy, uremic pericarditis, silent myocardial ischemia, and conduction system calcification are frequently encountered in adult dialysis patients. In addition, polypharmacy coupled with the constant alterations in fluid, electrolyte, and acid-base homeostasis may precipitate intradialytic arrhythmias. The range of electrocardiographic abnormalities that may be encountered in renal failure is shown in Table 95.1. QTc dispersion,

TABLE 95.1 Electrocardiographic Abnormalities in Renal Failure

Function	Abnormality Seen in Renal Failure
PR interval	Usually normal; prolongation in long-term HD. Calcification of mitral valve annulus may involve His bundle, resulting in complete heart block.
QRS interval	
Amplitude	Increases during ultrafiltration (correlates with reduction in left ventricular [LV] dimensions). LV hypertrophy (LVH) on voltage criteria found in up to 50%.
Duration	Prolonged (within normal range) by hemodialysis. Late potentials increased only in patients with preexisting coronary heart disease. Prolonged in hyperkalemia.
ST segment	Depression during HD does not predict coronary artery disease. Depression or elevation may occur in hyperkalemia. Depression during ambulatory monitoring poorly predictive of coronary artery disease.
QTc interval	Increases during HD (correlates with reduction in K^+ and Mg^{2+}). Increased QT dispersion reported in patients on dialysis.
T wave	Peaking or inversion may occur in hyperkalemia. Inversion in anterolateral leads in LVH with strain pattern.
Rhythm	Bradycardia and asystole in long intradialytic break and during HD. Atrial and ventricular arrhythmias during HD.

Risk factors include left ventricular dysfunction, wall motion abnormalities, known coronary artery disease, abnormal perfusion scans (even without coronary artery disease), use of cardiac glycosides, and low dialysate potassium concentration.
HD, Hemodialysis.

the difference between maximum and minimum QTc interval on a standard 12-lead electrocardiogram, is prolonged after HD and has been proposed as a prognostic indicator of cardiac complications in dialysis patients.

Preventive measures include the use of bicarbonate dialysate and careful attention to dialysate potassium and calcium levels. There are very few trials of the most appropriate dialysate potassium level, although recent observational evidence suggests that dialysate potassium levels below 2 mmol/l should be avoided in most patients.[19] Zero potassium dialysate should be avoided in the hyperkalemic individual because of its arrhythmogenic potential, particularly in patients receiving digoxin, because serum potassium levels can fall to less than 3.5 mmol/l during dialysis. Serum digoxin levels should be regularly monitored and the need for the drug regularly reassessed.

Sudden Death

Cardiac arrest occurs in 7 per 100,000 HD sessions and is more common in the elderly, patients with diabetes, and patients using central venous catheters.[20] Sudden deaths during dialysis are observed more frequently after the 3-day (classically weekend) interdialytic interval in patients receiving dialysis three times per week.[21,22] The etiology is complex but likely related to cardiac structural abnormalities related to long-standing hypertension and uremia coupled with the more marked fluid and solute accumulation seen in the long interdialytic period. Both peritoneal dialysis patients and patients undergoing frequent long-hours HD do not show this high event rate on a particular day of the week.[22] Recent analysis of data from implantable cardiac monitors in HD patients with sudden cardiac death found that the vast majority were due to bradycardia and asystole, rather than malignant ventricular arrhythmias raising uncertainty regarding β-blocker use in this population.[23]

Although coronary heart disease increases the risk for sudden death, other catastrophic intradialytic events need to be ruled out. The prompt recognition and treatment of hyperkalemia, as a reversible cause of cardiac dysfunction, is imperative. Profound generalized muscle weakness may be a warning sign of imminent life-threatening hyperkalemia.

When cardiopulmonary arrest occurs during dialysis, an immediate decision must be made as to whether the collapse is the result of an intrinsic disease or technical errors, such as air embolism, unsafe dialysate composition, overheated dialysate, line disconnection, or sterilant in the dialyzer. Air in the dialysate, grossly hemolyzed blood, and hemorrhage caused by line disconnection can be easily detected. However, if no obvious cause is identifiable, blood should not be returned to the patient, particularly if the arrest occurred immediately on initiation of dialysis. A patient exposed to formaldehyde may have reported earlier burning at the access site; fortunately this agent is rarely used today. If the possibility of a problem with dialysate composition is remote, blood may be returned to the patient. However, blood and dialysate samples should be immediately sent for electrolyte analysis, the dialyzer and blood lines saved for later analysis, and the dialysis machine replaced until all its safety features have been thoroughly evaluated for possible malfunction. It should be standard practice to have defibrillators in dialysis units. The management of cardiopulmonary arrest during dialysis should follow the standard principles of cardiopulmonary resuscitation; the diagnosis and management of technical errors are discussed later. All dialysis units should have established protocols for managing cardiac arrest and other common dialysis emergencies.

Prevention of sudden cardiac death in HD patients, including the role of implantable defibrillators, is discussed further in Chapter 81.

Pericarditis

The management of pericarditis in dialysis patients is discussed in Chapter 81.

Dialysis-Associated Steal Syndrome

The construction of an arteriovenous fistula (AVF) or arteriovenous graft (AVG) may result in reduction of blood flow to the hand. Although clinically significant ischemia does not usually result, symptoms are by no means rare, particularly in diabetic or elderly patients with peripheral vascular disease. Dialysis-associated steal syndrome is more common in upper arm AVFs (~4%) compared with both AVGs and forearm AVFs (~1%). The clinical presentation, differential diagnosis, and evaluation of dialysis-associated steal syndrome are summarized in Box 95.1 and are discussed further in Chapter 91.[24]

Treatment depends on the clinical severity of ischemia and vascular access anatomy.[24] Severe ischemia can cause irreparable injury to nerves within hours and must be considered a surgical emergency. Mild ischemia, manifested by mild pain during HD, subjective coldness, and paresthesias, and objective reduction in skin temperature but with no loss of sensation or motion, is common and generally improves with time.[25] Patients with mild ischemia should undergo symptom-specific therapy (e.g., wearing a glove) and frequent physical examination, with special attention to subtle neurologic changes and muscle wasting. Failure to improve may necessitate surgical or radiologic intervention (see Chapter 91). Persistent symptoms after an apparently successful correction of the vascular access flow should alert the clinician to other unrelated causes.

BOX 95.1 Dialysis-Associated Vascular Steal Syndrome

Clinical Presentations (Symptoms Often Aggravated on Dialysis)

- Hand numbness, pain, or weakness
- Coolness of distal arm
- Diminished pulses
- Acrocyanosis, gangrene

Differential Diagnosis

- Dialysis-associated cramp
- Polyneuropathy: Diabetes, uremia
- Entrapment neuropathy: β_2-microglobulin–derived amyloidosis
- Reflex sympathetic dystrophy
- Calciphylaxis

Evaluation of Steal Severity

- Pulse oximetry
- Plethysmography
- Doppler flow
- Angiography

Treatment Options (Depending on Severity)

- Symptomatic (e.g., gloves)
- Surgical, with preservation of vascular access: banding to reduce flow, distal revascularization–interval ligation (DRIL) procedure (see Fig. 91.6)
- Surgical, with loss of vascular access: ligation

NEUROMUSCULAR COMPLICATIONS

Muscle Cramps

Muscle cramps occur in 5% to 20% of patients late during dialysis and frequently involve the legs. They account for 15% of premature discontinuations of dialysis.[26] Electromyography shows increased tonic muscle electrical activity throughout dialysis, and serum creatine kinase may be elevated.

Although the pathogenesis is unknown, dialysis-induced volume contraction and hypoosmolality appear to be common predisposing factors. Indeed, the onset of muscle cramps may give an indication that the target weight has been reached. However, hypomagnesemia and carnitine deficiency also may play a role.

The acute management is directed at increasing plasma osmolality. Cessation of ultrafiltration is not useful. Parenteral infusion of 23.5% hypertonic saline (15 to 20 ml), 25% mannitol (50 to 100 ml), or 50% dextrose in water (25 to 50 ml) is equally effective. However, hypertonic saline may result in postdialytic thirst, and both hypertonic saline and mannitol cause transient warmth and flushing during the infusion. Furthermore, large and repetitive infusions of mannitol may lead to increased thirst, interdialytic weight gain, and fluid overload. Overall, dextrose in water is preferred, particularly in nondiabetics.

Preventive measures include dietary counseling about excessive interdialytic weight gain. In patients without clinical signs of fluid overload, it is reasonable to increase the dry weight by 0.5 kg and to observe the clinical response. Quinine sulfate (250 to 300 mg) or oxazepam (5 to 10 mg) given 2 hours before dialysis also may be effective. Although the U.S. Food and Drug Administration regards quinine sulfate as unsafe and ineffective for the prevention of cramps, this drug works well in some patients and is used freely in most parts of the world. Some reports also promote the use of vitamin E in this role.[27] The use of sodium gradients during dialysis may have some benefit as well. Proposed strategies include starting with a dialysate sodium concentration of 145 to 155 mmol/l and a linear decrease to 135 to 140 mmol/l by the completion of the treatment. A comparison of sodium modeling with an exponential, linear, or step program has yielded similar results.[13,28] In anecdotal reports, 5 mg of enalapril twice weekly may be effective, presumably by inhibiting angiotensin II–mediated thirst. Stretching exercises, magnesium, creatine monohydrate (12 mg before dialysis), and L-carnitine supplementation (20 mg/kg per dialysis session) also may be beneficial. An intradialytic blood volume biofeedback control system has been shown to reduce the incidence of muscle cramps.[29]

Restless Legs Syndrome

Restless legs syndrome is common in dialysis patients. The typical report is of crawling sensations in the legs that occur with inactivity, and symptoms may worsen during dialysis. The etiology, prevention, and management of restless legs syndrome are discussed in Chapter 85.

Dialysis Disequilibrium Syndrome

Despite a decline in its incidence, dialysis disequilibrium syndrome (DDS) is still observed sporadically in patients who are initiated on HD on high-flux dialyzers with large surface areas and short dialysis time. Risk factors include young age, severe uremia, rapid and marked intradialytic falls in urea at dialysis initiation, low dialysate sodium concentration, and preexisting neurologic disorders (see Chapter 85).

DDS commonly manifests with restlessness, headache, nausea, vomiting, blurred vision, muscle twitching, disorientation, tremor, and hypertension. More severe manifestations include obtundation, seizures, and coma. DDS usually develops toward the end of dialysis but may be delayed for up to 24 hours. Although cerebral edema is a consistent finding on computed tomographic scanning, DDS remains a clinical diagnosis because laboratory tests, including electroencephalography, are nonspecific. It is usually self-limited, but full recovery may take several days.

The pathogenesis of DDS is still a subject of debate. The reverse urea effect theory, which proposes that a transient osmotic disequilibrium occurs during dialysis as a result of a more rapid removal of urea from blood than from cerebrospinal fluid, has been disputed.[30] In animals undergoing rapid dialysis, despite the correction of systemic acidosis, a paradoxical cerebrospinal fluid acidosis develops that is aborted by slower dialysis. An additional mechanism is the intracerebral accumulation of idiogenic osmoles, such as inositol, glutamine, and glutamate.

In high-risk patients, preventive measures include the use of volumetric-controlled machines, bicarbonate dialysate, sodium modeling, earlier recognition of uremic states, and stepped initiation of dialysis (short initial treatment times with lower blood pump speeds). In addition, short and more frequent dialysis treatments are recommended with use of small surface area dialyzers and reduced blood flow rates. The target reduction in blood urea should initially be limited to 30%. The prophylactic use of mannitol or anticonvulsants is not recommended.

An extension of this syndrome may be one that mimics osmotic demyelination syndrome—similar to that seen with rapid correction of hyponatremia. Several cases have been reported in association with dialysis initiation, with clinical manifestations similar to those of the locked-in pontine picture of central demyelination. The difference is that with the dialysis-related condition, patients appear to recover over the ensuing 5 to 7 days and the condition seems to be related to edema rather than demyelination.[31]

Seizures

Intradialytic seizures occur in less than 10% of patients and tend to be generalized but easily controlled. However, focal or refractory seizures warrant evaluation for focal neurologic disease, particularly intracranial

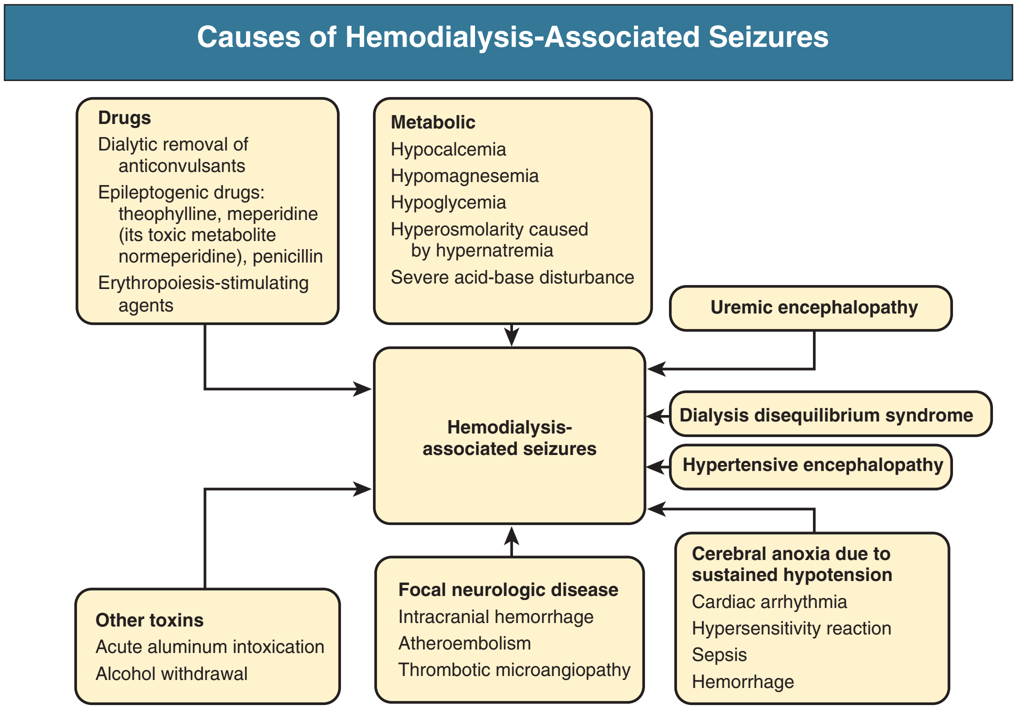
Causes of Hemodialysis-Associated Seizures
Drugs
Dialytic removal of anticonvulsants
Epileptogenic drugs: theophylline, meperidine (its toxic metabolite normeperidine), penicillin
Erythropoiesis-stimulating agents
Metabolic
Hypocalcemia
Hypomagnesemia
Hypoglycemia
Hyperosmolarity caused by hypernatremia
Severe acid-base disturbance
Uremic encephalopathy
Hemodialysis-associated seizures
Dialysis disequilibrium syndrome
Hypertensive encephalopathy
Other toxins
Acute aluminum intoxication
Alcohol withdrawal
Focal neurologic disease
Intracranial hemorrhage
Atheroembolism
Thrombotic microangiopathy
Cerebral anoxia due to sustained hypotension
Cardiac arrhythmia
Hypersensitivity reaction
Sepsis
Hemorrhage

Fig. 95.2 Causes of hemodialysis-associated seizures.

hemorrhage. Causes of seizures are summarized in Fig. 95.2 and are discussed further in Chapter 85.

Treatment of established seizures requires cessation of dialysis, maintenance of airway patency, and investigation for metabolic abnormalities. Intravenous diazepam, alprazolam, or clonazepam, and phenytoin may be required. Intravenous 50% dextrose in water should be administered promptly if hypoglycemia is suspected.

Headache

Dialysis headache is common and typically consists of a bifrontal discomfort that develops during dialysis and may become intense and throbbing, accompanied by nausea and vomiting. It is usually aggravated by the supine position, but there are no visual disturbances.[32]

Although its cause is unknown, dialysis headache may be a subtle manifestation of DDS or may be related to acetate, which is present in low concentrations (3 to 4 mmol/l) in almost all dialysate fluid. A role for nitric oxide also has been postulated. Alternatively, it may be a manifestation of caffeine withdrawal caused by dialytic removal of caffeine.

Management consists of oral analgesics (e.g., acetaminophen [paracetamol]). Preventive measures include slow dialysis with reduced blood flow rates, change to bicarbonate dialysate, sodium, and ultrafiltration modeling, coffee ingestion during dialysis, and use of reprocessed dialyzers. Attention should also be paid to adequate flushing of the lines and dialyzer before commencement of dialysis. Changing the dialyzer (especially to a synthetic membrane or an alternative synthetic membrane) is sometimes useful in refractory cases.

HEMATOLOGIC COMPLICATIONS

Complement Activation and Dialysis-Associated Neutropenia

During dialysis with unsubstituted cellulose dialyzers, which are now infrequently used, the free hydroxyl groups present on the membrane cause activation of the alternative pathway of complement.[33] This results in activation and increased adherence of circulating neutrophils to the endothelial capillary pulmonary vasculature, leading to transient neutropenia that reaches a nadir after 15 minutes of dialysis, followed by a rebound leukocytosis 1 hour later. Complement activation and neutropenia also have been detected with other more widely used dialyzer membranes, including cellulose acetate and polysulfone, but to a lesser degree. Although the long-term clinical relevance of this phenomenon remains speculative, its contribution to acute intradialytic morbidity is discussed later.

Intradialytic Hemolysis

Acute hemolysis can be caused by faulty dialysis equipment, chemicals, drugs, toxins, or patient-related factors (Fig. 95.3).[34] With the advent of better dialysis equipment design and the widespread use of reverse osmosis and/or deionization systems and carbon filters, traumatic red blood cell (RBC) fragmentation caused by poorly designed blood pumps and methemoglobinemia caused by water contamination with chloramine or copper are rarely seen today. However, nitrate or nitrite intoxication causing methemoglobinemia still occurs sporadically in patients on home HD who use well water contaminated with urine from domesticated animals. Furthermore, during dialyzer reprocessing, formaldehyde retention can result in hemolysis by inducing formation of cold agglutinins or inhibiting RBC metabolism.

The diagnosis of acute hemolysis is evident when grossly translucent hemolyzed blood is observed in the tubing. Patients with methemoglobinemia have nausea, vomiting, hypotension, and cyanosis, and oxygen therapy does not improve the black blood present in the extracorporeal circuit. Copper contamination should be suspected in the presence of skin flushing and abdominal pain or diarrhea.

Evaluation should include reticulocyte count, haptoglobin, lactate dehydrogenase, blood smear, Coombs test, and measurement of methemoglobin. Chromium 51 (^{51}Cr)-labeled RBC survival and bone marrow examination may occasionally be indicated if there is recurrent hemolysis.

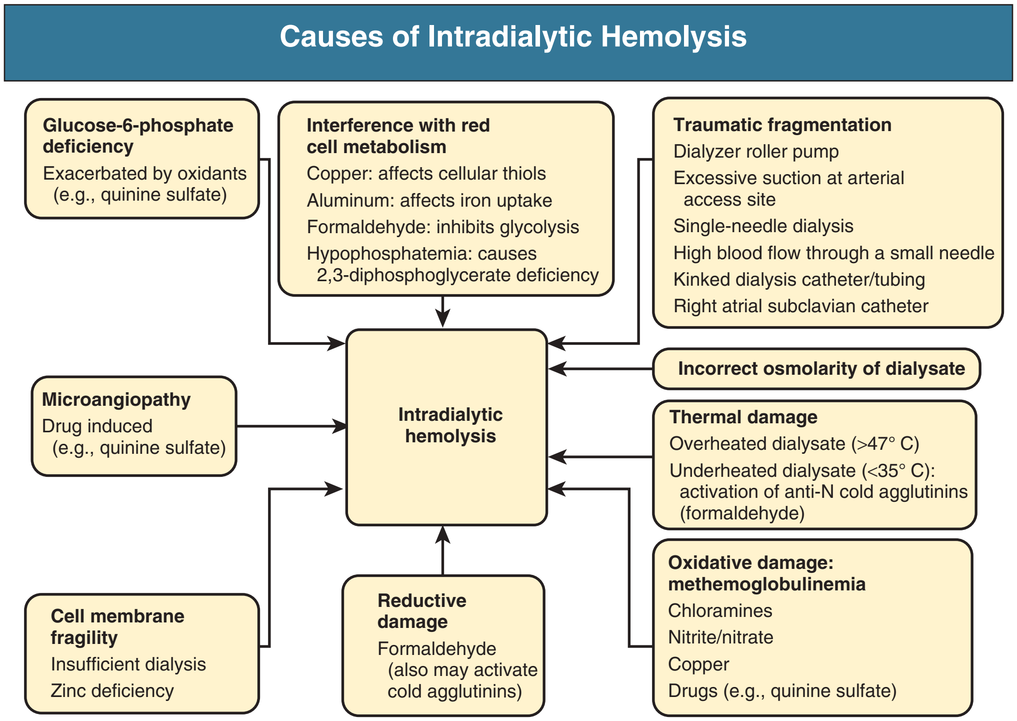
Causes of Intradialytic Hemolysis
Glucose-6-phosphate deficiency
Exacerbated by oxidants (e.g., quinine sulfate)
Interference with red cell metabolism
Copper: affects cellular thiols
Aluminum: affects iron uptake
Formaldehyde: inhibits glycolysis
Hypophosphatemia: causes 2,3-diphosphoglycerate deficiency
Traumatic fragmentation
Dialyzer roller pump
Excessive suction at arterial access site
Single-needle dialysis
High blood flow through a small needle
Kinked dialysis catheter/tubing
Right atrial subclavian catheter
Incorrect osmolarity of dialysate
Microangiopathy
Drug induced (e.g., quinine sulfate)
Intradialytic hemolysis
Thermal damage
Overheated dialysate (>47° C)
Underheated dialysate (<35° C): activation of anti-N cold agglutinins (formaldehyde)
Oxidative damage: methemoglobulinemia
Chloramines
Nitrite/nitrate
Copper
Drugs (e.g., quinine sulfate)
Cell membrane fragility
Insufficient dialysis
Zinc deficiency
Reductive damage
Formaldehyde (also may activate cold agglutinins)

Fig. 95.3 Causes of intradialytic hemolysis.

More important, analysis of tap water for chloramines and assessment of the status of charcoal filtration (which removes chloramines) and metal contaminants and thorough analysis of the dialysis equipment for clues of increased blood turbulence are recommended.

Hemorrhage

Bleeding complications are commonly related to the use of intradialytic anticoagulation, which exacerbates the uremic bleeding diathesis (see Chapter 83). In addition, dialysis patients are prone to spontaneous bleeding at specific sites, such as gastrointestinal arteriovenous malformations; subdural, pericardial, pleural, retroperitoneal, and hepatic subcapsular spaces; and the ocular anterior chamber. Despite its limitations, the bleeding time remains the best indicator of hemorrhagic tendency.

In addition to specific measures directed to the site of hemorrhage, reversal of uremic platelet dysfunction is imperative. Strategies include the use of erythropoiesis-stimulating agents or RBC transfusions to achieve a hematocrit above 30% to improve rheologic platelet–vessel wall interactions, intravenous conjugated estrogens at 0.6 mg/kg/day for 5 consecutive days, intravenous or subcutaneous 1-deamino-8-D-arginine vasopressin (DDAVP) at 0.3 mcg/kg administered over 15 to 30 minutes, and intravenous infusion of cryoprecipitate (see Box 83.2). For patients experiencing severe bleeding, it is advisable to consider heparin-free dialysis with use of normal saline flushes every 15 to 30 minutes with ultrafiltration adjustments. Other alternatives may include regional heparin or citrate anticoagulation, and in the long term the use of low molecular weight heparin, heparin modeling, or prostacyclin may be considered. More recently, the use of heparin-bound dialyzers (such as hemophan or AN69ST)[35] or citrate-containing dialysate have been advocated in patients at risk for bleeding, although they may not decrease the need for routine circuit anticoagulation.[36] In patients scheduled for elective surgery or invasive procedures, cessation of aspirin should be considered a week in advance, the dose of anticoagulant reduced to a minimum, and the hematocrit maintained above 30%. In some patients, intravenous DDAVP to reverse the uremic platelet defect also may be required. Tranexamic acid, a potent fibrinolytic inhibitor, can be used as an adjuvant treatment to control hemorrhage in dialysis patients.[37]

Thrombocytopenia

An increasingly important cause of thrombocytopenia in dialysis patients is heparin-induced thrombocytopenia. The diagnosis and management, including alternative strategies for anticoagulation for HD, are discussed in Chapter 83.

PULMONARY COMPLICATIONS

Dialysis-Associated Hypoxemia

In most patients, the arterial Pao_2 decreases by 5 to 20 mm Hg (0.6 to 4.0 kPa) during dialysis, reaching a nadir at 30 to 60 minutes, and resolves within 60 to 120 minutes after discontinuation of dialysis. This decrease is usually of no clinical significance to patients unless there is preexisting chronic cardiopulmonary disease.

Hypoventilation is the main implicated factor and is primarily central in origin as a result of a decrease in carbon dioxide production after acetate metabolism (specific to acetate dialysate), loss of carbon dioxide in the dialyzer (with both acetate and bicarbonate dialysate), and rapid alkalinization of body fluids (particularly with large surface area dialyzers).[38] In addition, acetate-induced respiratory muscle fatigue can lead to hypoventilation, especially in acutely ill patients. Furthermore, a commonly observed ventilation-perfusion mismatch may be caused by pulmonary leukocyte agglutination (in part resulting from complement activation) or impaired cardiac output (resulting from acetate-induced myocardial depression).

In high-risk patients with fluid overload, preventive measures consist of using intradialytic oxygen supplementation, conventional bicarbonate dialysate, and biocompatible membranes. Optimizing hematocrit values and performing sequential ultrafiltration followed by HD may further reduce the likelihood of hypoxemia.

TECHNICAL MALFUNCTIONS

Air Embolism

The most vulnerable source of air entry into the extracorporeal circuit is the prepump tubing segment, in which significant subatmospheric pressures prevail. However, other sources need to be considered, including intravenous infusion circuits especially with glass bottles, air bubbles from the dialysate, and (especially uncuffed) dialysis catheters. High blood flow rates may allow rapid entry of large volumes of air despite small leaks.

Clinical manifestations depend on the volume of air introduced, the site of introduction, the patient's position, and the speed at which air is introduced.[39] In the sitting position, air entry through a peripheral vein bypasses the heart and causes venous emboli in the cerebral circulation. The acute onset of seizures and coma in the absence of precedent symptoms such as chest pain and dyspnea is highly suggestive of air embolism. In the supine position, air introduced through a central venous line will be trapped in the right ventricle, where it forms foam, interferes with cardiac output, and, if it is large enough, leads to obstructive shock. Dissemination of microemboli to the pulmonary vasculature results in dyspnea, dry cough, chest tightness, or respiratory arrest. Furthermore, passage of air across the pulmonary capillary bed can lead to cerebral or coronary artery embolism. In the left Trendelenburg position, air emboli migrate to the lower extremity venous circulation, resulting in ischemia as a result of increased outflow resistance. Foam may be visible in the extracorporeal tubing, and cardiac auscultation may reveal a peculiar churning sound.

The immediate management of clinically suspected air embolism is summarized in Fig. 95.4. Prevention depends primarily on dialysis machines equipped with venous air bubble traps and foam detectors located just distal to the dialyzer and a venous pressure monitor at the venous end. The detector is attached to a relay switch that simultaneously activates an alarm, shuts off the blood pump, and clamps the venous blood line if air is detected. Therefore dialysis should never be performed in the presence of an inoperative air detection alarm system. Glass bottles should be avoided because they create vacuum effects that can permit air entry into the extracorporeal system. Dialysis catheters should be aspirated and flushed with saline before connection. Dialyzer rinsing, before use, should expand all compartments to remove residual air bubbles.

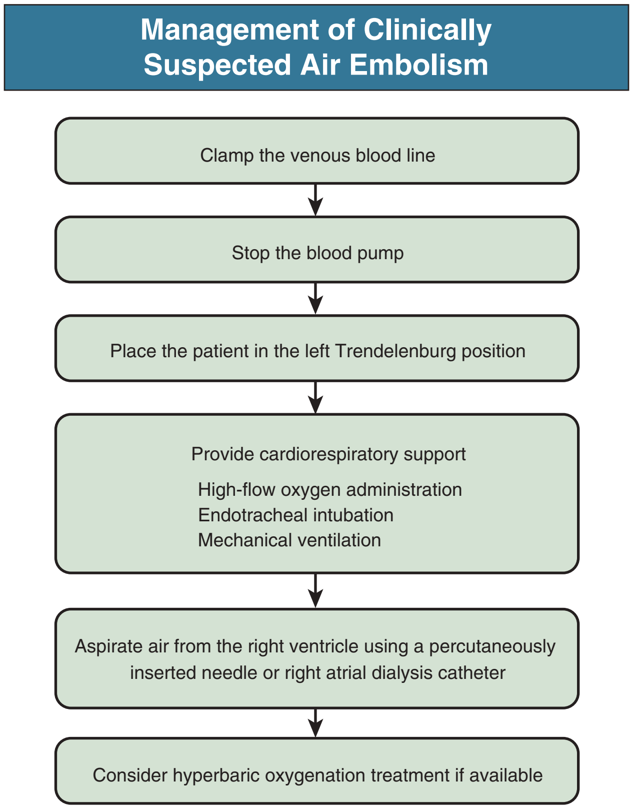
Management of Clinically Suspected Air Embolism
Clamp the venous blood line
Stop the blood pump
Place the patient in the left Trendelenburg position
Provide cardiorespiratory support
High-flow oxygen administration
Endotracheal intubation
Mechanical ventilation
Aspirate air from the right ventricle using a percutaneously inserted needle or right atrial dialysis catheter
Consider hyperbaric oxygenation treatment if available

Fig. 95.4 Management of clinically suspected air embolism.

Incorrect Dialysate Composition

Incorrect dialysate composition results from technical or human errors. Because the primary solutes constituting the dialysate are electrolytes, the dialysate concentration will be reflected by its electrical conductivity. Therefore proper proportioning of concentrate to water can be achieved by the use of a meter that continuously measures the conductivity of the dialysate solution as it is being fed to the dialyzer. Life-threatening electrolyte and acid-base abnormalities are avoidable if the conductivity alarm is functioning properly and the alarm limits are set correctly. However, in dialysis machines that are equipped with conductivity-controlled mixing systems, the system automatically changes the mixing ratio of the concentrates until the dialysate solution conductivity falls within the set limits. This may inadvertently lead to dialysate without any bicarbonate, with apparently acceptable conductivity. Therefore, if conductivity-controlled systems are used, it is safer to also check the dialysate pH before dialysis. Conductivity monitors can fail or can be improperly adjusted by human error. Therefore it is important to add human monitoring of dialysate composition before every treatment, whenever a machine has been sterilized or moved about, or whenever a new concentrate is used. Furthermore, many nonstandardized solutions are available, some of which may be used with an inappropriate proportioning system. Therefore it is also essential that the supplies match the machine-proportioning ratio for which they were prepared for the appropriate final dialysate composition to be obtained. Double checking of concentrate variations (e.g., potassium, calcium, and phosphate concentration) should be practiced, as it is for intravenous drug administration.

Hypernatremia

Hypernatremia occurs when concentrate or the ratio of concentrate to water is incorrect and the conductivity monitors or the alarms are not functioning properly. Hyperosmolality results in intracellular water depletion. Clinical manifestations include thirst, headache, nausea, vomiting, seizures, coma, and death. Aggressive treatment is mandatory and includes cessation of dialysis, hospitalization, and infusion of 5% dextrose in water. Dialysis should be resumed with a different machine; the dialysate sodium level should be 2 mmol/l lower than the plasma level, and isotonic saline should be concurrently infused. Dialysis against a sodium level 3 to 5 mmol/l lower than the serum level may increase the risk for disequilibrium. Ultrafiltration with equal volume replacement with normal saline is another option.

Hyponatremia

Failure to add concentrate, inadequate concentrate-to-water ratio, or conductivity monitor or alarm malfunction can cause hyponatremia. Hyponatremia also can occur during the course of dialysis with a proportioning system if the concentrate container runs dry and the conductivity set limits are inappropriate. Acute hypoosmolality causes hemolysis with hyperkalemia and hemodilution of all plasma constituents.

Symptoms include restlessness, anxiety, pain in the vein injected with the hypotonic hemolyzed blood, chest pain, headache, nausea, and occasional severe abdominal or lumbar cramps. Pallor, vomiting, and seizures may be observed. Treatment consists of clamping the blood lines and discarding the hemolyzed blood in the extracorporeal circuit. High-flow oxygen and cardiac monitoring are imperative because of hyperkalemia and potential myocardial injury. Dialysis should be restarted with a new dialysate batch containing low potassium, and high transmembrane pressure should be applied to remove excess water. Correction of serum sodium concentration should be achieved by no more than 1 to 2 mmol/l/h. Anticonvulsants are indicated for seizures and blood transfusions for severe anemia. Successful correction of severe hyponatremia has been reported in a single 3-hour HD session with a dialysate sodium concentration of 135 mmol/l without any adverse neurologic consequences despite a serum sodium correction rate of 3 mmol/l/h.[40] This suggests that elevated blood urea levels might protect uremic patients from the development of demyelinating syndromes when hyponatremia is rapidly corrected.

Metabolic Acidosis

Although acute intradialytic metabolic acidosis can be a manifestation of improper mixing of concentrates or failure of pH monitors, other causes need to be ruled out, including diabetic or alcoholic ketoacidosis, lactic acidosis, toxic ingestions, and dilutional acidosis.[41] The diagnosis is usually suggested by the acute onset of hyperventilation during HD and confirmed by laboratory evaluation. In most circumstances, correction of the underlying cause and use of bicarbonate dialysate at the appropriate concentration (32 to 35 mmol/l) are adequate measures.

Metabolic Alkalosis

Severe intradialytic metabolic alkalosis is rare and may be caused by error in dialysate concentrates, reversed connection of bicarbonate and acid concentrate containers to the entry ports of the dialysis machine, pH monitor malfunction, or use of regional citrate anticoagulation. The most common cause, however, is hydrochloric acid loss as a result of vomiting or nasogastric suction. Attention should also be directed to identification of sources of added alkali.[42]

Acute treatment is rarely necessary unless a technical error has occurred. Removal of the alkali source is usually sufficient, and H_2-antagonists or proton pump inhibitors may be successful if there is gastric acid loss. The administration of sodium chloride to anephric patients with chloride-sensitive alkalosis will not repair the alkalosis. If a more rapid reduction in serum bicarbonate is desired, modification of the dialysate bath by replacement of alkali with chloride, substitution of bicarbonate with acetate dialysate, use of acid dialysate, and infusion of hydrochloric acid are effective but cumbersome measures. The use of conventional or low-bicarbonate (25 to 30 mmol/l) dialysate is probably as effective.

Temperature Monitor Malfunction

Malfunction of the thermostat in the dialysis machine can result in the production of excessively cool or hot dialysate. Whereas cool dialysate is not dangerous and may have beneficial hemodynamic effects (see discussion regarding intradialytic hypotension), overheated dialysate can cause immediate hemolysis and life-threatening hyperkalemia, particularly if the dialysate temperature increases to more than 51°C. In such an event, dialysis must be stopped immediately and blood in the system discarded. The patient should be monitored for hemolysis and hyperkalemia. Dialysis should be resumed to cool the patient by use of a dialysate temperature of 34°C to treat hyperkalemia and allow blood transfusions if necessary. Visual and audible alarms are mandatory to prevent this complication.

Blood Loss

Intradialytic blood loss can result from arterial or venous needle disengagement from the access, separation of the venous or arterial line connections, femoral or central line dialysis catheter perforation or dislodgment, or rupture of a dialysis membrane with or without malfunction of the blood leak detector. Clinical findings include hypotension, loss of consciousness, and cardiac arrest. In addition, after traumatic insertion of a dialysis catheter, blood loss can result in pain or mass from a rapidly expanding hematoma; chest, shoulder, or neck pain from intrapericardial blood loss; back, flank, groin, or lower abdominal pain or distention from retroperitoneal bleeding; or hemoptysis from pulmonary bleeding. Acute management includes the discontinuation of HD, pressure application for local hemostasis, reversal of anticoagulation (e.g., protamine sulfate for heparin), hemodynamic support, oxygen administration, and surgical intervention if needed.

In the home dialysis setting, especially nocturnal HD, venous needle dislodgement is potentially catastrophic. A number of devices have been developed for early detection of blood leak resulting from needle dislodgment, including bed-wetting incontinence pads, Red-Sense and HEMOdialert blood detectors and other proprietary techniques. However, the most important component is prevention by repeated patient education about adequate taping of needles and dialysis lines.

Clotting of Dialysis Circuit

Clotting of the extracorporeal circuit during dialysis is a common practical problem, has many underlying causes, and warrants a thorough investigation. Technical factors include an inadequate or poor priming technique, resulting in retention of air in the dialyzer, and lack of or inadequate priming of the heparin infusion line. Such operator-induced errors are corrected through ongoing staff education and competency assessment. Incorrect heparin loading dose, insufficient time lapse after loading dose of heparin for systemic anticoagulation to occur, incorrect pump setting for constant heparin infusion, delayed start of the heparin pump, and failure to release the heparin line clamp are important correctible causes of clotting that also should be considered. Low molecular weight heparin is often used as a single bolus at the commencement of dialysis but may not maintain anticoagulation for extended hours of treatment (e.g., nocturnal dialysis). Vascular access–related problems from inadequate blood flow caused by needle or catheter positioning or clotting, excessive access recirculation, and frequent interruption of blood flow also can result in clotting. Immediate management requires prompt recognition of the underlying cause and implementation of corrective actions, including ongoing heparin dose adjustment and, if indicated, vascular access revision.

Heparin-free dialysis is sometimes medically indicated, such as in an actively bleeding patient or postoperatively. Although traditional approaches to avoid circuit clotting in this circumstance involve frequent saline flushes, an alternative approach is to employ predilution HDF.

DIALYSIS REACTIONS

During HD, blood is exposed to surface components of the extracorporeal circuit, including the dialyzer, tubing, sterilization processes, and other foreign substances related to the manufacturing and reprocessing procedures. This interaction between the patient's blood and the extracorporeal system can lead to various adverse reactions (Fig. 95.5).

Anaphylactic and Anaphylactoid Reactions

Clinical Presentation

Anaphylaxis is the result of an immunoglobulin E (IgE)-mediated acute allergic reaction in a sensitized patient, whereas anaphylactoid reactions

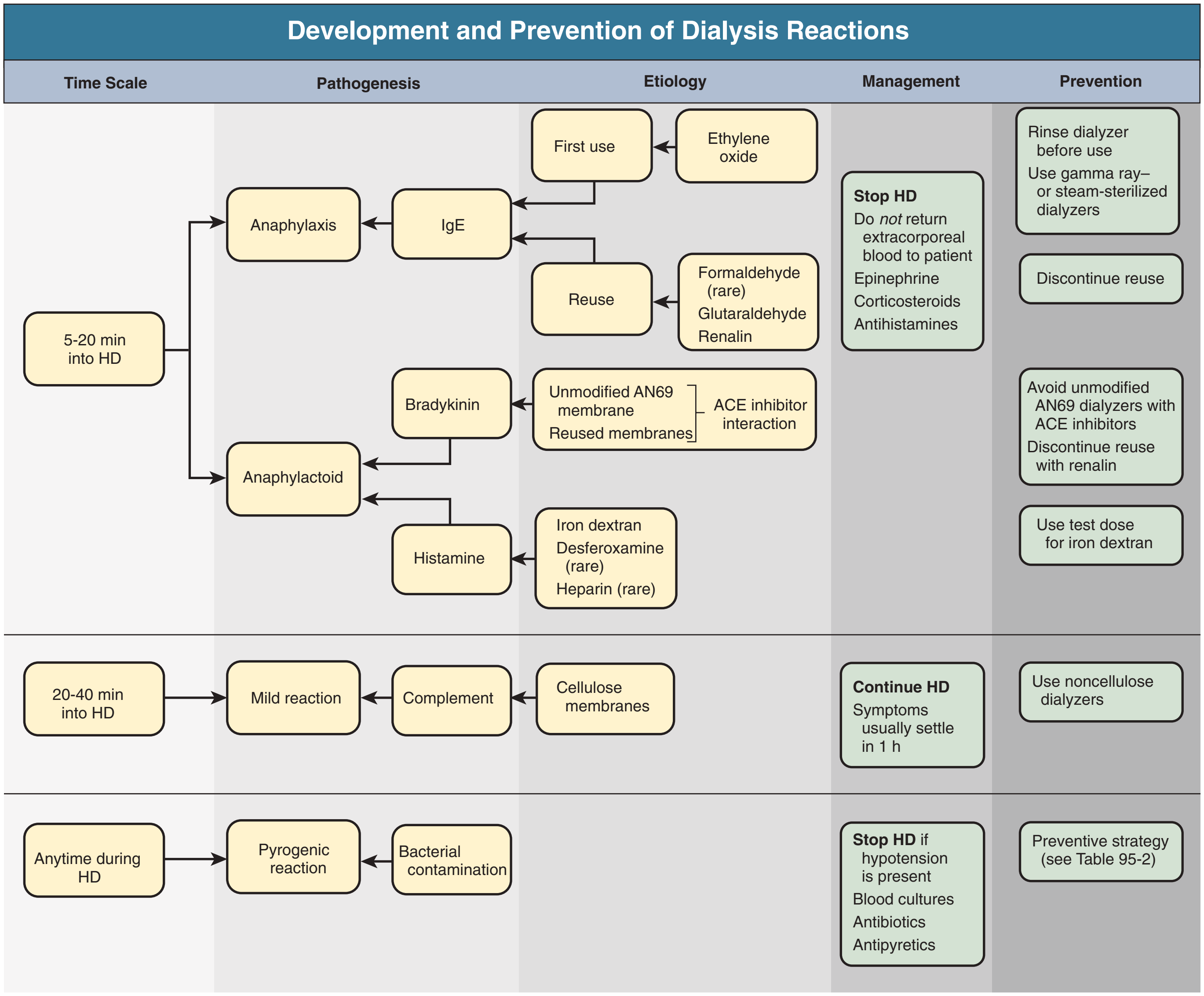
Development and Prevention of Dialysis Reactions
Time Scale
Pathogenesis
Etiology
Management
Prevention
First use
Ethylene oxide
Anaphylaxis
IgE
Reuse
Formaldehyde (rare)
Glutaraldehyde
Renalin
5-20 min into HD
Bradykinin
Unmodified AN69 membrane
Reused membranes
ACE inhibitor interaction
Anaphylactoid
Histamine
Iron dextran
Desferoxamine (rare)
Heparin (rare)
Stop HD
Do not return extracorporeal blood to patient
Epinephrine
Corticosteroids
Antihistamines
Rinse dialyzer before use
Use gamma ray– or steam-sterilized dialyzers
Discontinue reuse
Avoid unmodified AN69 dialyzers with ACE inhibitors
Discontinue reuse with renalin
Use test dose for iron dextran
20-40 min into HD
Mild reaction
Complement
Cellulose membranes
Continue HD
Symptoms usually settle in 1 h
Use noncellulose dialyzers
Anytime during HD
Pyrogenic reaction
Bacterial contamination
Stop HD if hypotension is present
Blood cultures
Antibiotics
Antipyretics
Preventive strategy (see Table 95-2)

Fig. 95.5 Development and prevention of dialysis reactions. *ACE,* Angiotensin-converting enzyme; *HD,* hemodialysis.

result from the direct release of mediators by host cells. Symptoms usually develop within the first 5 minutes of dialysis, although a delay of up to 20 minutes is possible. Symptoms vary from subtle to severe and include burning or heat throughout the body or at the access site; dyspnea, chest tightness, and angioedema or laryngeal edema; paresthesias involving the fingers, toes, lips, or tongue; rhinorrhea, lacrimation, sneezing, or coughing; skin flushing; pruritus; nausea or vomiting; abdominal cramps; and diarrhea. Predisposing factors include a history of atopy, elevated total serum IgE, eosinophilia, and the use of ACE inhibitors. The etiology of dialysis reactions is diverse, and a thorough investigation is required.

First-Use Reactions

The majority of first-use reactions were ascribed to the manufacturer's dialyzer sterilant ethylene oxide (ETO), which is now rarely used. The potting compound that anchors the hollow fibers in the dialyzer housing acts as a reservoir for ETO and may impede its washout from the dialyzer, leading to sensitization. When it is conjugated to human serum albumin (HSA), ETO acts as an allergen. By use of a radioallergosorbent test (RAST), specific IgE antibodies against ETO-HSA are detected in two thirds of patients with such reactions. However, 10% of patients with no history of dialysis reactions have a positive RAST result.

Reuse Reactions

Because most residual ETO is washed out of the dialyzer during first use, reuse reactions are likely to be a result of the disinfectants used for dialyzer reprocessing. These agents include formaldehyde, glutaraldehyde, and peracetic acid–hydrogen peroxide (Renalin); in allergic patients, specific IgE antibodies against formaldehyde are occasionally detectable.

Bradykinin-Mediated Reactions

In the early 1990s, anaphylactoid reactions appeared in Europe among patients dialyzed with modified acrylonitrile (AN69) dialyzers who were also taking ACE inhibitors. Investigation of these incidents revealed that binding of factor XII to this sulfonate-containing, negatively charged membrane resulted in the formation of kallikrein and release of bradykinin, which in turn led to the production of prostaglandin and histamine, with subsequent vasodilation and increased vascular permeability. ACE inactivates bradykinin, and therefore ACE inhibitors can prolong the biologic activities of bradykinin.[43] These membranes have since been chemically modified, thereby reducing this risk.

Anaphylactoid reactions also have been observed in patients taking ACE inhibitors who were dialyzed with membranes that had been reprocessed with Renalin; these reactions abated once reprocessing was discontinued, despite continued use of ACE inhibitors. It has been speculated that Renalin may oxidize cysteine-containing proteins that are adsorbed on the dialyzer membrane, leading to the formation of cysteine sulfonate and contact activation of factor XII.

Drug-Induced Reactions

Anaphylactoid reactions to parenteral iron dextran occur in 0.6% to 1% of HD patients. Significantly higher rates of anaphylactoid reactions have been observed among users of higher molecular weight compared with lower molecular weight iron dextran. In vitro, dextran produces a dose-dependent basophil histamine release. The National Kidney Foundation's Clinical Practice Guidelines recommend that resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be available whenever a dose of iron dextran is administered.[44] Alternative preparations of iron provoke fewer anaphylactoid reactions than iron dextran and are discussed further in Chapter 82.

Hypersensitivity to heparin formulations is rare and usually responds to substitution of beef with pork heparin or vice versa. An alternative is to substitute low molecular weight heparin. A nationwide outbreak in the United States of severe adverse reactions in HD patients was attributed to vials of heparin contaminated with oversulfated chondroitin sulfate.[45]

Treatment and Prevention

Treatment of anaphylactic and anaphylactoid reaction requires the immediate cessation of HD without returning the extracorporeal blood to the patient. Epinephrine, antihistamines, corticosteroids, and respiratory support should be provided, if needed. Specific preventive measures include rinsing the dialyzer immediately before first use, substituting ETO with dialyzers sterilized with gamma ray or steam, avoiding unmodified AN69 membranes in patients taking ACE inhibitors and discontinuing reprocessing procedures in selected patients.

Mild Reactions

Mild reactions particularly occur 20 to 40 minutes after initiation of dialysis, predominantly with first use of unsubstituted cellulosic dialyzers, and consist of chest or back pain. Dialysis can be continued because symptoms usually abate after the first hour, suggesting a relation to the degree of complement activation. Indeed, these reactions decrease with the use of substituted and reprocessed unsubstituted cellulose membranes. Administration of oxygen and analgesics is usually sufficient. Preventive measures include automated cleansing of new dialyzers and use of noncellulose dialyzers.

Fever and Pyrogenic Reactions

Fever during dialysis can be due to infection or excessive microbial contamination of the dialysis apparatus. The latter, known as *pyrogenic reaction*, is usually a diagnosis of exclusion. Several factors during dialysis place patients at risk for exposure to bacterial products, including contaminated water or bicarbonate dialysate, improperly sterilized dialyzers, use of central venous dialysis catheters, and cannulation of infected AVFs or AVGs.[46] Soluble bacterial products such as endotoxin fragments can diffuse across the dialyzer into the blood, resulting in cytokine production and, consequently, pyrogenic reactions. Whereas high-flux dialyzers have larger pores that may potentially allow larger fragments to cross from the dialysate to the patient, the synthetic high-flux membranes have a thick wall that tends to be very adsorptive for endotoxin fragments, thus mostly preventing this phenomenon.[47] Similarly, although HDF potentially has a higher risk for pyrogenic reactions because of the infusion of 10 to 25 liters of dialysate, the customary use of two serial ultrafilters in the dialysate circuit make this an uncommon occurrence. Strategies for the prevention of pyrogenic reactions are summarized in Table 95.2.[48]

When fever develops during HD, the first step is to address hemodynamic stability. If the patient is hypotensive, administration of fluids, cessation of ultrafiltration, and discontinuation of dialysis are often required, and refractory hypotension suggesting severe sepsis should trigger hospitalization.

The next step is to identify a potential source of infection. The dialysis vascular access should be carefully examined. If an infectious

TABLE 95.2 Strategies to Prevent Bacterial Contamination

Type of Fluid	Microbial Count (cfu/ml)	Endotoxin (EU)
Water products	<100	<0.25
Dialysate	<100	<0.50
Ultrapure dialysate (e.g., for HDF)	<0.1	<0.03
Reprocessed dialyzers	No growth	—
Use appropriate germicide: 4% formaldehyde* 1% formaldehyde heated to 40° C*,† Glutaraldehyde† Hydrogen peroxide–peracetic acid mixture (Renalin)*,† Heat sterilization (105° C for 20 hours) for reprocessing of polysulfone membranes†		
Wash and rinse the vascular access arm with soap and water.		
Before cannulation, inspect vascular access for local signs of inflammation.		
Scrub the skin with povidone-iodine or chlorhexidine and allow to dry for 5 minutes before cannulation.		
Record temperature before and after dialysis.		
When central delivery system is used: Clean and disinfect connecting pipes regularly. Remove residual bacteria or endotoxin by additional filtration.		
When single-patient proportioning dialysis machine is used: Freshly prepare bicarbonate dialysate on a daily basis. Discard unused solutions at the end of each day. Rinse and disinfect containers with fluids that meet AAMI standards. Air dry containers before dialysate preparation.		
Follow manufacturer's guidelines for use of preservative-free medications.		

From reference 48.

*A minimum of 11- or 24-hour exposure to peracetic acid or formaldehyde is required, respectively.

†These germicides are equivalent or superior to 4% formaldehyde. The action level for the total viable microbial count in the product water and conventional dialysate is 50 cfu/ml, and the action level for the endotoxin concentration is 50% of the relevant standard. Strict adherence to aami/iso 11663:2014 standards.

AAMI, Association for the Advancement of Medical Instrumentation; *cfu,* colony-forming units; *EU,* endotoxin units; *HDF,* hemodiafiltration; *SO,* International Organization for Standardization.

source related to non–vascular access is identified, specific therapy should be instituted on the basis of the working diagnosis. Nontunneled and tunneled central venous dialysis catheters always should be suspected as a likely cause of infection, even in the absence of local signs of infection such as erythema and exit site drainage. Catheters with evident signs of infection at the insertion site should be removed and the tip cultured.

Antipyretics should be administered, and blood culture specimens should be obtained before initiation of antibiotic therapy; this should include cultures from temporary access devices. The initial choice of antibiotics should include gram-positive and gram-negative bacterial coverage, and the regimen should be adjusted according to the culture results and local guidelines.

In the presence of a dialysis catheter, paired blood culture specimens should be obtained from a peripheral vein and the catheter lumen, and a broad-spectrum antibiotic regimen should be initiated. Catheter lock solutions that use either antibiotics or sterilants such as calcium citrate have been demonstrated to significantly reduce the rate of catheter-related bacteremia.[49,50] In the case of catheter-related bacteremia, removal of the dialysis catheter is strongly indicated, as is transesophageal echocardiography to rule out endocarditis, particularly with staphylococcal sepsis. A regimen of at least 14 days of antibiotic therapy after removal of the catheter is also recommended.

An outbreak of bacteremia among several dialysis patients involving a similar organism should prompt a thorough search for bacterial contaminants in the dialysis equipment.[46] Attention should also be paid to multiuse vials that are punctured several times, such as vials of EPO, which has been linked to an outbreak of bloodstream infection. Single-use vials are preferred, when available.

Investigation of a Dialysis Pyrogenic Outbreak

Although causes of dialysis outbreaks are usually easily identifiable, often the reason for the outbreak is less clear, such as water contamination with bacterial toxins,[51] medication chemical impurities,[45] bacterial contaminants, systemic embolization of degraded dialyzer membrane polymer after prolonged or improper storage,[52] and hemolysis from faulty blood tube sets.[53] Investigation of a dialysis outbreak requires a methodical approach, including a critical review of the medical records and the various steps of the dialysis procedure (Box 95.2).

BOX 95.2 Investigation of Dialysis Pyrogenic Outbreak

Review of Medical Records

- Demographics
- Underlying diseases
- Dialysis schedule
- Dialysis machine
- Dialyzer used
  - Membrane
  - Type
  - Manufacturer's sterilization method
  - Reuse germicide (if applicable)
- Medication history
- Signs and symptoms of illness
- Laboratory tests
- Interview of medical staff caring for patient during incident

Procedural Review

- Water treatment systems and practices
  - Disinfection
  - Distribution
  - Storage procedures
- Disinfection and maintenance of reprocessed dialyzers
- Disinfection and maintenance of dialysis machines
- Review of patient's dialysis sessions

MISCELLANEOUS COMPLICATIONS

Postdialysis Fatigue

An ill-defined "washed out" feeling or malaise during or after HD is a common nonspecific symptom that is observed in about one third of patients and has multifactorial origins. Reduced cardiac output, peripheral vascular disease, depression, poor conditioning, postdialysis hypotension, hypokalemia or hypoglycemia, mild uremic encephalopathy, myopathy caused by carnitine deficiency, and membrane bioincompatibility through cytokine production have all been incriminated. The use of bicarbonate dialysate with or without additional glucose (5 to 10 mmol/l) and L-carnitine supplementation (20 mg/kg/day) have been shown to improve postdialysis well-being. A trial of thrice-weekly L-carnitine at 20 mg/kg for 6 months resulted in a marked decrease in C-reactive protein level, which was paralleled by an increase in body mass index.[54] To date, however, there is no conclusive evidence that L-carnitine improves quality of life in unselected dialysis patients.[44]

Compared with thrice-weekly HD, more frequent dialysis, including short daily and nocturnal HD, has been associated with a marked shortening in the time it takes for patients to recover from a dialysis session and to resume their daily activities, which is a surrogate for postdialysis fatigue.

Pruritus

Pruritus is common and can be a very troubling symptom. The cause is often multifactorial, including xerosis, hyperparathyroidism, neuropathy, derangements in the immune system, and inadequate dialysis. In many patients, pruritus is more severe during or after dialysis and may be a manifestation of an allergic reaction to heparin, ETO, formaldehyde, acetate, or the dialysis membrane. In this subgroup of patients, use of gamma ray–sterilized dialyzers, discontinuation of formaldehyde use, switching to bicarbonate dialysate, and use of low-dialysate calcium and magnesium might result in cessation of itching. Eczematous reactions to antiseptic solutions, rubber gloves or puncture needle components, puncture needles, or adhesive tapes used to secure dialysis needles also should be considered.[55]

The management of uremic pruritus is discussed further in Chapter 87 (see Fig. 88.3).

Genitourinary Problems

Priapism occurs in less than 0.5% of male HD patients. It is not related to sexual activity and occurs while the patient is on dialysis. The patient is usually awakened from sleep by a painful erection. Although the majority of cases are idiopathic, secondary causes include hyperviscosity; high hematocrit from androgen or epoetin therapy; dialysis-induced hypoxemia and hypovolemia from excessive ultrafiltration, particularly in men with sickle cell disease; and use of α-blockers, such as prazosin, or an antidepressant, such as trazodone.[56]

Urgent urologic referral is mandatory. Acute treatment consists of corporal aspiration and irrigation. Although surgical bypass provides venous egress from the corpora cavernosa, secondary impotence commonly develops but may be effectively treated by a penile prosthesis.

An unusual case of testicular angina occurring during excessive ultrafiltration has been described. The patient was diabetic and had extensive vascular calcification evident on imaging. He eventually required orchidectomy.[57] A similar mechanism for this type of "angina" also has been described for the mesentery and right colon.

Hearing and Visual Loss

Intradialytic hearing loss may be caused by bleeding in the inner ear as a consequence of anticoagulation or cochlear hair cell injury from edema.

Intradialytic visual loss is rare but can be caused by central retinal vein occlusion, retinal hemorrhage secondary to heparin exposure in diabetics, precipitation of acute glaucoma, ischemic optic neuropathy secondary to hypotension, or Purtscher-like retinopathy secondary to leukocyte embolization.

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SELF-ASSESSMENT QUESTIONS

1. The most common cause of intradialytic hypotension is:
   - **A.** New-onset sepsis
   - **B.** Cardiac ischemia
   - **C.** Intravascular volume depletion
   - **D.** Altered thermal balance
   - **E.** Use of antihypertensive medications
2. The most appropriate preventive strategy to avoid intradialytic hypotension is:
   - **A.** Isothermic dialysis
   - **B.** Sodium modeling
   - **C.** Hematocrit-controlled volume removal
   - **D.** Avoidance of excessive interdialytic weight gains
   - **E.** Use of agents such as midodrine
3. Intradialytic hemolysis may be caused by all of the following *except:*
   - **A.** Copper in the dialysate
   - **B.** Residual formaldehyde
   - **C.** Chloramine spillover
   - **D.** Faulty dialysis pumps
   - **E.** Heparin exposure
4. Severe dialyzer reactions may occur as a result of exposure to:
   - **A.** New synthetic dialysis membranes
   - **B.** Potting compound
   - **C.** Sterilant effects related to steam or gamma radiation
   - **D.** Angiotensin-converting enzyme inhibitors
   - **E.** Peracetic acid
5. Management options for intradialytic cramps include:
   - **A.** Intravenous hypertonic saline
   - **B.** Oral magnesium salts
   - **C.** Oral carnitine supplementation
   - **D.** Intravenous 50% dextrose
   - **E.** All of the above

96

Peritoneal Dialysis: Principles, Techniques, and Adequacy

Bengt Rippe[†]

Peritoneal dialysis (PD) is used by approximately 200,000 end-stage renal disease (ESRD) patients worldwide, representing approximately 7% of the total dialysis population.[1] In PD the peritoneal cavity is used as a container for 2 to 2.5 liters of sterile, usually glucose-containing, dialysis fluid, which is exchanged four to five times daily by permanently indwelling catheter. The dialysis fluid is provided in plastic bags. The peritoneal membrane, via the peritoneal capillaries, acts as an endogenous dialyzing membrane. Across this membrane, waste products diffuse into the dialysate and excess body fluid is removed by osmosis induced by the glucose or another osmotic agent in the dialysis fluid (ultrafiltration [UF]). PD is usually provided 24 h/day and 7 days/wk in the form of continuous ambulatory peritoneal dialysis (CAPD). Approximately one third of the patients in most centers receive automated peritoneal dialysis (APD; sometimes also referred to as continuous cycling peritoneal dialysis [CCPD]), in which nightly exchanges are delivered via an automatic PD cycler. The use of PD as a modality for ESRD treatment varies widely among countries, mostly because of nonmedical factors such as the reimbursement policy.

ADVANTAGES AND LIMITATIONS OF PERITONEAL DIALYSIS

If patients or their caregivers are competent to undertake PD, the only absolute contraindications are large diaphragmatic defects, excessive peritoneal adhesions, surgically uncorrectable abdominal hernias, or acute ischemic or infectious bowel disease. These and other relative contraindications are discussed further in Chapter 97. PD is best used for patients with some residual renal function, although anuric patients may do very well. Most patients who start PD will eventually, after several years, transfer to other modalities of renal replacement therapy (RRT), such as hemodialysis (HD), if adequacy cannot be maintained or as a result of other complications, such as recurrent peritonitis or exit site or catheter problems. Only rarely do HD patients transfer to PD, most commonly because of failure to maintain adequate vascular access.

PD offers several advantages over HD, at least during the first 2 or 3 years of treatment. First, PD represents a slow, continuous, physiologic mode of removal of small solutes and excess body water, associated with relatively stable blood chemistry and body hydration status. Second, there is no need for vascular access. The absence of vascular access and the absence of the blood-membrane contact of HD make catabolic stimuli less prominent in PD than in HD. Furthermore, residual renal function is somewhat better preserved in PD patients than in HD patients. Because of its continuous nature, PD provides a standardized weekly *Kt/V* similar to that of thrice-weekly HD despite less efficient small-solute clearance.

PD also has potential disadvantages, including increased workload for patients and families, an increased risk for dyslipidemia, a relatively high glucose load when glucose-based solutions are used, and a tendency to mild chronic volume overload. In addition, not all patients are able to safely perform PD, although this can be mitigated by using professional or nonprofessional dialysis assistants. The issue of dialysis modality selection is discussed in Chapter 90.

PD is a home-based therapy, and most patients are trained to do the exchanges themselves. In general, home dialysis patients have a better quality of life than those on other types of dialysis. The number of hospital visits is reduced, and the ability to travel is increased. Furthermore, several studies have shown a lower incidence and severity of delayed graft function in PD patients after transplantation.[2] In children, PD (usually APD) is the preferred dialysis modality because it is noninvasive and socially acceptable, reducing hospital visits and allowing the child to attend school. Advocates of PD often recommend that RRT should ideally begin with PD according to the patient's choice and then proceed, as required when residual renal function declines, to HD or transplantation. PD should thus be regarded as part of an integrated RRT program, together with HD and transplantation.[3]

PRINCIPLES OF PERITONEAL DIALYSIS

Three-Pore Model

The major principles governing solute and fluid transport across the peritoneal membrane are diffusion, driven by concentration gradients, and convection (filtration or UF), driven by osmotic or hydrostatic pressure gradients. The capillary wall and the interstitium together serve to separate the plasma in the peritoneal capillaries from the fluid in the peritoneal cavity. For the transport of fluid (UF) and large solutes, the capillary wall is by far the dominating transport barrier. However, for small-solute diffusion the interstitium accounts for approximately one third of the transport (diffusion) resistance; the mesothelium lining the peritoneal cavity is of much less significance. The permeability of the capillary wall can be described by a three-pore model of membrane transport (Fig. 96.1).[4] In the capillary wall the major route for small-solute and fluid exchange between the plasma and the peritoneal cavity is the space between individual endothelial cells, the interendothelial clefts. The functional radius of the permeable pathways in these clefts, denoted *small pores,* is 40 to 50 Å, slightly larger than the radius of albumin (36 Å). The size of these pores markedly impedes the transit of albumin and completely prevents the passage of larger molecules (e.g., immunoglobulins and α_2-macroglobulin). However, larger proteins can transit via very rare large pores (radius ~250 Å) in capillaries and postcapillary venules. The large pores constitute only 0.01% of the total

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[†] Deceased.

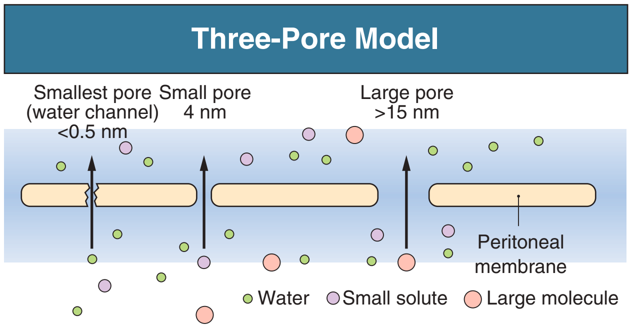

Fig. 96.1 Three-pore model. The small pores (4 nm) represent the major pathway across the peritoneum through which small solutes move by diffusion and water by convection driven by hydrostatic, colloid osmotic, and crystalloid osmotic pressure differences. Across large pores (>15 nm), macromolecules move out slowly by convection from plasma to the peritoneal cavity. The smallest pores (<0.5 nm) are represented by aquaporins permeable to water, but impermeable to solutes. Water moves here exclusively by crystalloid osmotic pressure.

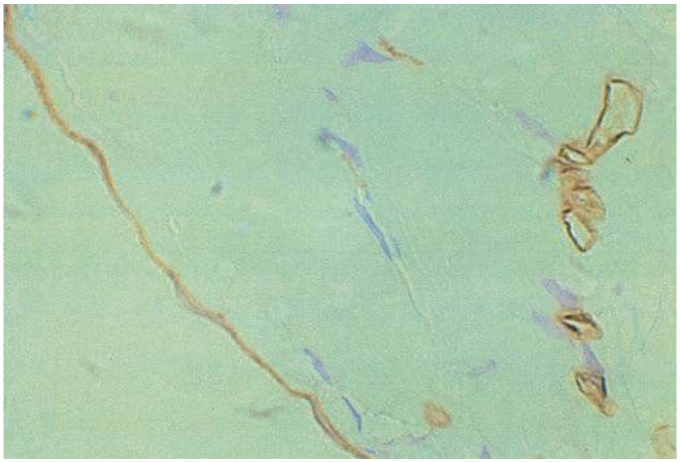

Fig. 96.2 Light microscopic section of a peritoneal membrane with capillaries and venules ***(to the right)*** **in an "amorphous" interstitium.** The peritoneum is lined by a thin layer of mesothelium *(to the left).* Capillaries and venules, as well as the mesothelium, are immunocytochemically stained for aquaporin-1 (AQP1) *(brownish color).* (From reference 51.)

number of capillary pores, and the transport across them occurs by hydrostatic pressure–driven unidirectional filtration from the plasma to the peritoneal cavity. In addition, the capillary wall has a high permeability to osmotic water transport via aquaporin-1 (AQP1) channels in the endothelial cell membranes (Fig. 96.2).[5]

Fluid Kinetics

Under normal (non-PD) conditions, most transport occurs via the small pores. Only 2% of peritoneal water transport occurs via AQP1. In PD, fluid removal is markedly enhanced by infusion of a hyperosmolar dialysate into the peritoneal cavity. The type of osmotic agent used markedly affects the mechanism of osmosis. Glucose will induce fluid flow through both AQP1 (~45%) and small pores (~55%), whereas large molecules, such as polyglucose (icodextrin) will remove fluid mainly via small pores (~90%). Thus glucose osmosis will result in a rapid dilution of the peritoneal dialysate, as reflected by a fall in sodium concentration (sodium sieving) during the first 2 hours of the dialysate dwell, caused by relatively large transport via the water-only AQP1 channels; this tends to correct later as diffusion across the small pores eventually increases the sodium concentration to that in the plasma.

Glucose is usually available at three concentrations that vary somewhat among manufacturers: low (1.36% or 1.5%), intermediate (2.27% or 2.5%), and high (3.86% or 4.5%). Fig. 96.3A demonstrates the intraperitoneal fluid kinetics, computer simulated using the three-pore model, over 12 hours of dwell time with these three solutions. Glucose is an intermediate-size osmolyte with a low osmotic efficiency (osmotic reflection coefficient [σ] = 0.03) across small pores, whereas glucose is 100% efficient as an osmotic agent across AQP1 ($\sigma = 1$). For that reason, glucose will markedly (30-fold) boost the transport of fluid through AQPs and thus redistribute fluid transport away from the small pores toward AQP1, resulting in significant sodium sieving. For example, for 3.86% glucose in the PD solution, the dialysate Na^+ concentration will drop from 132 mmol/l to 123 mmol/l in 60 to 100 minutes, which later increases toward serum Na^+ concentration (see Fig. 96.3B). On the other hand, icodextrin, with an average molecular weight of 17 kDa, has a high osmotic efficiency (σ ~0.5) across small pores and in relative terms is rather inefficient across AQPs. Hence, during icodextrin-induced osmosis only a very minor fraction of the UF will occur through AQP1, producing insignificant sodium sieving (see Fig. 96.4B).

In addition to the size of the osmotic agent, the degree of sodium sieving depends on the presence and quantity of AQP1, total rate of net UF (which is mainly determined by the glucose concentration), and diffusion capacity of Na^+. A high rate of small-solute transport (and thereby of sodium diffusion) in fast transporters will manifest as rapid equilibration of small solutes (creatinine and glucose) in the peritoneal equilibration test (PET; see later) and will also reduce sodium sieving.

In the absence of an osmotic agent in the PD fluid, the dialysate would be reabsorbed into the plasma within a few hours, mainly driven by the difference in colloid osmotic pressure between plasma and the peritoneum. This absorption will to a major extent occur via small pores, whereas approximately 30% of the peritoneal fluid will be removed by lymphatic absorption. The partial fluid flows in the peritoneal membrane modeled across different fluid conductive pathways in the three-pore model (for 3.86% glucose) are shown in Fig. 96.5. It is the presence of relatively high concentrations of glucose in the peritoneal fluid that prevents the reabsorption of fluid into the plasma during the first few hours of the dwell.

Patients who have a high rate of sodium diffusion (fast transporters) also have rapid transport of glucose out of the peritoneal cavity. Therefore the glucose gradient favoring UF dissipates more rapidly, and it is harder to achieve effective fluid removal compared with "slow transporters." In fast transporters the maximum UF volume is reduced and UF occurs earlier. There is usually also a more rapid reabsorption of fluid in the late phase of the dwell. The mechanism of fluid loss from the peritoneum is controversial, because some authors claim that the peritoneal fluid loss occurring in the late phase of the PD dwell is dominated by lymphatic absorption.[6]

Effective Peritoneal Surface Area

The functional surface area of the peritoneum reflects the effective surface area of the peritoneal capillaries.[7] The transport of small solutes, such as urea, creatinine, and glucose, is partly limited by the degree of perfusion of these capillaries—the "effective" peritoneal membrane blood flow. Furthermore, as mentioned earlier, some of the diffusion resistance for the smallest solutes (urea and creatinine) is located in the interstitium. The number of effectively perfused capillaries is increased

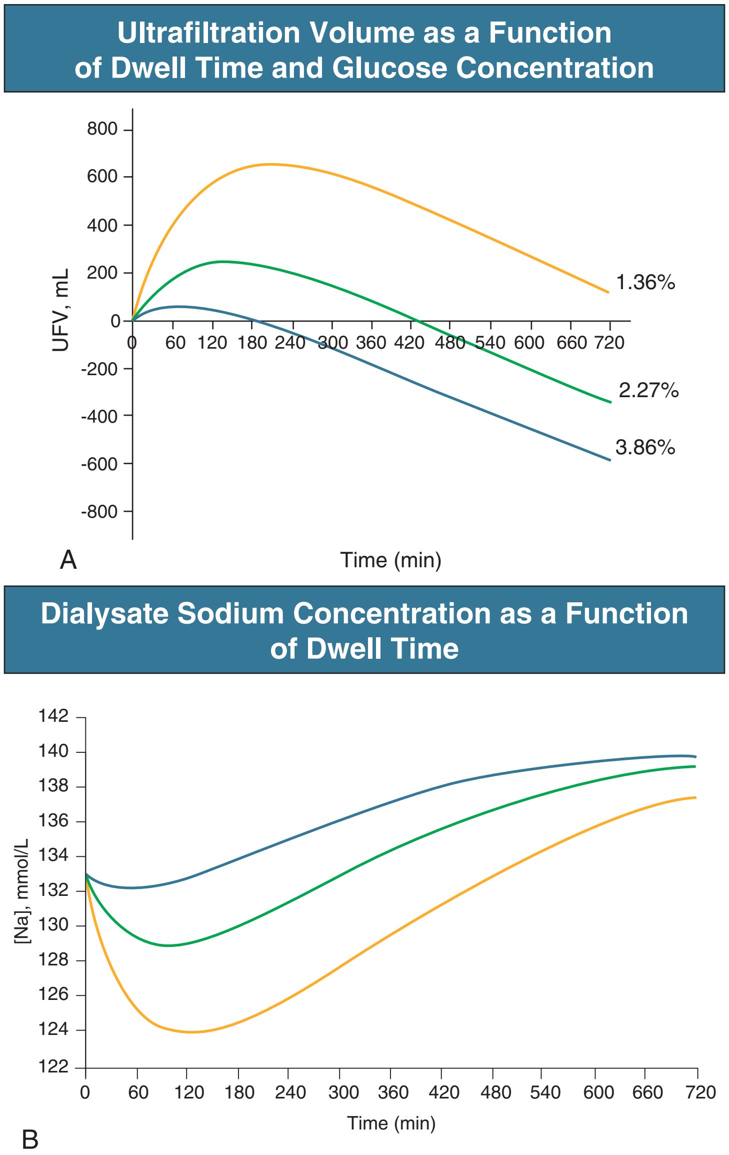

Fig. 96.3 (A) Ultrafiltration as a function of dwell time. Net ultrafiltration volume *(UFV)* as a function of dwell time for 3.86% *(yellow line),* 2.27% *(green line),* and 1.36% *(blue line)* glucose, computer simulated using the three-pore model of peritoneal transport. (B) Dialysate sodium as a function of dwell time. Dialysate sodium as a function of dwell time for 3.86% *(yellow line),* 2.27% *(green line),* and 1.36% *(blue line)* glucose, computer simulated according using the three-pore model of peritoneal transport.

by arteriolar vasodilation and reduced by vasoconstriction. These alterations often occur without large changes in the fluid permeability (hydraulic conductance [L_pS]) of the peritoneum. Thus, during vasodilation or vasoconstriction, there is usually a dissociation between changes in the permeability–surface area product (PS) for small solutes and in the L_pS of the membrane. Vasodilation, with recruitment of capillary surface area, occurs early in the dwell when glucose is used as the osmotic agent, causing early, transient increases in PS.[8]

Peritonitis is also associated with marked vasodilation, again leading to increases in small-solute PS, in the absence of large changes in L_pS, during the first 60 to 100 minutes of the dwell. However, in some patients with peritonitis, an increase in L_pS will result in relative increased fluid transport across the small pores. Furthermore, there is usually an opening of large pores in the capillaries (and postcapillary venules), resulting in enhanced leakage of macromolecules (e.g., albumin and immunoglobulins) from plasma to peritoneum. Peritonitis may thus result in relative difficulty in removing fluid (because of rapid dissipation of intraperitoneal glucose), a reduced sodium sieving (because of the reduced UF and increased Na^+ diffusion), and a markedly increased leakage of proteins to the dialysate.

The contact area between the dialysate and the peritoneal tissue varies as a result of posture and fill volume. Adult patients usually tolerate 2 to 2.5 liters of instilled volume, with larger volumes typically possible at night when the patient is supine. An intraperitoneal hydrostatic pressure (IPP) of less than 18 cm H_2O (supine position) is usually tolerated.[9] At higher pressures (>18 cm H_2O) the patient usually feels some discomfort. At intraperitoneal volumes of less than 2 liters there is a reduction in small-solute PS, whereas PS is only moderately increased at high fill volumes. Overall, an increased fill volume implies a more efficient exchange with regard to both small-solute exchange and UF, the latter being much more pronounced for hypertonic solutions.[10] For a long time it was thought that increased fill volumes would directly

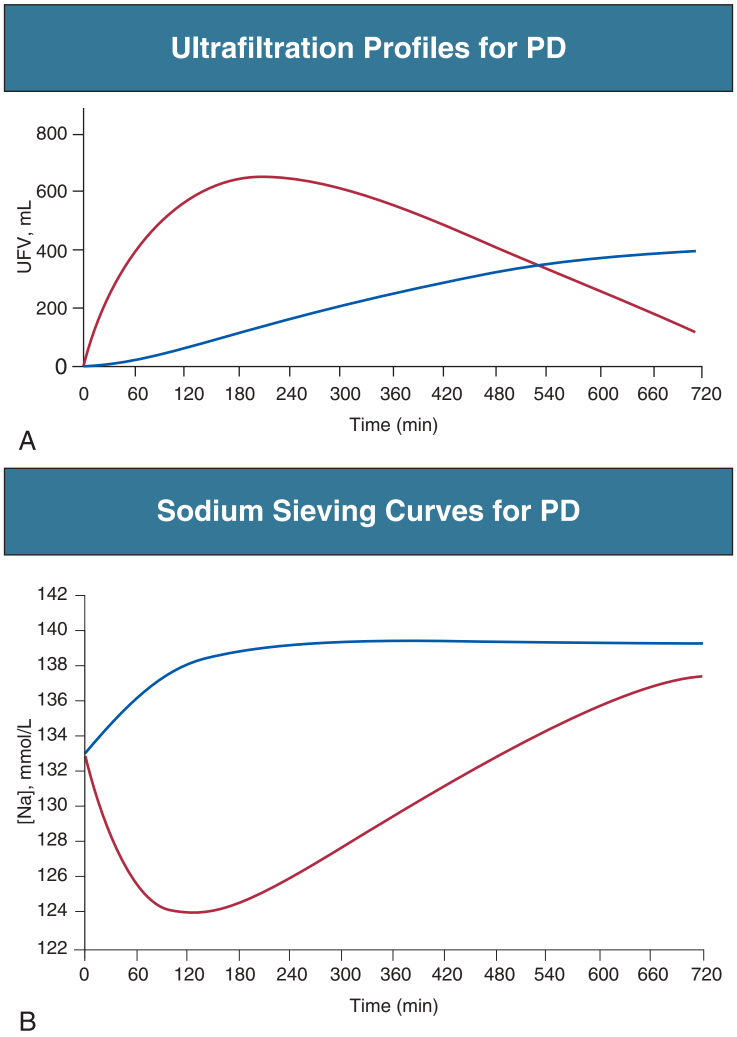

Fig. 96.4 (A) Ultrafiltration (UF) profiles for peritoneal dialysis *(PD).* Ultrafiltration profile for 7.5% icodextrin *(blue line),* computer simulated according to the three-pore model in an average patient who is not naïve to icodextrin, in comparison with the computer-simulated UF curve for 3.86% glucose *(red line). UFV,* Ultrafiltration volume. (B) Sodium sieving curves for PD. Sodium-sieving curves for 7.5% icodextrin *(blue line)* and 3.86% glucose *(red line)* (see Fig. 96.3). *Na,* Sodium. (A from reference 10.)

affect peritoneal fluid reabsorption by the hydrostatic pressure effect (increases in IPP). However, because 80% of any increase in IPP is transmitted via vein compression back to the capillaries, the actual changes in the transcapillary hydrostatic pressure gradient, which governs UF, will be rather small.[11] Thus the impact of IPP on fluid absorption is moderate.[12]

PERITONEAL ACCESS

The key to successful chronic PD is a safe and permanent access to the peritoneal cavity (Fig. 96.6). Catheter-related complications cause significant morbidity, sometimes forcing the removal of the catheter. Catheter-related problems are a cause of permanent transfer to HD in up to 20% of all patients. Most catheters are derived from that originally devised by Tenckhoff and Schechter.[13] The Tenckhoff catheter is a Silastic tube with side holes along its intraperitoneal portion. There are usually one or two Dacron cuffs, allowing tissue ingrowth, which secures the catheter in place and prevents pericatheter leakage and infection. The Tenckhoff catheter is straight, having one cuff lying on the peritoneum with the catheter tip pointing in the caudal direction; the outer cuff is close to the skin exit. Several centimeters of the catheter is thus located transcutaneously. Intraperitoneal and transcutaneous catheter modifications continue to appear, indicating that no single design is perfect (Fig. 96.7). Although several studies report less frequent catheter drainage failures with use of the arcuate “swan neck” catheter (see Fig. 96.7) compared with straight catheters, there is no hard evidence that any of the modified catheters on the market are actually superior to the original (one- or two-cuff) Tenckhoff catheter.[14]

Ideally, catheters should be inserted in the operating room under sterile conditions by an experienced and appropriately trained operator. Presurgical assessment for the presence of herniation or any weakness of the abdominal wall is essential. If present, it may be possible to correct these at the time of catheter insertion. Before the operation, eradication of nasal carriage of *Staphylococcus aureus* with locally applied antibacterial agents (such as mupirocin) significantly reduces exit site infection rates. A single preoperative intravenous dose of a first- or second-generation cephalosporin is also recommended. To avoid development of vancomycin-resistant enterococcus, vancomycin should not be used as a prophylactic agent. Several placement techniques have been described and practiced: surgical mini-laparotomy and dissection,

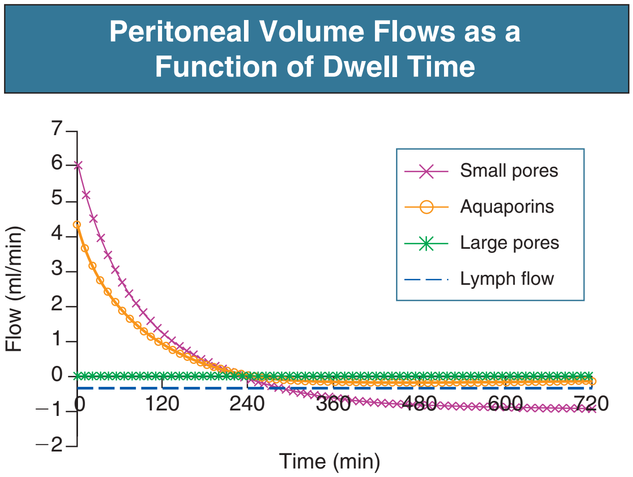

Fig. 96.5 Peritoneal volume flows as a function of dwell time. Peritoneal volume flows as a function of dwell time for 3.86% glucose partitioned among aquaporins, small pores, large pores, and lymphatic absorption. The small-pore volume flow is initially approximately 60% of total volume flow and becomes negative after peak time (220 min). The aquaporin-mediated water flow becomes slightly negative after approximately 250 min. The large-pore volume flow is negligible and remains constant throughout the dwell, as does lymphatic absorption (0.3 ml/min). (Modified from reference 52.)

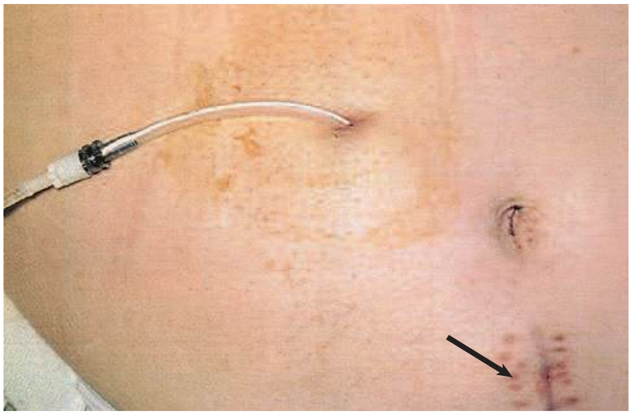

Fig. 96.6 A recently implanted peritoneal dialysis catheter in situ. Note the subumbilical midline scar where the catheter enters the peritoneal cavity *(arrow).*

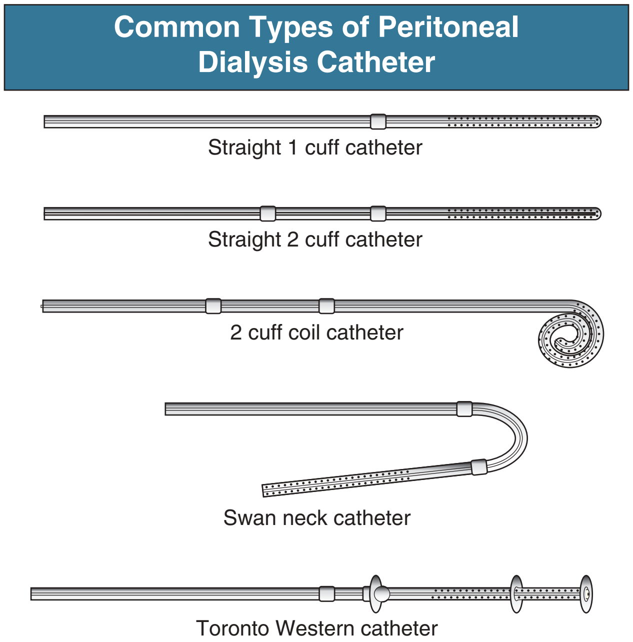

Fig. 96.7 Common types of peritoneal dialysis catheter.

blind placement using the Tenckhoff trocar, blind placement using a guidewire (Seldinger technique), mini-trocar peritoneoscopy placement, and laparoscopy. These techniques are discussed further in Chapter 92.

TECHNIQUES OF PERITONEAL DIALYSIS

In CAPD, 2 to 2.5 liters of dialysis fluid is instilled into the peritoneal cavity four or five times daily. In 4 to 5 hours there is 95% equilibration of urea and approximately 65% equilibration of creatinine, whereas the glucose gradient has dissipated to approximately 40% of the initial value. For glucose as an osmotic agent, 4 to 5 hours is a suitable dwell time. For night dwell exchanges, longer dwell times can be accepted (8 to 10 hours). Furthermore, there is room for individual exchange schedules that can be adjusted to suit individual patient convenience. Dwell times shorter than 4 to 5 hours can be performed with use of a machine (cycler). This technique can be used to maintain adequate dialysis when more frequent, lower volume exchanges are needed—for example, to minimize leakage in conjunction with catheter insertion, hernia repair, or abdominal operations. Rapid exchanges also may be required during treatment for peritonitis or in patients with fluid overload when the patient's hydration status needs to be corrected rapidly.

Today, double-bag systems (so-called Y systems) are in general use according to the principle "flush before fill." The double-bag system contains the unused dialysis fluid connected to an empty sterile drain bag via a Y-set tubing system. After the patient has connected the system and flushed the connection (for 2 to 3 seconds), a frangible (breakable) pin to the drain bag is opened, and the peritoneal cavity is drained over 10 to 15 minutes to fill the drain bag. Then this bag is clamped, and the fresh bag opened, to fill the peritoneal cavity over another 10 to 15 minutes. The time for exchange (instillation and drainage), if the catheter is in good order, should not exceed a total of 30 minutes. Usually the first 1.6 to 1.8 liters will drain rapidly (at ≥200 ml/min), whereas the last 200 to 300 ml will drain much more slowly. The breakpoint between the rapid and the slow phase may vary markedly from individual to individual.

APD is usually performed with use of a cycler overnight (8 to 10 hours), during which large volumes (10 to 20 liters) can be exchanged. During daytime the APD patient usually has a so-called wet day—that is, a long dwell, usually with icodextrin as the osmotic agent in the dialysis fluid. Some patients with nightly APD perform one daily exchange so that there are two long (6 to 8 hours) daily dwells. Most cyclers can be programmed to vary inflow volume, inflow time, dwell time, and drain time. Cyclers usually warm the fluid before inflow, and they also monitor outflow volume and the excess drainage (UF volume). Current APD machines have alarms for inflow failure, overheating, and poor drainage. Some cyclers interrupt drainage at the breakpoint between the fast and slow phases to make the exchange more efficient. Another way to accelerate exchanges is to allow a considerable sump volume in the peritoneal cavity by not letting all the fluid drain; subsequent inflow volumes are proportionally reduced, and after multiple cycles complete drainage occurs. This technique is called *tidal peritoneal dialysis* (TPD).

The exchange volume should be adjusted according to the patient's size. Adult patients weighing less than 60 kg should start with 1.5-liter bags. The average patient (60 to 80 kg) should receive 2-liter exchanges, and for patients weighing more than 80 kg, 2.5 liters should be used. If pressure monitoring systems are available, the IPP may inform the choice of exchange volume. In the supine position, most patients have an IPP of 12 cm H_2O.

PERITONEAL DIALYSIS FLUIDS

The majority of PD fluids used today have the composition of a lactate-buffered, balanced salt solution devoid of potassium, with glucose (1.36% or 1.5%, 2.27% or 2.5%, 3.86% or 4.5%) as the osmotic agent. The K^+ concentration in PD fluids is zero to aid control of potassium balance.

Lactate is used as a buffer instead of bicarbonate, because bicarbonate and Ca^{2+} may precipitate (to form calcium carbonate) during storage. With the advent of newer multichambered PD delivery systems, it is possible to replace lactate with bicarbonate and make a number of other solution modifications that previously were not feasible. However, the higher cost of the newer more physiologic fluid formulations should be borne in mind. For example, in the United Kingdom, icodextrin solution costs approximately 80% more per unit volume than glucose-based solutions.

Electrolyte Concentration

In current PD fluids the concentrations of Na^+, Cl^-, Ca^{2+}, and Mg^{2+} are selected to be close to the serum concentration. The removal of these ions across the peritoneum is therefore a result of the low diffusion gradient, more or less completely dependent on convection. For every deciliter of fluid removed in a 4-hour dwell, approximately 10 mmol of Na^+[15] and 0.1 mmol of Ca^{2+} are removed, provided that serum Na^+ and Ca^{2+} are within the reference ranges.[11]

The frequent use of calcium-containing phosphate binders requires an understanding of Ca^{2+} kinetics for various types of dialysis fluids to avoid hypercalcemia. The calcium concentration of current PD solutions is usually 1.25 to 1.75 mmol/l. However, because Ca^{2+}, like Na^+ and Mg^{2+}, has a UF-dominated transport, 1.25 mmol/l may be considered appropriate only for 1.36% glucose, to achieve a zero (neutral) peritoneal calcium removal. For example, UF-driven Ca^{2+} loss will occur during a 4-hour dwell with 3.86% glucose solution. With use of a three-compartment system for the PD bags, it would be possible to adapt the dialysis fluid Ca^{2+} concentration to obtain net zero peritoneal Ca^{2+} transport across the peritoneum, or to reach a preset calcium removal target, for each PD fluid glucose concentration used.[16] However, in currently available PD solutions, Ca^{2+} concentration is not variable as a function of glucose concentration; therefore 1.25 mmol/l Ca^{2+} is recommended when patients use calcium-containing phosphate binders. It should be noted that net peritoneal calcium removal with 1.25 mmol/l Ca^{2+} level can be achieved only by PD fluids containing 2.27% or 3.86% glucose.

The Mg^{2+} concentration commonly used in current PD solutions is 0.25 to 0.75 mmol/l. For 1.36% glucose, 0.25 mmol/l would be appropriate for zero Mg^{2+} transport during the dwell, whereas for higher dialysis fluid glucose concentrations there will be net Mg^{2+} losses.

Osmotic Agents

Glucose is the principal osmotic agent used for fluid removal (UF) in PD. Alternative commercially available osmotic agents are amino acids and icodextrin. Icodextrin is a polydisperse glucose polymer with an average molecular weight of 17 kDa.[17] However, because of the polydispersity of icodextrin, approximately 70% of the molecules have a molecular weight of 3 kDa or less.[10] Icodextrin is available as a 7.5% solution with essentially the same electrolyte composition as glucose-based dialysates. The osmolality of the glucose polymer solution, unlike that of 1.36% glucose (osmolality 350 mOsm/kg) dialysis fluid, is within the same range, or actually slightly lower, than that of normal serum. The presence of larger molecules in the icodextrin solution, compared with those in glucose-based solutions, improves the osmotic efficiency markedly across the small pores ($\sigma = 0.5$) and also reduces dissipation of the osmotic gradient over time. This yields a sustained UF over 8 to 12 hours (see Fig. 96.4A). Therefore icodextrin is preferable for long dwell exchanges, for example, overnight, and particularly for patients who tend to absorb glucose rapidly (fast transporters, see later). Icodextrin is slowly absorbed into serum and degraded (circulating α-amylase) to oligosaccharides, such as maltose, which may give false-positive results for glucose, leading to erroneous measures of hyperglycemia and inappropriate use of glucose-lowering agents.[18]

Another alternative osmotic agent that is commercially available is a 1.1% amino acid mixture having the same osmolality as 1.36% glucose.[19] According to some studies, regular use of this dialysate may increase certain nutritional indices, although there is also some evidence that amino acid solutions increase acidosis and raise plasma urea. Both icodextrin-based and amino acid–based solutions may be used to reduce the glucose exposure of the peritoneal membrane and total glucose load to the patient.

Until recently, conventional PD solutions have had a low pH and a high concentration of glucose degradation products (GDPs). GDPs are reactive carbonyl compounds that form during heat sterilization and/or storage of glucose-based solutions. GDPs are toxic to a variety of cells in vitro and also potentially toxic in vivo.[20] By the use of multicompartment systems reconstituted immediately before infusion, it has been possible to compose new solutions with much lower concentrations of GDPs and a neutral pH and also to use bicarbonate or bicarbonate-lactate mixtures as buffers.[21-23] Solutions using bicarbonate or bicarbonate-lactate mixtures result in significantly less infusion pain and are as effective as lactate at correcting acidosis, when used at the same total buffer ion concentration.[24] In prospective, randomized studies these fluids have been associated with improvement in dialysate effluent markers of peritoneal membrane integrity, particularly cancer antigen 125 (CA-125), a measure of peritoneal mesothelial cell mass.[21-23] There also have been some indications of improved residual renal function in patients with PD solutions low in GDPs,[23] although this was not confirmed in recent prospective, randomized studies.[25,26] One of those studies, however, the balANZ study,[26] suggested that biocompatible PD solutions may delay the onset of anuria and reduce the incidence of peritonitis compared with conventional solutions.

ASSESSMENTS OF PERITONEAL SOLUTE TRANSPORT AND ULTRAFILTRATION

Small-Solute Removal

The net removal of solutes and fluid during PD, in excess of residual renal excretion, can be measured by evaluating the drained dialysate. For this purpose the concentrations of urea and creatinine are measured in dialysate and plasma. The dialysate-plasma concentration ratios (D/P) of either of these solutes multiplied by the daily drain volume gives the 24-hour clearance. Weekly creatinine and urea clearances are obtained by multiplying these figures by 7. For comparison among patients, creatinine clearance is conventionally standardized to body standard surface area (1.73 m^2), and urea clearance (mostly for comparison with HD) is expressed as Kt/V (where Kt is the weekly clearance and V the volume of distribution of urea). In PD, routine assessment of V is imprecise, in contrast to the situation in HD, in which V can be mathematically derived directly from urea kinetics. V should preferably be determined by direct techniques, such as from the dilution of isotopic water (total body water); in practice, however, *V* is usually approximated from standard tables using BW and height as anthropometric parameters together with gender.[27] Criticism of the *Kt/V* concept in PD is based on the uncertainty of determining a correct value for *V*. In those who are markedly underweight or overweight the ideal body weight should be used for calculating *V*.[28]

Large-Solute Removal

For more insight into peritoneal transport, the clearance of larger solutes such as β_2-microglobulin, as well as markers for transport across the large pores, such as albumin, immunoglobulins and α_2-macroglobulin, can be measured. Although many centers assess the daily peritoneal removal of total protein and/or albumin, measurements of most other solutes are not made in routine clinical practice.

Ultrafiltration

UF can be assessed with a 24-hour collection. Even if done accurately, there is a considerable dwell-to-dwell and day-to-day variability in UF depending on drainage conditions, posture, and varying levels of residual (sump) intraperitoneal volume. Reasonably accurate estimations of daily UF volume can be obtained by averaging collections of all fluid over a period of several days. In clinical practice, the patient's own daily dialysis records also should be examined with respect to dwell-to-dwell UF volumes and the number of hypertonic bags used per day. For a 3.86% glucose dwell a UF volume less than 400 ml will indicate insufficient UF—that is, ultrafiltration failure (UFF). UF volume also can be determined by the PET, as described later. In a routine 2.27% glucose PET, less than 200 ml of UF in 4 hours signals UFF. More accurate determination of intraperitoneal volume can be achieved as a function of time with use of a marker, such as iodine-125 (^{125}I)–human serum albumin or dextran 70. This is not required in routine clinical practice but as a research tool allows more precise UF volume estimations.

Peritoneal Membrane Function

Peritoneal Equilibration Test

The PET yields approximate estimations of the rate of peritoneal transport of small solutes and of UF capacity.[9] The rate of small-solute transport depends on the effective peritoneal surface area, which is essentially dependent on the number of effectively perfused capillaries available for exchange (and the blood flow). The volume ultrafiltered in 4 hours is a function of the osmotic conductance to glucose (OCg; the peritoneal UF coefficient multiplied by the reflection coefficient for glucose) and the rate of dissipation of the glucose osmotic gradient (the rate of small-solute transport). In general, when the rate of glucose disappearance is high, UF volume is low.

The PET procedure is summarized in Box 96.1. After an overnight dwell (8 to 12 hours) the dialysate fluid is drained, and a 2-liter 2.27% glucose bag is infused for 10 minutes with the patient in the supine position (rolling from side to side every 2 minutes). After 10 minutes—that is, at completion of the infusion—200 ml is drained into the drainage bag and mixed, and a zero time dialysate sample taken. At the end of the 4-hour dwell period, dialysate is drained out and measured. The net volume is noted. Concentrations of glucose and creatinine in the outflow and plasma are measured, as well as the concentration of glucose in the zero sample. The results are expressed as the dialysate-plasma (D/P) solute concentration ratio and as the dialysate glucose at 4 hours–dialysate glucose at time zero (D/D_0) concentration ratio. The higher the D/P ratio for creatinine, the faster the rate of transport for small solutes. According to D/P ratios for creatinine or D/D_0 for glucose, patients can be divided into slow, slow average, fast average, or fast transporters (Fig. 96.8); transport status remains stable in approximately 70% of patients at 1 year and approximately half of patients at 2 years.

BOX 96.1 Peritoneal Equilibration Test

1. Two liters (warm) 2.27% fluid instilled for 10 minutes with the patient supine and rolling from side to side every 2 minutes.
2. Exactly at 10 minutes after start of the infusion, 200 ml is drained into the bag. Draw 5 ml (discard); the next 5 ml taken for creatinine and glucose determination.
3. After 2 hours, new samples collected as in 3.
4. After 4 hours (exactly), collect drainage over 20 minutes. Note total bag weight. Subtract empty bag weight. Take samples (after mixing) for creatinine and glucose.
5. Glucose D/D_0 (the ratio of dialysate glucose at 4 hours and at time zero) and creatinine D/P (the ration of dialysate and serum creatinine at 4 hours) are plotted versus time (as shown in Fig. 96.8). Record the total drain volume.

The night bag (8 to 12 hours) must be 1.36% or 2.27% glucose, drained for 20 minutes with patient sitting.

It should, however, be emphasized that D/P measurements give only an approximate estimation of small-solute transport rate. Additional information can be obtained by variations, including the modified PET (instilling a 3.86% solution and draining after 4 hours),[30] the mini-PET (instilling a 3.86% solution and draining after 1 hour), and the double–mini-PET (instilling sequentially a 1.36% solution and a 3.86% solution, draining each after 1 hour).

Mini–Peritoneal Equilibration Test

In the mini-PET, a 3.86% glucose solution is instilled and completely drained after 1 hour. The Na^+ concentration in the drained dialysate assesses the degree of sodium sieving and hence gives a measure of AQP-mediated ("free") water flow.[31,32] The fraction of "free" water transport can be evaluated in the early phase of the dwell from the 1-hour drained volume minus the 1-hour peritoneal Na^+ clearance (i.e., the drained Na^+ – the instilled Na^+ ÷ the serum Na^+ concentration). In the first hour when Na^+ diffusion is negligible, the peritoneal clearance of sodium (across small pores) will directly reflect the peritoneal small-pore fluid clearance (UF). This value is then subtracted from the total (1-hour) UF volume to yield an estimate of the free (AQP-mediated) water transport. Reductions in this parameter usually occur over time on PD, and marked reductions in free water transport are assumed to reflect peritoneal fibrosis.[33,34]

Double–Mini–Peritoneal Equilibration Test

The OCg can be measured with a double–mini-PET—that is, a 1-hour dwell with 1.36% glucose and also a 1-hour dwell with 3.86% glucose solution. The calculation of OCg is based on the difference in the 1-hour drained volume between the 3.86% and 1.36% glucose solutions.[35] In long-term PD, increases in D/P-creatinine and reductions in D/D_0-glucose are usually seen, eventually resulting in UFF. These changes are often combined with moderate reductions in OCg, the latter perhaps coupled with peritoneal fibrosis.[36] Marked reductions in OCg may signal imminent development of peritoneal sclerosis.[37]

Residual Renal Function

In PD, residual renal function is important for patient and technique survival. Residual renal function is somewhat better preserved over treatment time in PD than in HD.[38] Residual renal function can be assessed by collecting all urine over a day and assessing the urine concentrations of urea and creatinine and total urine volume. Because renal creatinine clearance, as a result of tubular secretion, yields an

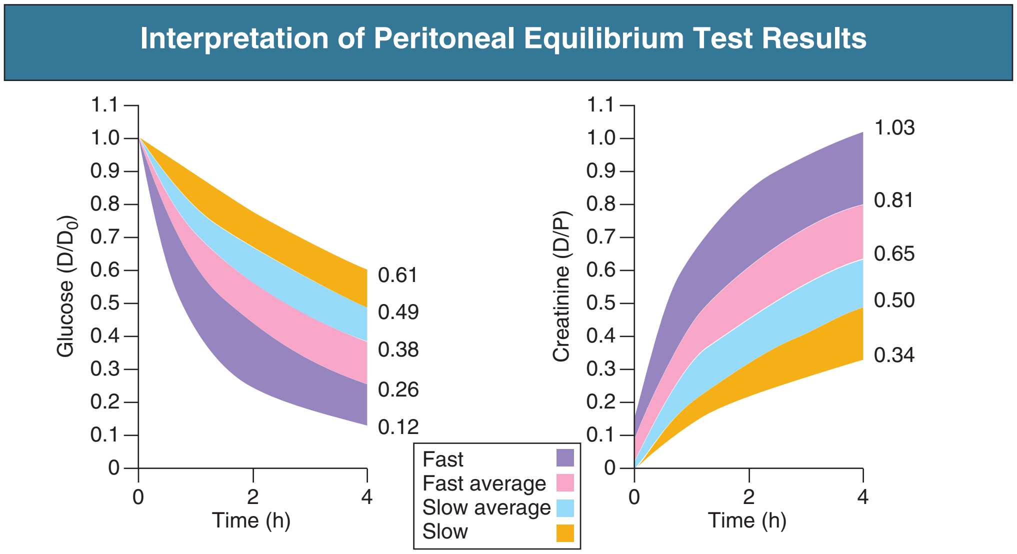

Fig. 96.8 **Interpretation of peritoneal equilibration test (PET) results.** Changes in solute concentration during a PET allow classification into different transport types. (Modified from reference 29.)

overestimate of the glomerular filtration rate (GFR) (by 1 to 2 ml/min) when the GFR is 10 ml/min or lower, and renal urea clearance yields an underestimate of GFR (by 1 to 2 ml/min) in the same interval of (reduced) GFR, a good estimate of actual GFR can be calculated as the average of renal creatinine clearance and urea clearance. However, if the daily urine volume is less than 200 ml, residual renal function will be too small to be measured accurately.

ADEQUACY

The most important measure of dialysis adequacy is the general clinical state of the patient, as manifested by a good nutritional status (maintained muscle mass) and the absence of anemia, edema, hypertension, electrolyte and acid-base disturbances, neurologic symptoms, pruritus, and insomnia. Management of anemia and bone disease in ESRD patients is discussed in Chapters 82 and 84, respectively. Some criteria for PD adequacy are given in Table 96.1.

Small-Solute Clearance

Few prospective randomized studies define adequate PD. From a clinical point of view it hasbeen suggested that a weekly *Kt/V* above 1.7 and a weekly creatinine clearance above 50 l/1.73 m^2 would be (minimally) adequate for patients on CAPD. In a large prospective study (CANUSA), the outcome for a cohort of 680 patients starting CAPD was studied with an average follow-up of 2 years.[39] Patients who maintained a high *Kt/V* or creatinine clearance over time did better than those who did not. An increase of 0.1 unit of *Kt/V* (peritoneal + renal) per week was associated with a 5% decrease in relative risk for death, and an increase of 5 l/1.73 m^2 of creatinine clearance per week (peritoneal + renal) was associated with a 7% decrease in the relative risk for death. Further analysis of the CANUSA study findings indicated that the survival advantage of patients with higher total small-solute clearance was entirely attributed to the residual renal function. For each increase of 250 ml of urine output per day, there was a 36% decrease in the relative risk for death. In the Adequacy of Peritoneal Dialysis in Mexico (ADEMEX) study,[40] a large randomized controlled trial (RCT) designed to test the value of increasing peritoneal small-solute clearance, there was no survival advantage of increasing the peritoneal clearance to obtain a total weekly creatinine clearance above 60 l/1.73 m^2 at an average peritoneal *Kt/V* of 2.12 (intervention group) compared with a clearance above 50 l/1.73 m^2 at an average peritoneal *Kt/V* of 1.56 (control group). However, although overall mortality, hospitalization, withdrawal, and technique survival were similar in the two groups, the causes of withdrawal were different. Relatively more patients in the control group withdrew because of uremia, hyperkalemia, and acidosis and died from congestive heart failure than in the intervention group.

TABLE 96.1 Criteria for Peritoneal Dialysis Adequacy Criteria for Peritoneal Dialysis Adequacy

Clinical	Patient feels well and has stable lean body mass No symptoms of anorexia, asthenia, nausea, emesis, insomnia Stable nerve conductance velocity
Small-solute clearance	Weekly *Kt/V* urea >1.7 (renal + peritoneal) Weekly creatinine clearance >50 l/1.73 m^2
Large-solute clearance	Albumin clearance <0.15 ml/min
Fluid balance	No edema No hypertension No postural hypotension
Electrolyte balance	Serum potassium <5 mmol/l
Acid-base balance	Serum bicarbonate >24 mmol/l
Nutrition	Daily protein intake ≥1.2 g/kg Daily calorie intake >35 kcal/kg/day Serum albumin >3.5 g/l BMI 20-30 kg/m^2 Stable midarm muscle circumference

BMI, Body mass index.

From these studies it seems that renal and peritoneal clearance are not mutually comparable. High residual renal function is of greater survival advantage than high peritoneal solute transport capacity. The fact that the survival of PD patients is equal to or supersedes that of HD patients during the first 2 to 3 years of dialysis (see later), despite the fact that PD provides approximately 50% of the total *Kt/V* of HD, indicates that the benefit of PD goes beyond the clearance of small solutes. In a European multicenter study of APD, the European Automated Peritoneal Dialysis Outcomes Study (EAPOS), small-solute clearance did not correlate with survival in anuric patients.[37] On the contrary, total volume removal and hydration state were important factors. Still, there is reasonably good evidence that a weekly *Kt/V* above 1.7 and a weekly creatinine clearance above 50 l/1.73 m^2 are adequacy targets that should be reached and maintained in a majority of patients. Lower values of *Kt/V* and creatinine clearance have been found to be associated with more clinical problems and higher consumption of erythropoiesis-stimulating agents in a large RCT. [41]

Commercially available computer programs can predict urea and creatinine clearances and peritoneal UF performance and provide suggestions for treatment options, based on drained volumes and on plasma and dialysate creatinine and urea values. These parameters are often obtained by PET or standardized schedules for specified dwell exchanges. Some of the programs yield an estimate of peritoneal albumin clearance, which to a great extent depends on the filtration occurring across large pores, being increased in "inflammation." Recommended dialysis schedules based on the categorization of the PET are given in Table 96.2.

Fluid Balance

As in all types of RRT, long-term maintenance of adequate fluid and electrolyte balance is crucial for the survival of patients on PD. As already mentioned, the outcome of PD is directly related to residual renal function, particularly a high urine output. Furthermore, patients with fast transport in the PET (a more rapid absorption of glucose and a more rapid loss of the osmotic gradient) have a reduced technique survival. It seems evident that after 2 or 3 years of PD, when residual renal function is low, most patients on PD are fluid overloaded.[42,43] It is likely that volume overload not only aggravates hypertension but also leads to progression of left ventricular hypertrophy, often already present at the start of PD. However, during the first year of PD there is often a fall in blood pressure (BP) and a reduced need for antihypertensive agents. Unfortunately, with time on PD, BP usually rises and the number of antihypertensive drugs needed usually again increases.[44] In patients with evidence of volume overload, PET tests can clarify the mechanism and guide adjustments to the dialysis regimen, if required. Therefore it is advisable to regularly assess dialytic fluid removal in such patients over time, at least every 6 months, with a modified PET (4-hour 3.86% glucose dwell, in conjunction with a standard 2.27% 4-hour PET).

TABLE 96.2 Typical Peritoneal Dialysis Regimens Required for Achievement of Adequate Solute Clearances

	PERITONEAL SOLUTE TRANSPORT CHARACTERISTICS: D/P CREATININE AT 4 HOURS			
Patient Body Surface Area (m2)	**Slow (<0.5)**	**Slow Average (0.5 to <0.65)**	**Fast Average (0.65-0.82)**	**Fast (>0.83)**
<1.7	CAPD/APD 10-12.5 l	CAPD/APD+ 10-12.5 l	APD+* 10-12.5 l	APD* 10-12.5 l
1.7-2.0	CAPD+/APD 12.5-15 l	APD+ 12.5-15 l	APD+* 12.5-15 l	APD+* 12.5-15 l
>2.0	CAPD+, HD	APD+ 15-20 l	APD+* 15-20 l	APD+* 15-20 l

*The use of glucose polymer (icodextrin) solution for the long exchange will enhance both solute clearance and ultrafiltration. Typical peritoneal dialysis regimens required to achieve adequate solute clearance according to patient size and membrane characteristics in anuric patients. The total volume of dialysate fluid required increases with body size, with use of 2.5- or even 3.0-liter exchanges. As solute transport increases, the use of automated peritoneal dialysis (APD) with shorter overnight exchanges is favored over continuous ambulatory peritoneal dialysis (CAPD). Both CAPD and APD may have to be augmented by the use of an additional exchange (denoted by +); This is given by way of an additional afternoon exchange in CAPD patients or by use of an exchange device that delivers a single additional exchange at night.
D/P, Dialysate-plasma concentration ratios; *HD*, hemodialysis.

Management of Fluid Overload

As total urinary water (and sodium) excretion and peritoneal UF volume decline, it is advisable to instruct patients to restrict salt and water intake. In view of the difficulty in compliance with salt restriction, the use of PD solutions with lower sodium concentration has been advocated. Preliminary studies of low-sodium PD solutions have been promising with regard to reducing the need for BP-lowering drugs to control hypertension[45]; however, low-sodium solutions are not yet commercially available. Loop diuretics such as furosemide 250 to 500 mg/day can be used to maintain urine volumes but do not maintain renal clearance. If salt and water restriction and diuretics are not effective in maintaining UF, it can be enhanced by increasing the dialysis glucose concentration. Patients with alterations in peritoneal membrane function, appearing over the first few years of PD, usually have increased small-solute transport combined with only a moderate change in peritoneal UF capacity,[36] and there is an increased reabsorption of fluid in the late phase of the dwell. These patients can benefit from switching to APD and the use of icodextrin for one of the (daily) exchanges. RCTs using icodextrin for the long daytime dwell in APD have demonstrated an improved UF and a reduced extracellular fluid volume.[46] Patients who have been on PD for several years may have a reduced UF capacity (reduced OCg).[35,36] These patients would (theoretically) benefit less from switching to icodextrin because of the reduced UF capacity.[10]

Nutrition

During their first year of treatment, CAPD patients typically have evidence of net anabolism; the average weight gain may exceed 5 kg without any clinical signs of fluid overload. Contributing to this weight gain is the peritoneal glucose reabsorption (on average 100 to 150 g/day), which adds 400 to 600 kcal of energy intake daily and results in metabolic syndrome in approximately 50% of prevalent PD patients.[47] As residual renal function declines, the nutritional and metabolic abnormalities in CAPD become increasingly manifest, with reductions in lean body mass. The main cause of protein-energy malnutrition and wasting, apart from poor food intake, is the impaired metabolism of protein and energy in uremia. Despite glucose absorption, many patients on long-term CAPD have signs of energy malnutrition, a major component of the uremic wasting syndrome. Contributing factors are (low-grade) inflammation associated with carbonyl and oxidative stress and with accelerated atherosclerosis, the malnutrition inflammation atherosclerosis syndrome.[48] It is important that CAPD patients be prescribed an adequate amount of protein (>1.2 g protein/kg/day) and energy (total energy intake >35 kcal/kg/day) and a sufficient dose of dialysis, enabling the patient to ingest this diet. It should be noted that the daily losses of protein to the dialysate are not negligible, but approximately 5 to 7 g daily, of which approximately 4 to 5 g is albumin. This is comparable to the losses occurring in nephrotic range proteinuria. The nutritional management of PD patients should include frequent assessments of their nutritional status, and, if inadequate, referral for HD (or transplantation) should be considered. Nutrition in dialysis patients is discussed further in Chapter 86.

OUTCOME OF PERITONEAL DIALYSIS

Registry data have indicated a lower risk for death in patients treated with PD during the first 3 years of treatment compared with those treated with HD, although overall the mortality of patients on PD compared with HD is not significantly different.[49] Survival differences seem to vary substantially according to the underlying cause of ESRD, age, and baseline comorbidity. In a study based on U.S. Medicare registry data,[50] HD was associated with a higher risk for death among diabetic patients with no comorbidity and among younger patients (age 18 to 44), whereas PD was associated with a higher risk for death among patients aged 45 to 64. In patients with mortality rates adjusted for comorbidity at start of dialysis, there were no differences between HD and PD among nondiabetic patients and among younger diabetic patients (ages 18 to 44), but mortality was higher on PD for older diabetic patients with baseline comorbidity. Limited data address comparative survival for HD versus PD in patients older than 70, but small studies from the NTDS study (in the United Kingdom) and the REIN study (in France) suggest that the risk for serious outcomes such as hospitalization and death are similar, regardless of the modality selected. In summary, it appears that dialysis modality does not substantially affect major adverse clinical outcomes, provided patients are appropriately selected.

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SELF-ASSESSMENT QUESTIONS

1. In peritoneal dialysis (PD), the fraction of aquaporin (AQP) (ultrasmall pore)-mediated water flow is much higher for glucose than for icodextrin (ICO) as osmotic agent. Why?
   - **A.** Glucose will induce more initial vasodilation and recruitment of exchange vessel surface area than ICO.
   - **B.** The glucose molecules are smaller than the ICO molecules and therefore are relatively "inefficient" as osmotic agents in small pores, but relatively more efficient across AQP.
   - **C.** Glucose, but not ICO, will regularly induce increases in the number of AQPs.
   - **D.** Glucose, but not ICO, can increase the peritoneal capillary filtration coefficient (L_pS).
   - **E.** Oncotic agents such as ICO cannot pull fluid across AQP at all.
2. Which of the following PD catheters has a superior clinical outcome?
   - **A.** The Toronto Western catheter
   - **B.** The Swan neck catheter
   - **C.** The straight one-cuff (original) Tenckhoff catheter
   - **D.** The straight two-cuff (original) Tenckhoff catheter
   - **E.** None of the catheters above shows significant clinical superiority.
3. Long-term changes in peritoneal transport parameters usually involve:
   - **A.** Increases in the mass transfer of small solutes (e.g., PET_{creat}) and marked increases in the peritoneal ultrafiltration (UF) coefficient (L_pS)
   - **B.** Reductions in small-solute mass transport (PET_{creat}) and increases in the peritoneal UF coefficient (L_pS)
   - **C.** Increases in small-solute transport (PET_{creat}) combined with no or only moderate increases in the UF coefficient (L_pS)
   - **D.** Increases in large-solute transport together with increases in UF coefficient (L_pS)
   - **E.** Increases in large-solute transport combined with reductions in the UF coefficient (L_pS)
4. Glucose-based dialysis fluids for PD, low in glucose degradation products, have the following advantages:
   - **A.** They prevent peritoneal fibrosis and encapsulating peritoneal sclerosis.
   - **B.** They preserve residual renal function.
   - **C.** They prevent increases in small-solute transport over treatment time.
   - **D.** They produce higher concentrations of the dialysate effluent marker CA-125.
   - **E.** They increase peritoneal UF capacity.
5. Which of the following is true about icodextrin as a high molecular weight osmotic agent?
   - **A.** Icodextrin is monodispersed.
   - **B.** Icodextrin is polydispersed, but with 100% of the molecules being larger than 3 kDa.
   - **C.** Icodextrin is polydispersed, but with 80% of the molecules being larger than 3 kDa.
   - **D.** Icodextrin is polydispersed, but with 50% of the molecules being larger than 3 kDa.
   - **E.** Icodextrin is polydispersed, but with 30% of the molecules being larger than 3 kDa.
6. Net fluid reabsorption from the peritoneal cavity occurs via lymphatic reabsorption plus backfiltration through:
   - **A.** Small pores
   - **B.** Aquaporin-1
   - **C.** Large pores
   - **D.** Larges pores + aquaporin-1
   - **E.** Small pores + large pores

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Complications of Peritoneal Dialysis

Simon J. Davies, Martin E. Wilkie

CATHETER MALFUNCTION

Optimal Timing and Placement of the Peritoneal Dialysis Catheter

Catheter dysfunction adversely affects patient outcome by preventing commencement of the chosen dialysis modality, as well as by being disruptive to training schedules and increasing health care costs. Published literature does not give a strong indication that one insertion technique is better than another, although a recent meta-analysis suggested an advantage of the laparoscopic compared with the open surgical insertion technique.[1] It is clear that the enthusiasm and experience of the operator are key determinants of catheter outcome,[2] and international guidelines describe the optimal conditions for catheter insertion.[3] Timing is also important; patients randomized to the late start arm of the Initiating Dialysis Early and Late (IDEAL) study (estimated glomerular filtration rate [eGFR] 5 to 7 ml/min), were less likely to start on PD than those starting early (eGFR 10 to 14 ml/min), despite PD being their preferred treatment.[4] Early catheter problems are more difficult to manage in the absence of residual kidney function. For optimized catheter function it is necessary that each center audit its success with catheter placement against internationally agreed-on standards as part of local quality improvement.[2,3]

Catheter Function: Inflow

A 2-liter bag of dialysate should normally take 15 minutes or less to run into the peritoneal cavity. If inflow has stopped or significantly slowed, mechanical causes should be suspected. After checking to ensure that the tubing and catheter are not kinked, that all clamps or rollers are open to the inflow position, and that any frangible seal is fully broken, the catheter should be flushed vigorously with 20 ml of heparinized saline. If the catheter is cleared, heparin should be added (500 U/l) to the next few cycles because the cause of the blockage is often a fibrin plug. Should the catheter remain blocked, a plain abdominal radiograph is required. If this shows that the catheter is in a satisfactory position in the pelvis, an attempt to restore patency should be made with a thrombolytic agent (urokinase, 5000 U or tissue plasminogen activator [tPA], 2 mg in 40 ml of normal saline),[5] which can be instilled into the PD catheter for approximately 1 hour before being withdrawn. If inflow is restored, heparin should be added to the dialysate for the next few cycles. We no longer recommend the use of an endoscopic brush because of safety concerns.

If the radiograph shows the catheter to be malpositioned, an attempt should be made to reposition the catheter tip into the pelvis (Fig. 97.1). This can be done under radiologic guidance with a sterile guidewire inserted into the catheter, alternatively the catheter can be repositioned at laparotomy or with the laparoscope. Sometimes the catheter becomes wrapped in omentum, suggested usually by complete inflow and outflow failure. This requires a partial omentectomy or an omental hitch, a surgical procedure in which the omentum is temporarily held away from the catheter by a dissolvable suture (omentopexy). The value of laparoscopy in this context is that it can provide a diagnosis as to the cause of catheter flow failure and provide a solution—for example, by repositioning the catheter, removing an omental wrap, or performing a limited omentectomy.

Catheter Function: Outflow

The most common reason for outflow failure is constipation, although causes of inflow failure discussed previously also should be considered. Loading of the bowel with fecal material is often obvious on a plain radiograph, but treatment for constipation should be initiated without recourse to this investigation because it is so common. Constipation should be treated with oral laxatives or an enema. Subsequently, bowel action should be kept regular by increasing the fiber in the diet and, if necessary, adding a mild laxative. Slow outflow can be a problem in patients using automated peritoneal dialysis (APD), resulting in excessive machine alarms. This can be managed by switching to tidal APD and using a relatively large residual volume, for example, 25% to 50% of the fill volume. Recently concerns have been raised about the risk for excessive intraperitoneal dialysate volume that might occur during tidal PD, and, as a precaution, cycler algorithms have been altered to incorporate a complete drain into the treatment schedule.

Fibrin in the Dialysate

The mesothelial cells of the peritoneal membrane have a range of physiologic functions, including the production of fibrinolytic agents such as tPA. This process is disrupted during peritonitis when the appearance of fibrin in the dialysate is common. If fibrin causes restriction of dialysate flow, heparin (500 U/l) should be added to each bag. A small number of patients have fibrin formation in the absence of peritonitis. Immediately on drainage the bag may appear cloudy, but on standing the fibrin will aggregate and the fluid becomes clear. The first time this happens, a sample must be sent to the microbiology laboratory to exclude infection. If the results of this testing prove negative, the patient can be reassured.

FLUID LEAKS

Fluid leaks occur in which dialysate leaks out of the peritoneal cavity—which can be either visible externally or not. It is recommended that after PD catheter surgery, patients be allowed to heal sufficiently before use (2 weeks) to minimize this risk. If the catheter must be used early, low volumes should be used (start with 1 liter) in the supine position (e.g., APD with a dry day), with the patient instructed not to mobilize while dialysate is in the peritoneal cavity during the first 2 weeks after catheter insertion. Although PD catheters can be used successfully as the primary approach to manage late-presenting patients or for acute kidney injury, the incidence of leaks is higher under these conditions unless precautions are taken.[6,7]

External Leaks

On occasion, fluid may leak from the exit site or even the incision used to insert the catheter into the peritoneal cavity. A leak of dialysate, which is confirmed by measuring glucose concentration in the leaking fluid, is a risk factor for infection. It is important that PD catheters be adequately immobilized if used for early-start PD to reduce the risk for tugging and leak.

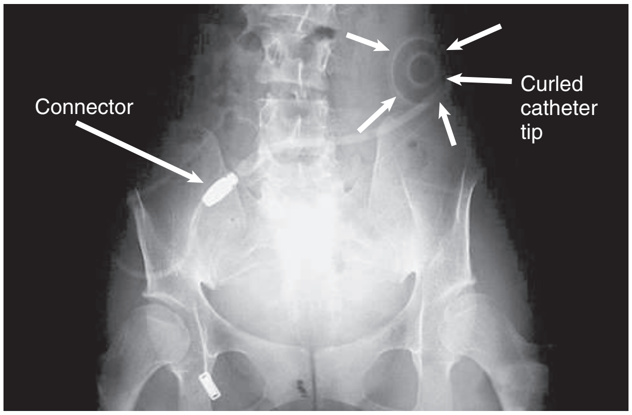

Fig. 97.1 Catheter malposition. Plain radiograph of the abdomen with curled catheter *(arrows)* misplaced in the upper left abdomen.

Internal Leaks

Isolated edema of the abdominal wall suggests an internal leak from the peritoneal cavity, either spontaneously or in association with a surgical hernia. In contrast, genital edema suggests an inguinal hernia or patent processus vaginalis. On occasion, both can be present. The site of the leak can be visualized on computed tomography (CT) scanning after intraperitoneal instillation of contrast material or on magnetic resonance imaging without the use of contrast. It may be necessary for the patient to stand or perform other maneuvers to increase intra-abdominal pressure before the leak is demonstrated (Fig. 97.2A). An alternative diagnostic test is to perform scintigraphy after injection of a compound such as technetium Tc-99m–labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA; see Fig. 97.2B). A surgical repair will be required if a major leak is visualized and should always be considered when there is a hernia. Most leaks, however, will heal after resting or with APD, using dry days, or temporary HD.

Hydrothorax

A pleural effusion can occur with generalized fluid overload or local lung disease, but it is occasionally caused by a leakage of dialysate through the diaphragm (Fig. 97.3A). This occurs more commonly on the right side. A leak is most simply indicated by aspirating a sample of the effusion and demonstrating that its glucose concentration is higher than the patient's blood glucose concentration, which can be confirmed by scintigraphy after intraperitoneal instillation of isotope, usually ^{99m}Tc-DTPA (see Fig. 97.3B). If one can be confident that the pleural effusion is not caused by the PD, then PD can be continued while the effusion is investigated and managed. Although there are

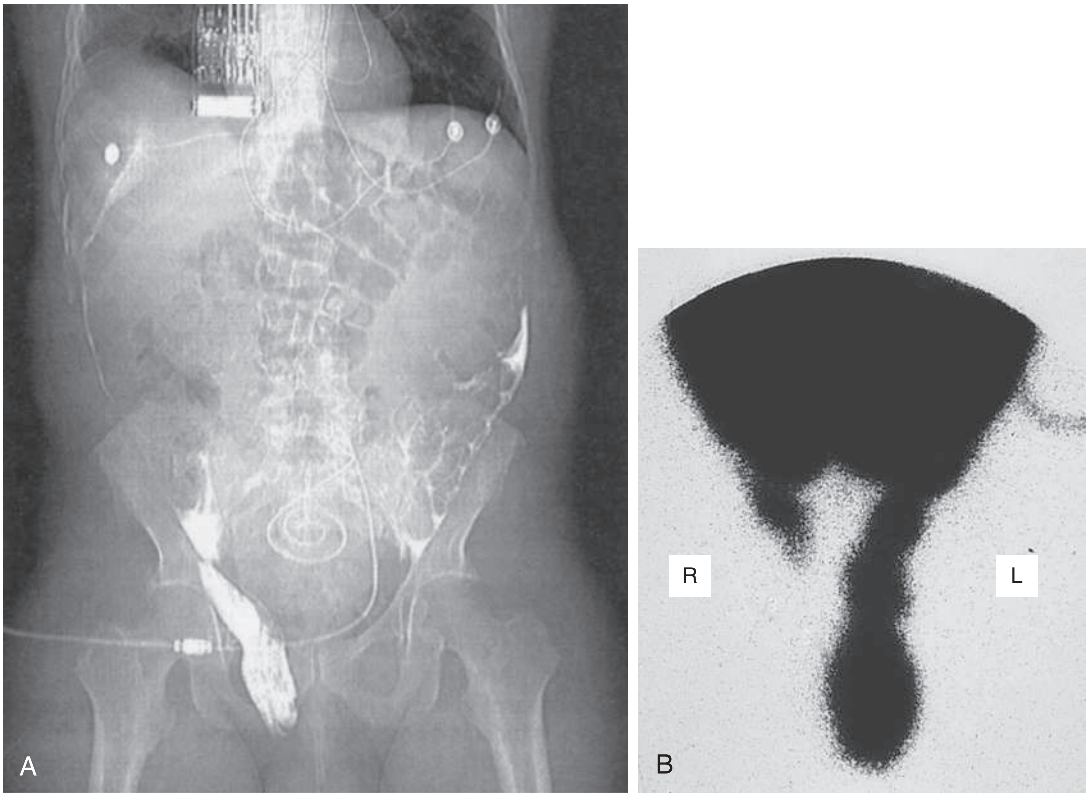

Fig. 97.2 Inguinal hernia during peritoneal dialysis. (A) CT scan after intraperitoneal injection of contrast material in a male patient showing dialysate flowing into a right inguinal hernia. (A from reference 43.) (B) Peritoneal scintigram of a male patient on peritoneal dialysis showing bilateral inguinal hernias. The left hernia extends into the scrotum; the right hernia is less extensive.

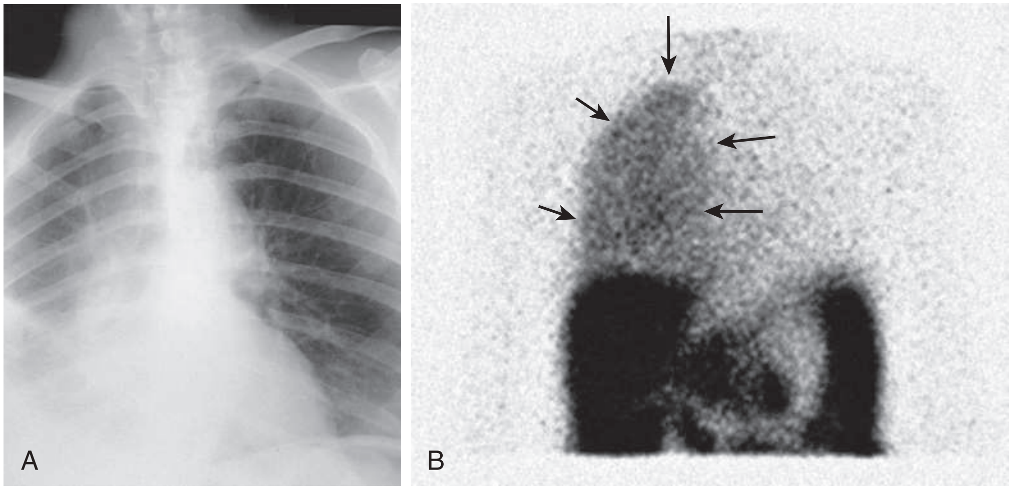

Fig. 97.3 **Hydrothorax in peritoneal dialysis.** (A) Chest radiograph showing a right-sided pleural effusion with partial collapse of the right lung caused by a diaphragmatic leak. (B) Scintigram in a peritoneal dialysis patient showing isotope in the right hemithorax *(arrows)* confirming a right pleural effusion.

reports that repairing pleural leaks allows subsequent PD, the best advice is to transfer the patient to HD unless there are very strong reasons not to do so.

PAIN RELATED TO PERITONEAL DIALYSIS

Inflow Pain

Soon after starting PD, patients may experience pain during fluid inflow, and occasionally pain affects the shoulders and is pleuritic, possibly because of diaphragmatic irritation, which usually resolves over the following days. Slowing the rate of fluid inflow will often reduce the symptoms, and peritonitis should be excluded and treated. A small number of individuals have persistent inflow pain, and the use of bicarbonate-lactate–buffered dialysate at physiologic pH improves symptoms in such patients.[8]

Outflow Pain

Some patients have discomfort or pain when the fluid is drained out, which can be experienced in the genital area or rectum and is commonly a result of pelvic irritation related to the catheter tip. This emptying sensation is abolished when the next cycle runs in and is best treated by leaving a small residual volume of fluid in the peritoneal cavity at the end of the drain, for example, by using tidal APD. Tidal APD is where a residual volume is left in the peritoneal cavity at the end of each dialysis cycle (e.g., 20% of the drain volume). To reduce the risk for intraperitoneal volume overload the treatment algorithm includes at least one complete drain during and at the end of treatment.

Blood-Stained Dialysate

Blood-stained dialysate is uncommon. It is rarely serious but causes considerable alarm to the patient. There is sometimes a clear history of trauma to the abdomen or of unexpected strain. A range of rare conditions are associated with this complication[9]; a few female patients relate the episode to their time of ovulation or menstruation. The treatment is to flush the abdomen with a few cycles of dialysate containing heparin (500 U/l) to minimize the chances of clotting in the catheter. The problem usually resolves spontaneously and often is visible only in one outflow. It is unusual for the blood-stained dialysate to be associated with infection, although it is wise to have the fluid cultured. Routine use of antibiotics is not necessary.

BOX 97.1 Relevant International Society for Peritoneal Dialysis Guidelines

Cardiovascular and Metabolic

- ISPD Cardiovascular and Metabolic Guidelines in Adult Peritoneal Dialysis Patients
    - Part I: Assessment and Management of Various Cardiovascular Risk Factors
    - Part II: Management of Various Cardiovascular Complications
- Encapsulating Peritoneal Sclerosis
    - Length of Time on Peritoneal Dialysis and Encapsulating Peritoneal Sclerosis: Position Paper For ISPD

Infections

- ISPD Catheter-Related Infections Recommendations: 2017 Update
- ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment 2016
- ISPD Position Statement on Reducing the Risks of Peritoneal Dialysis–Related Infections 2011
- Peritoneal Dialysis-Related Infections Recommendations: 2010 Update

ISPD, International Society for Peritoneal Dialysis.
All available at ISPD.org

INFECTIOUS COMPLICATIONS

Peritonitis

There are wide variations in peritonitis rates both between and within countries. Reducing peritonitis rates requires a multifaceted, multidisciplinary approach based on the use of preventive measures around the time of catheter insertion, the use of modern disconnect systems, exit site management, and education of patients and health care professionals.[10] This should be supported by regular local audit of peritonitis rates including causative organisms and local sensitivities, which is increasingly important because of the emergence of resistant organisms, and the requirement to use antibiotics effectively. Root cause analysis (e.g., inquiring about breaches in sterile technique) should be performed after each episode of PD peritonitis, with retraining as appropriate. Guidelines for the diagnosis and management of PD peritonitis are published by the International Society for Peritoneal Dialysis (ISPD; www.ispd.org) (Box 97.1).[10] The spectrum of peritonitis and its management in children have also recently been described in detail.[11] The reader is directed to a detailed review on reducing peritonitis risk.[12]

Diagnosis of Peritonitis

Peritonitis should be suspected in any patient who develops abdominal pain or a cloudy bag when PD fluid is drained; patients with these symptoms should be advised to contact their dialysis center immediately. Fever may be present but is not a universal feature. Samples of the dialysate should be taken for cell count and microbiologic examination. The diagnosis is confirmed by finding more than 100 white blood cells/mm^3 (1×10^7 cells/l). A Gram stain of the spun deposit should be performed to help identify the type of causative organism, although initial treatment will usually be empiric pending culture and sensitivity results. Various culture techniques have been proposed, but white cell lysis and inoculation into blood culture media is often helpful in increasing the yield of a positive growth.

The dialysate leukocyte count will be affected by dwell length, and this needs to be considered in APD patients. In short dwells, the count will be lower, and under these circumstances, if the proportion of cells that are neutrophils exceeds 50%, empiric treatment of peritonitis should be commenced. Conversely, if the patient has had a dry abdomen during the day, the initial drain on connection may be cloudy. This will clear within one or two cycles, and most of the cells found will be mononuclear leukocytes.

Treatment of Peritonitis

The empiric treatment of peritonitis will vary according to center and should be developed in close collaboration with the local microbiology service, taking into account sensitivity patterns and infection control policy. Initial regimens must cover both gram-positive and gram-negative organisms; the latest ISPD guidelines (www.ispd.org) give examples of appropriate antibiotics and their doses, including vancomycin, cephalosporins, and aminoglycosides. Antibiotic regimens are adjusted as soon as culture results are available, usually after about 48 hours.[10] The preferred route of administration is intraperitoneal (IP) unless the patient has features of systemic sepsis. IP gentamicin can be administered as daily intermittent dosing at a dose of 0.6 mg/kg/day (aiming to maintain the trough serum concentration of <2 mg/l); IP vancomycin also can be administered intermittently every 5 to 7 days, at a dose of 15 to 30 mg/kg, aiming to maintain the serum vancomycin level above 15 µg/ml. IP cephalosporin be administered either continuously (in each exchange) or on a daily intermittent basis.[10]

Dosage regimens will depend on whether the patient is on CAPD or APD. For CAPD, the antibiotic is administered as a loading dose in the first bag and then as a maintenance dose in subsequent bags. The intermittent IP dose can be given in the day dwell of APD patients; however, APD results in a higher peritoneal clearance of antibiotics than CAPD, and therefore extrapolation of data from CAPD to APD may result in underdosing.

Once the culture result is available, the regimen should be modified accordingly (Table 97.1). If the organism is methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin will be continued as part of the regimen. If the culture is negative, empiric therapy should be continued for 2 weeks, assuming there is a clinical response. If a gram-negative organism is identified, the subsequent management will depend on the sensitivity (Fig. 97.4). The isolation of multiple organisms with or without anaerobes strongly suggests perforation of the small or large intestine or biliary system. Metronidazole should be added to the regimen to cover anaerobic organisms, antibiotic therapy augmented to intravenous administration, and prompt surgical review obtained with necessary imaging (CT scan if appropriate).

TABLE 97.1 Antibiotic Regimens for Bacterial Peritoneal Dialysis Peritonitis

Culture	Antibiotic
Gram positive: Based on sensitivities	Vancomycin or other appropriate antibiotic
Coagulase-negative staphylococci	Treat for 14 days
_Staphylococcus aureus_*	Treat for 21 days: Screen for carriage
Enterococci	Treat for 21 days
Other streptococci	Treat for 14 days
Gram-negative bacilli or mixed bacterial growth	Continue gram-negative coverage based on sensitivities Consider switching to third- or fourth-generation cephalosporins
_Pseudomonas_* or _Stenotrophomonas_ spp.	Two antibiotics based on sensitivity, treat for 21-28 days
Other gram-negative bacilli	Treat for 21 days Mixed gram-negative or gram negative + gram-positive, consider metronidazole and ampicillin/vancomycin.

From reference 10.

*Examine for exit site or catheter tunnel infection.

Suggested antibiotic regimens when dialysate fluid culture is available. Except for culture-negative episodes, empiric treatment is stopped once the sensitivities are known. All antibiotic regimens should be adjusted for local microbiologic practices.

A wide variety of antibiotics other than those cited have been used with success, and these are documented in the ISPD 2016 guideline.[10] A commonly used strategy is to include an oral quinolone, such as ciprofloxacin. There is debate surrounding the role of aminoglycosides—advantages being simplicity of use and good coverage for gram-negative organisms; however, there are concerns regarding ototoxicity and nephrotoxicity, the former of which is irreversible. Reports regarding the impact of these agents on residual renal function are inconsistent, but serious episodes of peritonitis tend to adversely affect residual renal function. It is, however, advisable to avoid recurrent or protracted courses of aminoglycosides, with an early switch to alternative agents (e.g., third-generation cephalosporins) if they are used as empiric first-line treatment. There is evidence for the use of concomitant *N*-acetylcysteine, which should be considered to block the ototoxicity.[13] Current recommendations are that for gram-positive organisms, therapy should be for 14 days except in the case of *S. aureus,* for which 21 days is suggested. For culture-negative episodes, 14 days of therapy should suffice. The same is true in the case of single-organism gram-negative peritonitis.

Many patients can be treated successfully as outpatients. It is extremely important, however, that they be followed either in the clinic or by telephone. In most patients, clinical resolution (as judged by the clearing of the bags) starts within 48 hours. If there is no improvement within 96 hours despite use of the correct antibiotic, as judged by sensitivity tests, the fluid must be retested by cell count, Gram stain, and culture. The ISPD recommends that the catheter be removed if there is no improvement in 5 days; however, in a severe infection this should be done earlier, and in a more indolent case the period of observation can be longer. A specific recommendation is that the catheter should be

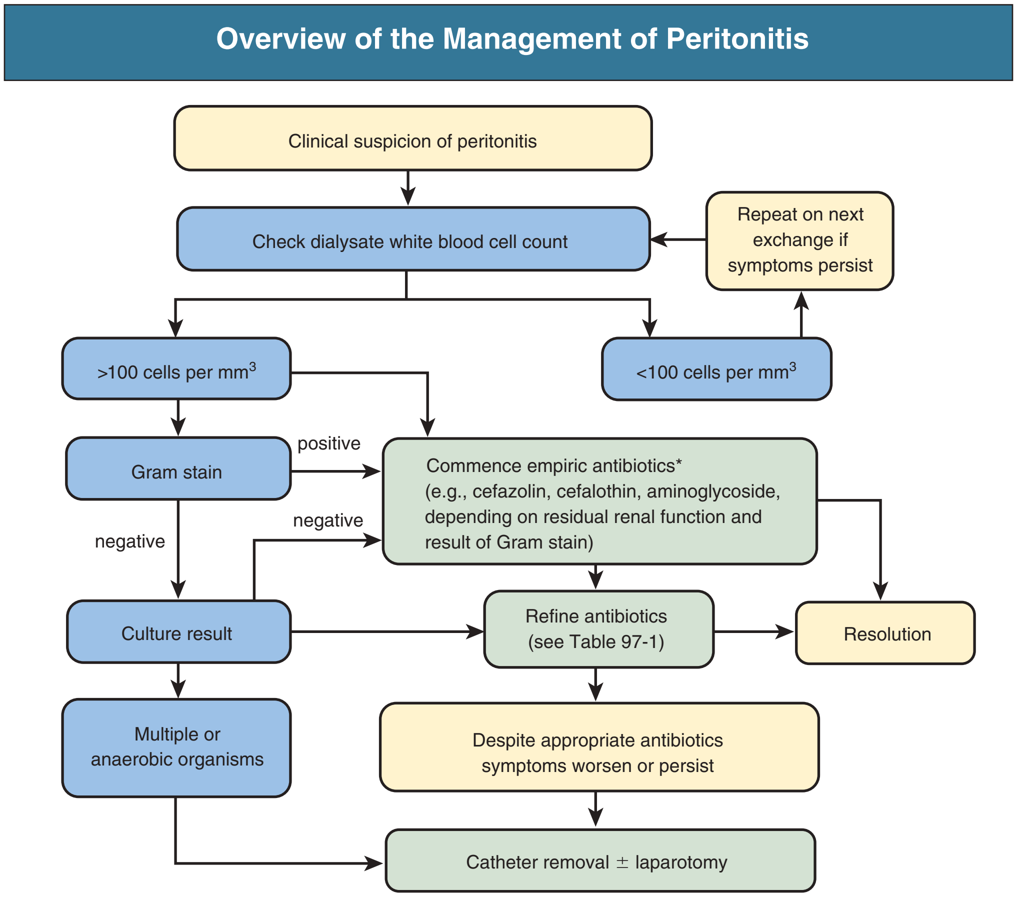
Overview of the Management of Peritonitis
Clinical suspicion of peritonitis
Check dialysate white blood cell count
Repeat on next exchange if symptoms persist
>100 cells per mm3
<100 cells per mm3
Gram stain
positive
negative
negative
Commence empiric antibiotics* (e.g., cefazolin, cefalothin, aminoglycoside, depending on residual renal function and result of Gram stain)
Culture result
Refine antibiotics (see Table 97-1)
Resolution
Multiple or anaerobic organisms
Despite appropriate antibiotics symptoms worsen or persist
Catheter removal ± laparotomy

Fig. 97.4 Overview of the management of peritonitis.

removed where a *Pseudomonas* or *S. aureus* peritonitis occurs in conjunction with an exit site or tunnel infection.[10] In addition, the possibility of intraabdominal or gynecologic disease or the presence of unusual organisms such as mycobacteria should be considered. Under these circumstances, a mini-laparotomy should be performed to exclude intraabdominal disease, and if mycobacterial infection is suspected, a peritoneal biopsy specimen should be obtained for culture.

Fungal Peritonitis

If peritonitis is caused by yeasts or fungi, the peritoneal catheter should be removed promptly. This should be combined with treatment with an appropriate antifungal for at least 2 weeks after catheter removal. Fungal peritonitis is a serious complication of PD, commonly requiring hospitalization and transfer to hemodialysis (HD), with a high associated mortality. It is essential to review the appropriate antifungal agent with the local microbiologic team; options are described in some detail in the 2016 peritonitis update from the ISPD.[10] Amphotericin B should not be given intraperitoneally because it causes chemical peritonitis and pain. Appropriate antifungal therapy should be continued for at least 2 weeks after catheter removal.

Relapsing Peritonitis

Relapsing peritonitis is defined as infection caused by the same organism as the original infection occurring within 4 weeks, whereas *recurrent peritonitis* is defined as a different organism within 4 weeks of completion of an appropriate course of antibiotics. In general, the advice is to treat as for a primary infection but to try to establish an underlying cause. For example, recurrence of *S. aureus* infection should trigger a search for pericatheter infection. If enterococci or gram-negative organisms are the cause of a relapse, the possibility of intraabdominal disease or an abscess should be considered (although these organisms are frequently water-borne). If a patient has other gastrointestinal symptoms, such as change in bowel habit, appropriate investigation should be conducted. Some organisms (including coagulase-negative staphylococci) produce biofilm that can lead to a relapse of the infection. Consideration should be given to changing the PD catheter once the infection has been treated; of course, the catheter will need to be removed if the infection does not respond to treatment. Current practice in most units is to allow up to 3 weeks of treatment before a new catheter is inserted.

Culture-Negative Peritonitis

Culture-negative peritonitis is associated with increased risk for treatment failure. Commonly the cause relates to the sampling technique or the microbiologic approach; alternatively, concurrent antibiotic use may be responsible. It is important to be aware of the possibility of fastidious organisms (e.g., atypical mycobacteria, suspicious of contaminated water sources, or yeasts). In addition, other causes of peritoneal inflammation may responsible; these include the presence of an intraabdominal malignancy or surgical pathology or eosinophilic reactions—for example, in the case of vancomycin allergy or some fungal infections. Chylous effluent is a rare finding in PD; the cause is often unclear, but if recurrent, conditions affecting lymphatic drainage should be considered.

Exit Site Infection

Exit site infection (ESI) is an important complication of long-term PD. The diagnosis is suspected on clinical grounds, usually by the presence

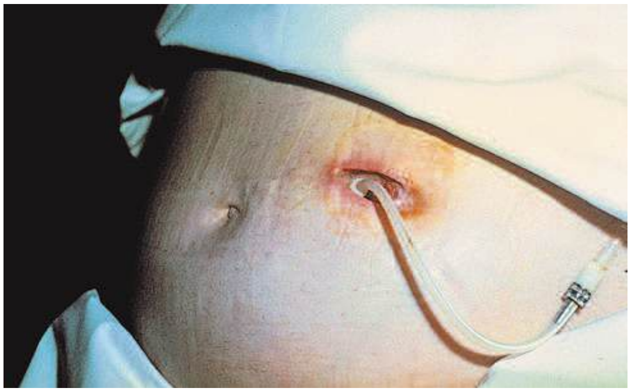

Fig. 97.5 Exit site infection. A severe exit site infection that has exposed the outer cuff of the catheter.

of marked erythema or discharge from the exit site (Fig. 97.5). A scoring system for exit sites has been developed to determine the likelihood of infection and grade its severity, with points assigned for crusting, swelling, pain, and discharge according to severity; if the discharge is purulent, this mandates treatment.[14] Extension of the infection into the tunnel may be assessed either clinically or by ultrasound. The most common infecting organism is *S. aureus.* There is evidence for the use of prophylactic topical antibiotics at the exit site, the strongest being for mupirocin for the prevention of ESI caused by *S. aureus.*[14] There is also evidence for the use of topical gentamicin, although there were some reports of an increase in ESI caused by Enterobacteriaceae*, Pseudomonas* spp., and probably nontuberculous mycobacteria after a change of prophylactic protocol from topical mupirocin to gentamicin.[10]

All suspected infected exit sites should be swabbed; routine swabbing of healthy exit sites should be avoided, and incidental bacterial growth does not require treatment. Unless there is prior evidence that the patient carries MRSA or *Pseudomonas,* initial treatment should be with an antibiotic effective against *S. aureus*—such as a penicillinase resistant penicillin (e.g., dicloxacillin or flucloxacillin—it is important to be aware of the risk for associated hepatotoxicity with the latter) or a first-generation cephalosporin if the patient is allergic to penicillin. In most patients, the drug can be given orally; but if the individual is systemically ill, the antibiotics should be administered intravenously until clinical improvement occurs. Hospitalization, parenteral antibiotics, and often urgent catheter removal are required if there is evidence of spread into the tunnel. If the infection is with MRSA, eradication therapy should be attempted with systemic vancomycin, as for peritonitis. Should the culture grow a gram-negative organism, ciprofloxacin (500 mg twice daily orally) will be effective empiric treatment in most patients. ESIs caused by *Pseudomonas* spp. are particularly difficult to treat and often require prolonged therapy with two antibiotics.

Treatment is recommended for a minimum of 2 weeks, extended to 3 weeks in *Pseudomonas* infections. In gram-positive infections, if there is no improvement within 7 days, ultrasound of the catheter tunnel should be performed because a collection of fluid around the catheter signifies a tunnel infection. If complete healing does not take place after 4 weeks of therapy, further measures should be considered, such as exteriorizing and shaving the outer cuff because it may be involved in the infection. If the infection persists or relapses, catheter removal must be considered because there is a high risk that the ESI will lead to peritonitis. It is important that the new exit site be formed in a different part of the anterior abdominal wall.

REDUCED ULTRAFILTRATION AND ULTRAFILTRATION FAILURE

Definition and Significance of Ultrafiltration Failure

There are two complementary approaches to defining ultrafiltration (UF) failure. The first is based solely on the net fluid removal (termed *ultrafiltration capacity*) from a standard 4-hour peritoneal equilibration test (PET). The conduct and interpretation of the PET are further discussed in Chapter 97. Account should be taken of the overfill of dialysis bags by the manufacturers, which can be as much as 200 ml. A net UF capacity below 400 ml with a hypertonic glucose exchange (3.86%) is indicative of an inadequate membrane,[15] bearing in mind that this may not be clinically relevant in a patient with well-preserved residual renal function. If a middle-strength glucose solution is used (2.27%), the equivalent value is 0 ml (again excluding overfill). Although this definition is clear enough, the main limitation is that it relies on a single measurement of UF capacity, which is subject to significant error (coefficient of variation is up to 25%). The second approach to defining UF failure is more holistic in that it considers patient factors that affect fluid status (e.g., comorbid conditions) and an acceptable glucose exposure required to maintain adequate hydration. Many clinicians now take the view that regular use of hypertonic solutions is not acceptable unless the life expectancy is shorter than the likely time to development of severe membrane failure and its complications, unusual before 5 years.

UF failure is a significant cause of technique failure[16]; it results in low UF, which in turn increases the risk for mortality in anuric patients[17,18] and is also a risk factor for encapsulating peritoneal sclerosis (EPS).[19] Although it is impossible to set a fluid removal goal that applies to all patients, the European Automated Peritoneal Dialysis Outcomes Study (EAPOS) found that anuric patients who failed to reach an UF target of more than 750 ml/day had less efficient membranes (specifically lower osmotic conductance, see later) and higher mortality.[18] Patients whose total fluid removal is less than 1 l/day because of poor UF should have their membrane function assessed.

Establishing the Causes of Ultrafiltration Failure

Failure of the membrane to ultrafiltrate needs to be distinguished from other causes of inadequate peritoneal fluid removal such as catheter dysfunction, leak, or excessive fluid reabsorption.[20] The latter can occur if the intraperitoneal cavity pressure is too high, suspected if the UF falls after an increase in dialysate volume. If there is doubt, a dialysate sodium concentration below 125 mmol/l 1 hour into a PET using 3.86% glucose, an indicator of preserved sodium sieving (see later) suggests that UF is preserved.

There are two main causes of UF failure: a *fast peritoneal solute transport rate* (fPSTR) or low membrane UF efficiency despite a preserved osmotic gradient, termed *reduced osmotic conductance.* Both can exist at the start of PD or can be acquired with time on therapy, although it is rare for a patient to develop reduced osmotic conductance without also having rapid transport.

Fast Peritoneal Solute Transport Rate–Related Ultrafiltration Failure: Diagnosis and Management

With the 4-hour PET, a dialysate–plasma creatinine ratio greater than average (0.64) could contribute to poor UF. This is because more rapid diffusion of small solute across the membrane leads to earlier dissipation of the osmotic gradient driving UF. Furthermore, once the gradient is lost, membranes with a larger diffusive area will reabsorb fluid more rapidly. In continuous ambulatory PD patients, fPSTR is associated with increased mortality, technique failure, and hospitalization,[21] whereas this association is attenuated or possibly reversed when APD is used.[22,23]

Thus both theoretically and empirically the short exchanges used in APD prescription are associated with better outcomes in fPSTR-associated poor UF. Prevention of fluid reabsorption during the long day or night exchange is also required in these patients, and this can be achieved by use of icodextrin (polyglucose solution), which also improves the fluid status[24] and reduces episodes of fluid overload.[25] The main determinant of fPSTR is increased intraperitoneal inflammation, which is independent of systemic inflammation.[26] Only the latter is an independent predictor of mortality.

Low Osmotic Conductance–Related Ultrafiltration Failure: Diagnosis and Management

This problem should be suspected if UF failure persists despite adjustment of the prescription to accommodate the peritoneal solute transport rate (PSTR). Osmotic conductance is a measure of the efficiency of the peritoneal membrane to ultrafiltrate for a given osmotic agent, typically glucose. Reduced osmotic conductance can be demonstrated quite easily in the clinic. Sodium sieving is the consequence of free water entering the peritoneal cavity via the transcellular endothelial aquaporin pathway, resulting in a drop resulting from dilution in the dialysate sodium concentration; it is independent of the sodium-coupled UF that occurs across endothelial tight junctions. Thus the absence of a fall in the dialysate sodium concentration 1 hour after using a high glucose exchange indicates the lack of sodium sieving, which implies reduced free water UF. This can be combined with the double–mini-PET,[20] which requires back-to-back 1-hour exchanges using low (1.36%) and high (3.86%) glucose concentrations; a difference of less than 400 ml net UF between the two exchanges indicates poor osmotic conductance. The two causes so far identified are reduced aquaporin function, possibly constitutive and thus present at the start of treatment, and progressive fibrosis of the membrane as a result of acquired membrane injury. There is no specific treatment, so clinical effort should focus on prevention (see next section) and timely switch to HD or transplantation.

CHANGES IN PERITONEAL STRUCTURE AND FUNCTION

It is widely assumed that alterations in peritoneal function, a combination of an increased PSTR and loss of osmotic conductance, are related to structural changes in the peritoneal membrane.[27] There is accumulating evidence that continuous exposure to dialysis solution components and repeated episodes of bacterial peritonitis are the main drivers of this process (Fig. 97.6). The relationship between structure and function is becoming clearer: increased PSTR is likely to reflect a greater vascular surface area, whereas loss of osmotic conductance requires an additional mechanism that is associated with progressive membrane fibrosis and an increased risk for EPS. The submesothelial collagenous zone shows progressive increase in thickness with time on PD (Figs. 97.7 and 97.8), and this is associated with progressive changes to the structure of small venules ranging from subtle thickening of the subendothelial matrix to complete obliteration of vessels (Fig. 97.9).[28,29] This process is accompanied by a reduction in sodium sieving, implying reduced free water transport, but no change in aquaporin expression, suggesting that the fibrosis is the main cause of UF failure.[30]

Preventing Membrane Injury

The main clinical factors associated with more rapid and severe membrane injury are early loss of residual renal function, recurrent or severe peritonitis, and the earlier use of higher glucose–containing solutions (often associated with loss of diuresis but an independent risk factor).[31] Hypertonic solutions may induce injury because of direct glucose toxicity; glucose degradation products (GDPs) manifest as a result of the sterilization process, or both. The prevention of membrane injury should focus on all of these drivers and include (1) preservation of residual renal function by avoiding both volume depletion and the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs); (2) use of loop diuretics to maintain urine volume and delay use of hypertonic exchanges; (3) use of icodextrin in the long exchange; (4) avoidance of peritonitis; and (5) use of low-GDP neutral pH solutions.[32] The balANZ study shows that the increase in PSTR over the first 2 years of PD is prevented by use of ultralow-GDP dialysis fluid. More importantly, this study showed that achievement of less UF, lower use of hypertonic glucose, and in particular low-GDP solutions early in the course of PD, now confirmed in meta-analyses of several trials is associated with preservation of residual kidney function.[25,33] This, combined with trial evidence that fluid status is stable in patients with residual kidney function,[34] supports the main strategy clinicians should adopt in preserving the membrane—prescribing to maintain adequate but not excessive UF, which will only drive thirst and increase the risk for volume depletion.

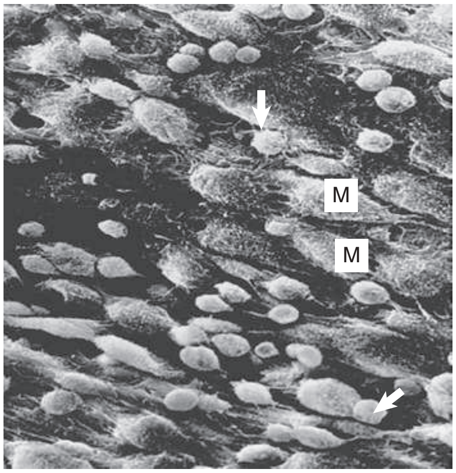

Fig. 97.6 **Peritonitis.** Scanning electron micrograph of the peritoneum from a patient receiving peritoneal dialysis who has peritonitis. The small round cells *(arrows)* are phagocytes, which are widely distributed among the mesothelial cells *(M)*. (Magnification, ×1800.)

Encapsulating Peritoneal Sclerosis

A minority of patients on PD develop EPS, in which the bowel is enveloped in a thick cocoon of fibrous tissue, causing intestinal obstruction (Fig. 97.10).[19] It is variable in severity but may be life-threatening, causing death from malnutrition or intraabdominal catastrophe; but with experienced management by a multidisciplinary team, overall survival compares well with that of matched controls. Diagnosis of this syndrome requires both clinical signs and symptoms of bowel obstruction leading to weight loss and malnutrition (with or without features of systemic inflammation) combined with either typical features on imaging (CT scanning) or confirmation of fibrous cocooning at laparotomy. Although UF failure is a risk factor for EPS (especially when there is also loss of osmotic conductance), EPS appears to be a different pathologic process that predominantly affects the visceral membrane, is usually associated with another trigger (such as severe peritonitis or interruption of PD), and frequently has a systemic inflammatory phase (biopsy material more often shows inflammation and fibrinous exudates).

The single most important risk factor for EPS is time on PD; at 5 years the incidence is 2% to 3%, whereas by 10 years, this rises to 6% to 20%.[19] Recent reports from Japan[35] and the Netherlands suggest that the incidence of EPS is decreasing, possibly because of a better

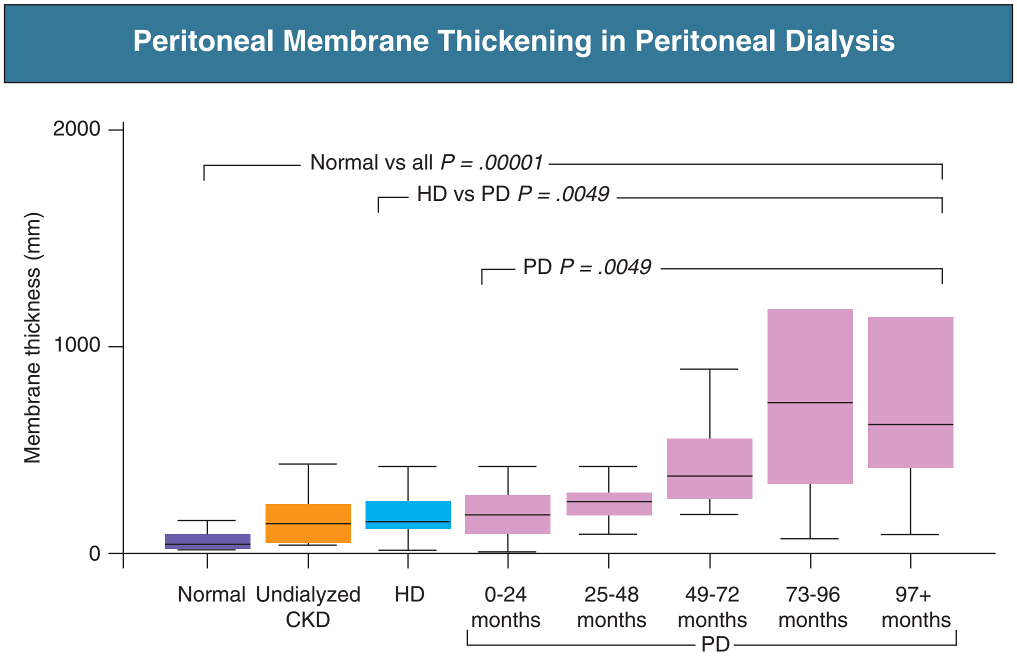

Fig. 97.7 Peritoneal membrane thickening in peritoneal dialysis *(PD).* The thickness of the submesothelial collagenous zone of the peritoneal membrane in normal individuals, in undialyzed patients with advanced chronic kidney disease *(CKD),* patients with uremia, in patients receiving hemodialysis *(HD),* and in those who have received PD for different periods. Membrane thickness is significantly increased in all uremic and dialysis patients compared with normal individuals. Membrane thickness increases significantly with duration of PD and is increased in PD patients as a group compared with HD patients.

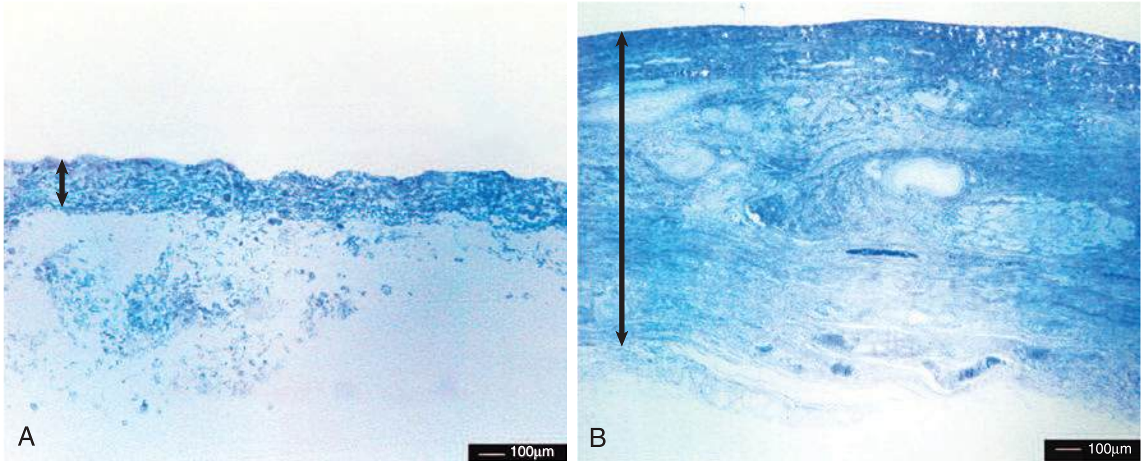

Fig. 97.8 Morphologic changes in the parietal peritoneal membrane. (A) Normal. (B) A patient who has been on peritoneal dialysis (PD) for 10 years. Note the marked thickening of the submesothelial compact zone *(arrows).* (Toluidine blue stain.)

understanding of the management of risk factors. There is increasing evidence that surgical treatment (extensive adhesion lysis and excision of the peritoneum while avoiding enterotomy) is most effective, especially when there are obstructive symptoms. This should be undertaken by an experienced surgical team, which can achieve cure rates of 70% to 80%. Parenteral nutrition can be used as a preparation for surgery and occasionally as a long-term solution. In about 50% of patients, symptoms are less severe and gradually resolve. There is no role for preemptive screening by CT scanning, but this is helpful in diagnosis. Most commonly, EPS develops after transfer from PD to either HD or transplantation; but if it develops in a patient on PD, the consensus is that PD should be stopped to avoid continued exposure to nonphysiologic dialysis solutions. Other strategies, such as continued irrigation, dual-modality treatment with PD and HD, and use of antifibrotic drugs such as tamoxifen, are practiced, but an evidence base for such management is lacking.

NUTRITIONAL AND METABOLIC COMPLICATIONS

Undernutrition

Cross-sectional surveys of patients receiving PD show that about 40% have evidence of mild and 8% severe protein-calorie depletion as judged

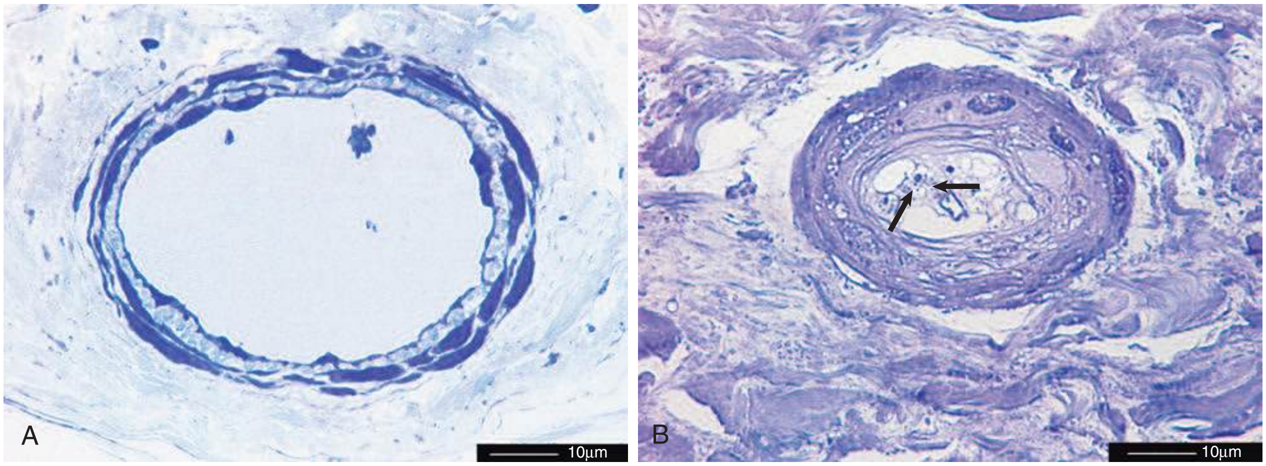

Fig. 97.9 **Blood vessels in the parietal peritoneum: transverse sections of peritoneal arterioles.** (A) Normal. (B) Vasculopathy in a patient on peritoneal dialysis; the vascular lumen *(arrows)* is occluded by connective tissue containing fine calcific stippling.

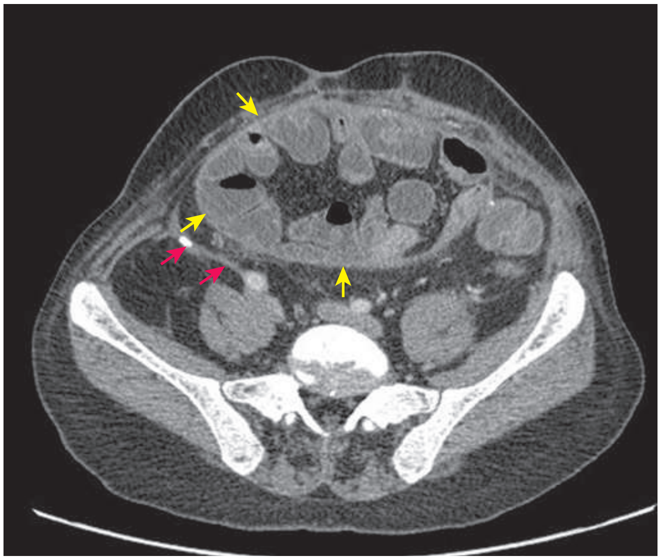

Fig. 97.10 **Encapsulating peritoneal sclerosis.** Abdominal CT scan from a patient with encapsulating peritoneal sclerosis. *Red arrows* indicate thickened parietal peritoneum with calcification; *green arrows* indicate thickened visceral peritoneum forming a cocoon containing loops of bowel.

by the subjective global assessment of nutritional state. Malnutrition is a risk factor for morbidity and mortality of patients on PD and often associated with systemic inflammation. The assessment and management of malnutrition are discussed further in Chapter 86. One obvious contributing factor is protein loss through the peritoneum, which averages 8 g/day. Protein loss is proportional to effective membrane area and so is most marked during peritonitis and in patients with fast peritoneal transport. The ensuing hypoalbuminemia exacerbates the extravascular extracellular fluid expansion in these patients.[36] Therefore it has been recommended that PD patients should consume daily at least 1.2 to 1.3 g of protein per kilogram of body weight. In practice, many patients take only about 0.8 g/kg/day, and nitrogen balance is maintained partly as a result of calories from dialysate. However, especially once patients are anuric, there is a progressive loss in lean body mass.[34] Despite concerns over hypoalbuminemia in peritoneal dialysis patients, the association with mortality is not worse than for HD patients.[37]

PD patients have abnormal eating behavior with smaller meals, slow eating, and impaired gastric emptying, which causes nausea, especially in patients with diabetes. This is worst when using more hypertonic glucose and least severe with icodextrin. Amino acid–based dialysate improves nitrogen balance in malnourished patients, but the long-term nutritional benefit is marginal.[38]

Acid-Base Status

Correction of acidosis is best achieved by use of dialysate with higher levels of potential buffer,[39] but if necessary, oral bicarbonate may be added. There is evidence that correction of acidosis, by whatever means, to within the upper half of the normal range for serum bicarbonate reduces protein catabolism, resulting in weight gain and increased midarm muscle circumference.[38] The use of amino acid–containing dialysate fluid can worsen acid-base status, requiring close monitoring.

Lipids and Obesity

PD results in significant daily glucose absorption, which may range from 80 to 200 g/day (300 to 800 kcal). Therefore PD patients tend to develop features of metabolic syndrome: central obesity, hyperglycemia, dyslipidemia, and hyperinsulinemia; they may even develop frank diabetes, although there is no evidence that this or worsening obesity is more common than in HD patients.[40] These problems can be reduced by use of icodextrin and amino acid solutions in place of glucose with better glycemic control in diabetics.[41] Blood glucose monitoring in diabetic patients using icodextrin must not use glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) test strips because this will lead to falsely high estimates and risk for severe hypoglycemia.

Despite these concerns, there is no evidence to suggest that PD should be avoided in obese patients even though the survival advantage seen in HD associated with a higher body mass index is not seen with PD.[42]

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SELF-ASSESSMENT QUESTIONS

1. Regarding catheter function, which of the following statements is/are false?
   - **A.** Introducing the routine use of laparoscopic technique for catheter insertion will improve early catheter survival more than carefully audited standard methods used by an experienced surgeon.
   - **B.** Slow catheter drainage is most commonly a result of constipation.
   - **C.** Pain on draining in (“inflow pain”) is best solved by use of tidal peritoneal dialysis (PD).
   - **D.** Pain on draining out is best solved in automated PD (APD) patients by use of tidal PD.
   - **E.** Poor drainage associated with edema in the genital area indicates an inguinal hernia or patent processus vaginalis.
2. Regarding peritonitis and infection, which of the following statements is/are *false*?
   - **A.** Treatment of suspected peritonitis should always commence with antibiotics covering both gram-positive and gram-negative organisms.
   - **B.** Fungal peritonitis usually can be successfully treated with intraperitoneal agents without requiring catheter removal.
   - **C.** Redness and pain at the exit site always should be treated immediately with oral antibiotics.
   - **D.** Prophylactic use of mupirocin or gentamicin at the exit site has been shown to reduce the chances of peritonitis.
   - **E.** Culture of more than one organism in a patient with peritonitis should raise serious concerns of a perforated viscus and lead to mini-laparotomy as well as catheter removal.
3. Regarding membrane function, which of the following statements is/are *false*?
   - **A.** Regular use of hypertonic glucose exchanges is associated with an increased risk for acquired membrane injury.
   - **B.** There should be a minimum target of 1 liter of ultrafiltration (UF) per day.
   - **C.** Rapid solute transport contributes to poor UF but can be addressed by use of APD and icodextrin such that it no longer is associated with increased mortality.
   - **D.** Routine computed tomography (CT) scanning to look for progressive membrane thickening and calcification is the best way to screen for encapsulating peritoneal sclerosis (EPS).
   - **E.** Progressive loss of osmotic conductance is thought to represent increasing fibrotic damage, may predispose to EPS, and is a reason for switching to hemodialysis.

98

Extracorporeal Therapies for Drug Overdose and Poisoning

Nigel Suren Kanagasundaram, Andrew Lewington

Poisoning and drug overdose, whether intentional or accidental, is a common medical emergency, accounting for around 170,000 hospital admissions per year in the United Kingdom—as many as for myocardial infarction.[1] Most exposures do not require hospitalization, with nearly 70% of U.S. cases in 2014 being managed in a non–health care facility, usually at the site of the incident.[2] Overall exposure-related mortality remains relatively low, with approximately 1400 fatalities recorded in nearly 2.2 million exposures in this same U.S. report.[2] Poisoning, however, remains a significant cause of death in young people.[3]

The spectrum of agents ingested is wide, ranging from overdose of prescribed and nonprescribed medicinal drugs to poisoning with nonpharmacologic substances and recreational drugs. The pattern of toxin ingestion has changed over the years and varies according to geographical location. Frequently implicated agents in industrialized societies include analgesics (acetaminophen, opioids, and salicylates), antidepressants, sedatives, and antipsychotics. Pesticides remain a frequent cause of poisoning in areas of the developing world.[3] Legislation has been used to reduce the availability of potential toxins; in the United Kingdom, for instance, paraquat was withdrawn from sale in July 2008, although occasional exposures continue as a result of residual stored product.[1] Similarly, U.K. legislation limiting pack size of paracetamol (acetaminophen) in 1998 was followed by a significant reduction in the number of deaths from paracetamol overdose.[4]

The mainstays of management of poisoning include hemodynamic, respiratory, and other supportive care, prevention of further poison absorption (through oral activated charcoal in specific patients), neutralization of toxicity (e.g., with intravenous *N*-acetylcysteine after significant acetaminophen overdose or digoxin immune Fab [Digibind]), and enhancement of endogenous toxin elimination (e.g., through urinary alkalinization). These aspects of management are well described by resources such as Toxbase in the United Kingdom (www.toxbase.org) and via the American Association of Poison Control Centers website (www.aapcc.org). Other local and regional poison information services are linked through the website of the European Association of Poisons Centers and Clinical Toxicologists (www.eapcct.org).

Extracorporeal techniques for poison elimination include renal replacement therapies (RRTs) and other modalities such as hemoperfusion or therapeutic plasma exchange. However, they are only occasionally needed; in the United States in 2014, for instance, only around 2500 patients were treated, mostly through hemodialysis (HD).[2] Only 43 patients were recorded as receiving hemoperfusion, reflecting a long-term decline explained partly by the increasing rarity of theophylline and barbiturate overdose (historically, the main indications for this technique) but also by the increased use of high-efficiency, high-flux HD, allowing removal of toxins previously regarded as being nondialyzable.[5,6]

Extracorporeal treatment has long been used to manage poisoning,[5] but common practices are often not supported by high-quality evidence, at least partly because of the practical and ethical barriers to randomized controlled trials.[5] Despite these barriers the EXTRIP (EXtracorporeal TReatments in Poisoning) consensus group (www.extrip-workgroup.org)[6] has created several useful resources for clinicians, endorsed by various national and international stakeholder societies.

WHEN SHOULD EXTRACORPOREAL REMOVAL BE CONSIDERED?

Extracorporeal treatment is most commonly used for lithium, toxic alcohol, and salicylate ingestions[7]; other potential indications are shown in Table 98.1. Extracorporeal elimination should be considered when it is evident that other treatments (e.g., activated charcoal; specific antidotes) will not reduce poison levels below toxic thresholds. It is important, therefore, to understand the general principles underpinning the use of extracorporeal treatment to make decisions about management of poisonings, particularly for those for which no consensus or evidence base exists.

Extracorporeal removal is appropriate for only a small proportion of poisonings. Against the potential advantages of therapy must be balanced with the risks that are generic to all extracorporeal techniques (e.g., acute transfer to a specialist center, vascular access, anticoagulation[8,9]) and those specific to its use in poisoning (as discussed later under individual modalities). Factors that help determine whether extracorporeal therapy might be helpful are summarized in Box 98.1. It should be noted that effective clearance does not necessarily prevent ongoing end-organ toxicity[5] and a fatal outcome, as may occur in cases of paraquat poisoning.[10]

Molecular Weight

Most ingested poisons have a molecular weight (MW) in the 100 to 1000 Da range and would therefore be amenable to removal by HD,[11] which is the modality of choice for clearance of small solutes. Higher flux membranes extend the range of dialyzable solutes up to approximately 10,000 Da, particularly if performed for long hours, and allow removal of toxins such as theophylline and carbamazepine, for which hemoperfusion might historically have been indicated.[11] Molecules toward the upper end of this range and up to about 40 kDa are more effectively removed using modalities with a significant convective component such as hemofiltration (HF) or hemodiafiltration (HDF). Even larger solutes may be removed by non–RRTs such as plasma exchange or one of the albumin-dialysis techniques used for liver support.

Protein Binding

Diffusive and convective modalities (HD, HF, HDF; either intermittent or continuous) are generally unsuitable for removing poisons with protein binding greater than 80%.[11] However, certain toxins (e.g., salicylate, valproate) are highly protein-bound under normal circumstances, but saturate protein-binding sites during poisoning, leading to high (and therefore dialyzable) serum concentrations of free agent.[5] In addition, easy dissociation of protein-toxin complexes may allow significant diffusive removal, as with phenytoin.[5] Agents with very high (>90%) protein binding and that are not amenable to diffusive or convective elimination may be removed by plasma exchange (e.g., L-thyroxine and cisplatin).[11]

The interplay between MW and protein binding and their impact on modality choice are graphically illustrated in Fig. 98.1.

TABLE 98.1 Some Poisonings for Which Extracorporeal Removal May Be Indicated*

Agent	Preferred Modality	Other, Acceptable Modalities
Acetaminophen	IHD	IHP, CRRT, Ex
Long-acting barbiturates	IHD	HP, CRRT
Carbamazepine	IHD	IHP, CRRT
Ethylene glycol	IHD	CRRT
Lithium	IHD	CRRT*
Metformin	IHD	CRRT*
Methanol	IHD	CRRT
Phenytoin	IHD	IHP
Salicylates	IHD	IHP, CRRT, Ex
Thallium	IHD	IHP, CRRT
Theophylline	IHD	HP, CRRT, Ex
Valproate	IHD	IHP, CRRT

See reference 6.

*After initial treatment, both IHD and CRRT are equally acceptable. Other agents that may be amenable to removal by extracorporeal techniques include β-blockers, meprobamate, deferoxamine, aminoglycosides (with high flux membranes), pentoxyfilline, sodium edetate, *Amanita phalloides* toxin and paraquat.

CRRT, Continuous renal replacement therapy; *Ex,* exchange transfusion in neonates; *IHD,* intermittent hemodialysis; *IHP,* intermittent hemoperfusion.

Volume of Distribution

The efficacy of toxin removal is also influenced by the theoretical volume of distribution (V_D). Substances confined to the bloodstream will have a low V_D (~0.07 l/kg body weight), those distributed in the extracellular space, a V_D of approximately 0.2 l/kg, and those confined to total body water, approximately 0.6 l/kg. Higher distribution volumes are often found in those substances with avid tissue binding, lipophilicity, or sequestration. As V_D increases, more solute must be removed for achievement of a particular blood level. The ideal solute would therefore have a low distribution volume and would be located within a single, well-mixed compartment that is directly accessible by extracorporeal treatment. There are exceptions; carbamazepine, metformin, and thallium all have high distribution volumes but are amenable to extracorporeal removal.[11]

Solute Compartmentalization

Solutes are often distributed across one or more body compartments that may not be directly accessible by extracorporeal therapy (Fig. 98.2). If there is any resistance to solute movement between the accessible

BOX 98.1 Factors Affecting Toxin Removal by Extracorporeal Therapy*

- Molecular weight
- Protein binding
- Volume of distribution
- Solute compartmentalization
- Contribution of extracorporeal toxin removal relative to endogenous clearance

*See text for explanation.

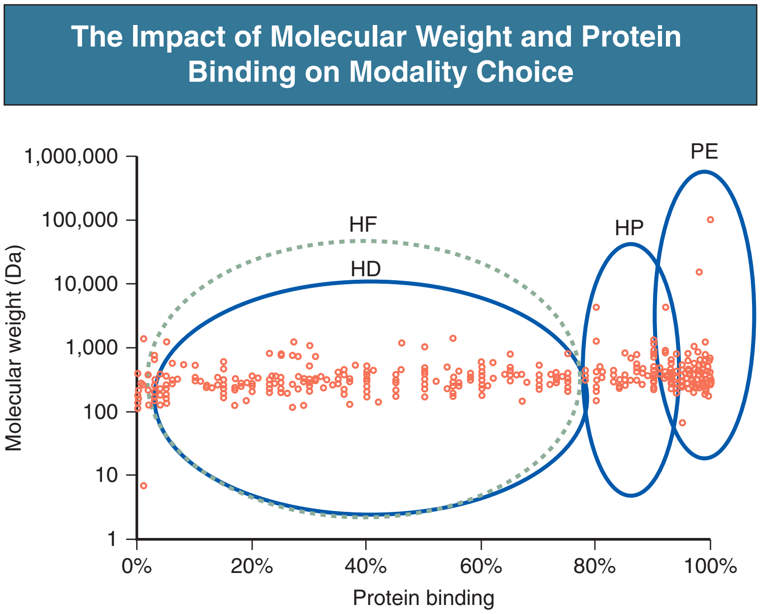
The Impact of Molecular Weight and Protein Binding on Modality Choice

Fig. 98.1 The impact of molecular weight and protein binding on modality choice. *Circles* indicate for which poisons a specific modality might be most useful. *HD,* Hemodialysis; *HF,* hemofiltration; *HP,* hemoperfusion; *PE,* plasma exchange. (With permission, from reference 11). The decline in use of hemoperfusion in many parts of the world means that it may be unavailable as a treatment option. In these circumstances, plasma exchange, which is widely available, may be used.

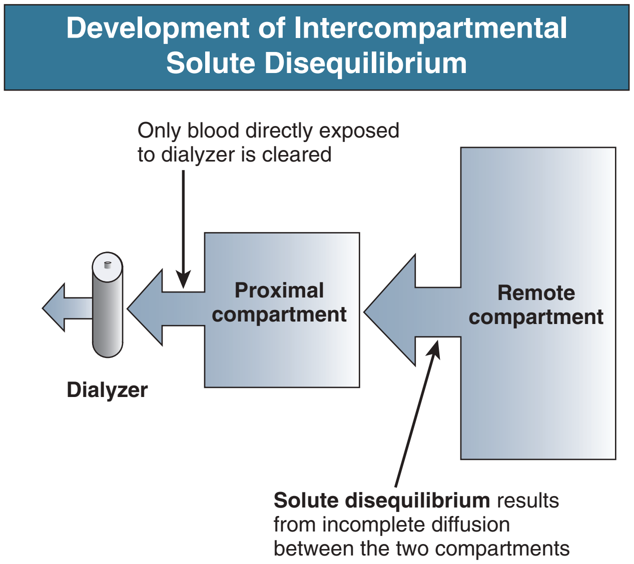
Development of Intercompartmental Solute Disequilibrium
Only blood directly exposed to dialyzer is cleared
Proximal compartment
Remote compartment
Dialyzer
Solute disequilibrium results from incomplete diffusion between the two compartments

Fig. 98.2 **Intercompartmental solute disequilibrium.** Access of dialyzer to toxin is limited by disequilibrium, which retains toxin in the remote compartment.

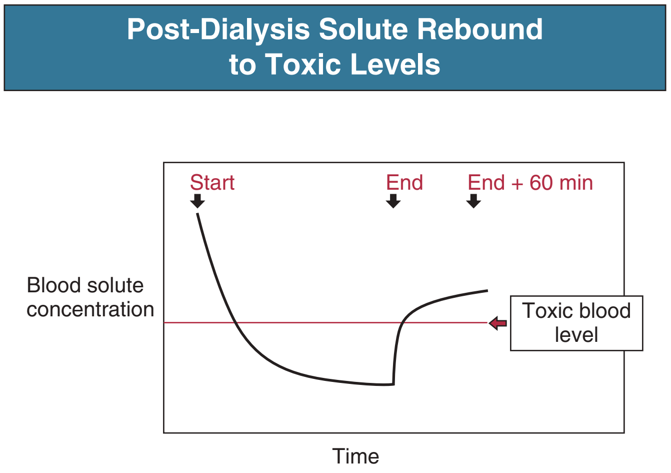

Fig. 98.3 **Postdialysis rebound.** Falling solute concentration during dialysis with rapid postdialysis rebound to toxic levels.

proximal and the remote compartments, disequilibrium will develop during an extracorporeal treatment, reducing the overall efficiency of toxin removal, and potentially leading to a large postsession rebound in toxin blood levels. Potentially toxic post-treatment levels may be missed if the immediate postdialysis blood level is used to estimate elimination (Fig. 98.3). After extracorporeal treatment for lithium poisoning for instance it is recommended that levels be rechecked after 6 to 12 hours to detect clinically significant rebound.[12] Vigilance for rapidly rising levels is also important if ongoing toxin absorption is suspected and may require earlier and more frequent monitoring.

High clearance techniques (i.e., intermittent HD or HDF) rapidly reduce blood solute levels but are more likely to result in intercompartmental disequilibrium. Extending sessions beyond 4 hours can ameliorate rebound but intermittent HD and the diffusive component of intermittent HDF are inherently inefficient processes that depend on the solute concentration presented to the dialyzer. Most solute removal will therefore occur at the start of dialysis so any gains in solute removal will be disproportionately lower as dialysis time extends. Increasing treatment frequency can mitigate the risk for significant rebound to toxic blood levels.

Compartmentalization need not preclude HD-/HDF-mediated toxin removal, but the total body burden of extremely compartmentalized toxins (e.g., digoxin; tricyclic antidepressants [TCAs]) cannot be effectively reduced by HD even though blood levels are rapidly reduced. Therefore extracorporeal treatment is not recommended in digoxin or TCA poisonings[6] despite occasional reports of successful clearance of TCAs with dialysis.[5]

Contribution of Extracorporeal Toxin Relative to Endogenous Clearance

Even toxins that may be readily cleared by extracorporeal therapy may not require such treatment if endogenous clearance rates are high. It is proposed that extracorporeal therapy is justified if it increases total body clearance by at least 30%[13] or if endogenous clearance is less than 4 ml/min/kg body weight.[14] Unfortunately, these thresholds can be difficult to estimate at the bedside, although an indication of endogenous clearance rates are available for some drugs (see www.medicines.org.uk/emc/) and estimates of dialyzer clearances can be obtained from the product insert. For HF, an estimate of clearance can be provided by the ultrafiltration rate. Maximal clearances for the extracorporeal therapies are approximately 240 ml/min (for intermittent HD/HF/hemoperfusion), 50 ml/min (for continuous RRTs [CRRTs] and plasma exchange) and 10 ml/min (for exchange transfusion).[11]

However, endogenous elimination in the setting of poisoning may be markedly lower than in health. High endogenous clearances of approximately 2000 ml/min (e.g., for cocaine, labetalol, toluene, verapamil)[11] would appear to obviate the need for extracorporeal treatment. However, if these elimination routes are limited by end-organ dysfunction (e.g., by renal or liver failure), extracorporeal therapy may be life-saving.

These considerations are summarized in Fig. 98.4.

TREATMENT MODALITIES

The range of extracorporeal techniques employed for toxin elimination with parameters that might be manipulated to enhance toxin clearances are shown in Box 98.2. Generic considerations, including the basics of physical process, nomenclature, and vascular access (and its care) are detailed, elsewhere.[8,9]

Intermittent Hemodialysis, Hemofiltration, and Hemodiafiltration

Diffusion against a steep concentration gradient (as in intermittent HD) encourages the rapid removal of smaller solutes, including most poisons. Clearances can be enhanced by increasing dialyzer efficiency (indicated by the KoA, the urea mass transfer area coefficient) or membrane surface area. Larger solute removal can be enhanced by increasing dialyzer flux (Kuf) when intermittent HD is used (for toxins with MW between 500 Da and 10,000 Da, e.g., deferoxamine, aminoglycosides) or by introducing convective removal (with HF or HDF), which can allow removal of toxins up to approximately 40,000 Da.

Intermittent HD is usually the first-choice extracorporeal modality because of its common availability, the rapidity of toxin removal, and the low MW of common poisons. The role of other renal replacement modalities is less clear because of a lack of published data.

Peritoneal Dialysis

Peritoneal dialysis is not an “extracorporeal” technique, per se, and is rarely used to treat poisoning because of the comparatively slow rate of clearance, the risks associated with acute peritoneal dialysis catheter

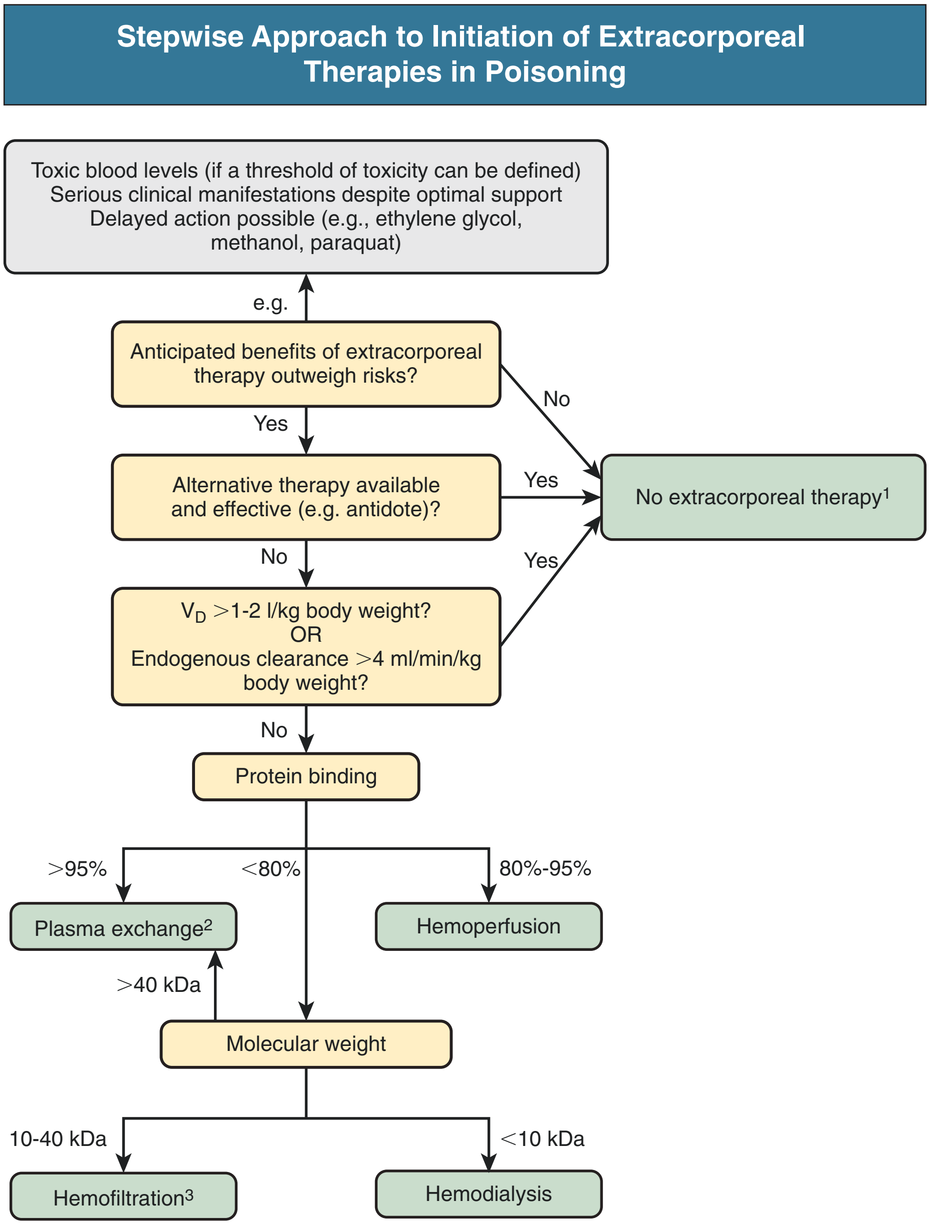
Stepwise Approach to Initiation of Extracorporeal Therapies in Poisoning
Toxic blood levels (if a threshold of toxicity can be defined)
Serious clinical manifestations despite optimal support
Delayed action possible (e.g., ethylene glycol, methanol, paraquat)
e.g.
Anticipated benefits of extracorporeal therapy outweigh risks?
No
Yes
Alternative therapy available and effective (e.g. antidote)?
Yes
No extracorporeal therapy^1
No
Yes
V_D >1-2 l/kg body weight? OR Endogenous clearance >4 ml/min/kg body weight?
No
Protein binding
>95%
<80%
80%-95%
Plasma exchange^2
Hemoperfusion
>40 kDa
Molecular weight
10-40 kDa
<10 kDa
Hemofiltration^3
Hemodialysis

Fig. 98.4 **Stepwise approach to the initiation of extracorporeal techniques for enhanced elimination in poisoned patients.** [1]Unless other indication (e.g., acute kidney injury [AKI] (e.g., from acetaminophen overdose), severe metabolic acidosis, severe liver failure, hypothermia or hyperthermia). Choice of technique will depend on the indication (e.g., one of the renal replacement therapies for AKI). [2]Or albumin dialysis if available. [3]Or hemodialysis with high cut-off membrane, if available (pore size cut-off ~65 kDa). V_D = Solute volume of distribution. Modified with permission from reference 11.

insertion, and the widespread availability of other modalities, at least in the industrialized world. It may have a role in the treatment of poisoning in childhood because its lower clearance may be sufficient for the smaller solute distribution volumes in children and because of technical challenges associated with HD in very young children.

Continuous Renal Replacement Therapy

CRRT may be used when intermittent HD is not immediately available or when more rapid solute removal would be compromised by significant intercompartmental disequilibrium. For small-solute clearances, continuous HF and continuous HD have near kinetic equivalence. Full saturation of dialysate effluent in continuous HD, because of its slow flow rates, gives a small-solute concentration similar to both the ultrafiltrate from HF and plasma water as it leaves the hollow-fiber device. CRRT gives better solute clearances when applied over the course of several days but elimination is not as rapid as with intermittent HD. Delivered small-solute clearances of CRRT can be maximized by combining diffusion and convection in continuous HDF. If it is logistically possible, an ideal combination may be initial use of intermittent HD for rapid reduction of toxin levels, with continuous therapy then used to ameliorate any postdialysis rebound when this is anticipated.

Although small-solute clearances are similar in continuous HF and continuous HD, the former should be used in preference to remove larger toxins.

Because RRT modalities are often applied for drug elimination in the absence of renal dysfunction or serious electrolyte disturbance,

BOX 98.2 Practical Considerations in Prescribing Extracorporeal Therapy for Poisonings

Intermittent hemodialysis:

- Maximize Qb and dialyzer membrane surface area
- Aim for Qb/Qd ratio of ≥2.5 : 1 (although diminishing benefits gained from increasing Qd beyond ~600 ml/min)[33]
- Maximize treatment times to at least 4 hours
- Use high-flux (Kuf), high-efficiency (KoA) dialyzer, particularly if middle molecular weight solutes (>1000 Da) are to be cleared

Intermittent hemofiltration/filtrative component of intermittent hemodiafiltration:

- Aim for postdilution fluid replacement to maximize efficiency with high-flux membrane
- Maximize Quf according to filtration fraction*

Continuous renal replacement therapies†:

- Aim for high convective clearances (i.e., postdilutional CVVH with high-flux membrane) for larger solutes (>1000 Da)
- Aim for high diffusive clearances (i.e., CVVHD) for small solutes (≤1000 Da)
- For CVVH, maximize Quf according to filtration fraction*
- For CVVHD, CVVHDF, maximize Qd up to at least 2.5 l/ h‡ for small solutes;
  - for larger solutes (e.g., of an equivalent size to β_2-microglobulin; MW 11,800) there may be little gain from a Qd >1.5 l/h.[34]

Hemoperfusion:

- Limit Qb to ~100 to 250 ml/min (see section on hemoperfusion)
- Change cartridge every 3 to 4 hours
- Consider benefits of charcoal vs resin cartridges depending on poison[15]

Plasma exchange:

- Aim for two plasma volume exchanges per day
- Modify replacement fluid according to poison (see text for details)

*The chief risk with postdilutional fluid replacement is hemoconcentration. This can be minimized by keeping the filtration fraction (FF) ≤50%.

The minimum Qb to achieve this can be calculated from the following formula[35]:

$\text{Minimum Qb} = \text{Quf}/(05 * [1 - \text{Hematocrit}])$

Alternatively, the maximum Quf would solve as:

$\text{Quf} = \text{Qb} * 05 * (1 - \text{Hematocrit})$

In addition, transmembrane pressures should be kept <400 mm Hg to help prevent membrane fiber rupture.

†Aiming for conventional effluent flow rates (i.e., 25 ml/kg/h[36]) for support of the patient with acute kidney injury may fail to maximize potential poison clearances.

‡For small solutes at Qb 150 ml/min, there appears to be a direct linear relationship between increasing clearances and Qd to flow rates of at least 2.5 l/h.[34] It would seem reasonable, therefore, to maximize Qd as machine hardware, dialyzer specifications, and practicalities (fluid availability, nursing workload) allow.

Qb, extracorporeal blood flow; *Qd*, dialysate flow; *Quf*, ultrafiltration rate; *CVVH*, continuous venovenous hemofiltration; *CVVHD*, continuous venovenous hemodialysis; *CVVHDF*, continuous venovenous hemodiafiltration.

Adapted from reference 33, with permission.

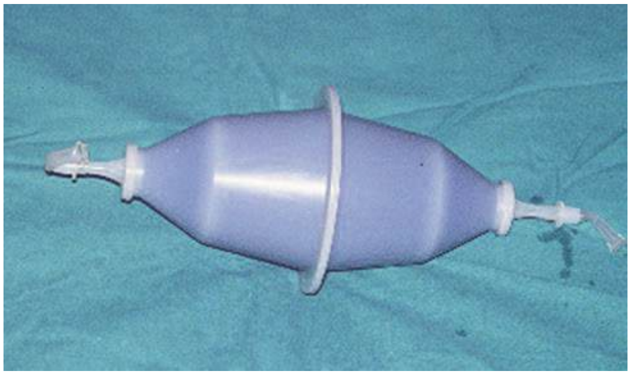

Fig. 98.5 A charcoal hemoperfusion cartridge.

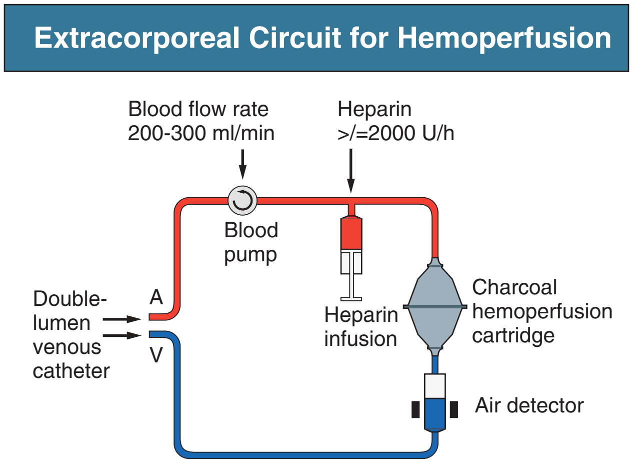
Extracorporeal Circuit for Hemoperfusion
Blood flow rate 200-300 ml/min
Heparin >/=2000 U/h
Blood pump
Double-lumen venous catheter
A
V
Heparin infusion
Charcoal hemoperfusion cartridge
Air detector

Fig. 98.6 Extracorporeal circuit for hemoperfusion.

careful monitoring for evolving biochemical abnormalities is required. Hypokalemia can be corrected by adjusting the dialysate or replacement fluid composition and by supplementation. Hypophosphatemia can be addressed with standard supplements. At least for intermittent HD, the risk of developing metabolic alkalosis can be attenuated in patients with normal kidney function and baseline serum bicarbonate by using a dialysate bicarbonate concentration at the lower end of the deliverable range. Because the bicarbonate concentration of premanufactured replacement or dialysate fluid in CRRT cannot be manipulated, intermittent HD against a low bicarbonate dialysate may be preferable if severe metabolic alkalosis is present.

Hemoperfusion

The technique involves the extracorporeal circulation of blood through a hemoperfusion cartridge (Fig. 98.5) containing an adsorbent material such as activated charcoal or a resin. Hemoperfusion removes substances that bind to the adsorbent material. It is effective at removing uncharged molecules through competitive binding, especially those that are significantly plasma protein bound and lipophilic, although those toxins exceeding about 5000 to 10,000 Da are less well removed.[15] As with other modalities, the likely proportional contribution to total toxin elimination should be considered before hemoperfusion is begun along with the availability of other, potentially safer techniques such as long-hours, high-flux dialysis (see later).

Other than the cartridge and the lack of dialysate and other replacement fluid circuits, the disposables and hardware are those used for intermittent HD (Fig. 98.6). Blood flows should be limited to approximately 100 to 250 ml/min to minimize the risk of hemolysis during passage through the cartridge.[16]

Standard anticoagulation protocols may be insufficient for hemoperfusion because heparin is also adsorbed. A larger initial bolus and maintenance dose of unfractionated heparin is usually required (e.g., ≥2000 U/h), with adjustments guided by regular monitoring of clotting times during the procedure. The manufacturer's instructions should be reviewed carefully, because some cartridges require priming with dextrose solution to prevent hypoglycemia. Other complications include hypocalcemia, hypophosphatemia, charcoal embolization, leukopenia, thrombocytopenia (usually uncomplicated and self-limiting), pyrogenic reactions, and adsorption of coagulation factors.[15]

The charcoal sorbent particles may be coated with a polymer or other substance to increase biocompatibility and reduce the risk of embolization. Pretreatment of cartridges with albumin, plasma, or heparin to improve biocompatibility and reduce removal of endogenous molecules is of uncertain benefit.[15]

Saturation of the adsorbent material limits the duration of treatment with any individual hemoperfusion cartridge. It is usually recommended that cartridges are changed approximately every 3 to 4 hours, but treatments of this length are usually adequate for a significant lowering of toxin blood levels.[15]

If a toxin is equally removed by intermittent HD and hemoperfusion, intermittent HD should be used preferentially, because it is less risky and also allows correction of fluid balance, electrolyte status, and other metabolic abnormalities.

Decreasing familiarity with hemoperfusion and increasing scarcity of the requisite cartridges, coupled with the ready availability of alternative treatment (long-hours, high-flux renal support) is likely to propagate this decline in the Western world, although the modality continues to be employed in China, India, and elsewhere.[15]

Other Modalities

Some of the advantages of both continuous and intermittent RRTs are combined in the hybrid modalities, such as sustained low-efficiency dialysis (SLED), but these require further evaluation.

There are a few reports of the use of plasma exchange and the molecular adsorbent recirculating system (MARS) in poisoning. In principle, both should be useful for toxins that are strongly protein bound but not lipid soluble, are tissue bound, or have a large V_D outside the blood compartment.[17] Plasma exchange is most commonly used in *Amanita phalloides* poisoning but also has been reported to prevent limb loss in snake envenomation and reduce toxic levels of biologic therapeutic agents (e.g., monoclonal antibodies).[17] Plasma exchange can clear the red cell fragments and free hemoglobin that result from poisoning with sodium chlorate or other agents that can cause hemolysis. The replacement fluid used in plasma exchange warrants some consideration because the plasma free fraction of toxins that are highly albumin-bound may rebound after treatment if insufficient albumin is administered.[17] Some toxins have a greater affinity for other plasma proteins such as α1-acid glycoprotein than for albumin (e.g., dipyridamole, quinidine, imipramine, propranolol, and chlorpromazine) arguing for the use of plasma- rather than albumin-based replacement in these situations.[17] Plasma replacement may be preferable where there is a significant coagulopathy, such as in certain instances of snake envenomation.[17] One to two plasma volume exchanges per day is likely to be sufficient until toxic manifestations and tissue release have subsided.[17]

Exchange transfusion may be useful in neonates and small children who have been poisoned with toxins that have a low volume of distribution (e.g., theophylline, salicylates).[11]

EXTRACORPOREAL THERAPY FOR SPECIFIC DRUGS AND POISONS

Alcohols

Ethylene glycol (MW 62 Da) and methanol (MW 32 Da) can be found in antifreeze, de-icing solutions, and windscreen cleaning fluid. The ingestion of as little as 1 g/kg body weight of either methanol or ethylene glycol is potentially lethal. Toxicity results from the metabolism of ethylene glycol and methanol by alcohol dehydrogenase to glycolic acid and formic acid, respectively, and may result in optic nerve damage, seizures, coma, and ultimately death. Poisoning should be suspected in any patient presenting with nausea, vomiting, abdominal pain, impaired consciousness, severe metabolic acidosis, and acute kidney injury (AKI).

Early recognition of ethylene glycol or methanol poisoning may allow treatment with ethanol or fomepizole to inhibit hepatic alcohol dehydrogenase. Fomepizole has now replaced ethanol as first-line therapy[18,19] because it is safe and is better tolerated.

Fomepizole should be prescribed if there is a clear history of ethylene glycol and/or methanol ingestion, if the osmol gap is greater than 10 mOsm/kg, or the ethylene glycol/methanol blood level is greater than 20 mg/dl (3.2 mmol/l for ethylene glycol and 6.2 mmol/l for methanol). Fomepizole is administered as a loading dose of 15 mg/kg intravenously (IV). This is followed by 10 mg/kg every 12 hours for 4 doses and then 15 mg/kg every 12 hours until the metabolic acidosis has resolved and the serum concentration of ethylene glycol and methanol is less than 20 mg/dl (or <10 mg/dl in the presence of end-organ damage). Patients who have ingested methanol also should receive folinic acid 50 mg IV every 6 hours to enhance the metabolism of formic acid. The administration of thiamine 100 mg IV or pyridoxine 50 mg IV should be considered in patients with poor nutritional status after ethylene glycol ingestion. If fomepizole is not available, intravenous 10% ethanol should be administered as a loading dose of 800 mg/kg followed by an infusion of 80 to 160 mg/kg/h to achieve a serum ethanol concentration of 1 to 1.5 g/l. Ethanol should be administered until no ethylene glycol or methanol is detectable in the blood. Intravenous sodium bicarbonate should be considered to help correct any associated metabolic acidosis.

Ethylene glycol and methanol have low MWs, limited protein binding, single-compartment kinetics, and a limited volume of distribution. Immediate HD is recommended if ingestion of ethylene glycol or methanol is confirmed with a serum concentration greater than 50 mg/dl (8.1 mmol/l for ethylene glycol and 15.6 mmol/l for methanol) in the setting of coma, seizures, severe metabolic acidosis (pH 7.15), or the presence of end-organ damage such as AKI or visual disturbance. Because fomepizole is removed by HD, a maintenance infusion of 1 to 1.5 mg/kg/h should be prescribed for the duration of the HD session after administration of the loading dose. Similarly, ethanol doses should be doubled during the dialysis session.

To achieve optimal clearance the dialyzer should have a large surface area (>1.5 m^2) and the blood flow rate should be greater than 300 ml/min. Bicarbonate buffer should be used and serum concentrations of ethylene glycol and methanol should be measured 2 hours after the treatment to take account of rebound. HD should continue until the pH has normalized and the concentration of ethylene glycol or methanol is below 25 mg/dl (4.0 mmol/l for ethylene glycol and 7.8 mmol/l for methanol). Patients who have ingested large quantities of ethylene glycol and methanol may require further HD treatment.

The EXTRIP workgroup recommends intermittent HD as the modality of choice; continuous modalities are acceptable if intermittent HD is not available, although they are not as effective at removing methanol.[20]

β-Blockers

β-Blocker overdose will manifest with bradycardia and hypotension and may also include altered mental state, seizures, bronchospasm, hypoglycemia, and cardiogenic shock. Extracorporeal removal is rarely required unless patients have not improved despite maximal medical therapy. Extracorporeal treatment is only effective for hydrophilic, minimally protein-bound drugs such as atenolol, sotalol, nadolol, and acebutolol. Propranolol, timolol, and metoprolol are not removed. Intermittent HD is recommended in hemodynamically stable patients. CRRTs may be considered in patients who are hemodynamically unstable.

Lithium

Severe lithium poisoning may manifest with arrhythmias, hypotension, confusion, coma, or seizures. Lithium (MW 7 Da) is removed easily by HD because of its low MW and negligible protein binding. The clearance of lithium by HD is superior to that achieved by the kidneys, which is limited by significant proximal tubular reabsorption. HD is recommended if the serum lithium concentration is greater than 4 mmol/l or greater than 2.5 mmol/l in a patient with central nervous system manifestations.[12] Lithium equilibrates relatively slowly between the extracellular and intracellular compartments; thus postdialysis rebound may be significant[21] and extended or frequent HD treatment may be needed to minimize its impact. Serum lithium levels should be checked 6 hours postdialysis to guide further therapy. CRRT may complement intermittent HD by helping mitigate the impact of the postdialysis rebound.

Metformin

Patients who have taken an overdose of metformin (MW 166 Da) may present with tachypnea, nausea, abdominal pain, tachycardia, hypotension, and, in the setting of AKI, severe lactic acidosis. Metformin is normally excreted unmetabolized by the kidneys and has negligible protein binding. Metformin causes lactic acidosis by inhibiting hepatic gluconeogenesis from lactate and promoting the conversion of glucose to lactate in the small intestine. Medical management involves supportive measures and the intravenous administration of sodium bicarbonate. Extracorporeal therapy is recommended in patients who are unresponsive to medical management.[22] Both intermittent HD and CRRT can provide effective extracorporeal removal.

Salicylates

The clinical manifestations of salicylate overdose include fever, sweating, tinnitus, epigastric pain, nausea, vomiting, diarrhea, vertigo, and blurring of vision. Severe overdoses may progress to depression of mental state, noncardiogenic pulmonary edema, and death. Salicylate intoxication initially results in hyperventilation and respiratory alkalosis. This is followed by metabolic acidosis secondary to the accumulation of lactic acid and ketoacids. Therefore patients may present with either respiratory alkalosis or mixed respiratory alkalosis–metabolic acidosis. Diagnosis is based on the presenting history and clinical examination and confirmed with plasma salicylate levels.

Increased salicylate tissue penetration and toxicity can occur with only small decreases in pH as a result of increased concentration of nonionized salicylate. Intravenous sodium bicarbonate should be given to decrease tissue penetration and facilitate the excretion of salicylate through the kidneys unless the patient has oliguric AKI, pulmonary edema, or cerebral edema.

Although salicylate (MW 180 Da) is 90% protein-bound, saturation of protein binding in significant poisoning and its limited volume of distribution makes it amenable to removal by dialysis. Extracorporeal therapy is recommended in patients with severe salicylate poisoning, reflected by altered mental state, the acute respiratory distress syndrome, and failure to respond to medical management irrespective of salicylate levels. Extracorporeal therapy is also indicated, regardless of signs and symptoms, at levels greater than 100 mg/dl (7.2 mmol/l). Lower thresholds are applied for patients with AKI. Intermittent HD carries advantages over hemoperfusion because the former allows rapid correction of associated electrolyte abnormalities and acidemia. CRRT is acceptable if intermittent HD is not available.[23]

Theophylline

Theophylline (MW 180 Da) overdose manifests with nausea, vomiting, diarrhea, gastrointestinal hemorrhage, hypokalemia, seizures, arrhythmias, and hypotension. Overdose may be acute or chronic. Theophylline is readily cleared by either HD or hemoperfusion because of its low volume of distribution and minimal protein binding. Extracorporeal therapy is recommended for severe acute theophylline poisoning (theophylline level >100 mg/l [555 μmol/l], or the presence of seizures, life-threatening arrhythmias, shock, or failure of standard therapy). In chronic poisoning, extracorporeal therapy is suggested if theophylline levels are greater than 60 mg/l (333 μmol/l) or greater than 50 mg/l (278 μmol/l) and the patient is older than 60 years of age. High-flux, high-efficiency HD is more effective in removing theophylline than hemoperfusion and is associated with fewer side effects. Continuous venovenous HF can be used but requires a more sustained period of treatment.[24]

Valproate

Although valproate (MW 144 Da) is highly protein bound, saturation of protein binding after significant poisoning makes it amenable to removal by extracorporeal therapy. Overdose may manifest with mild confusion, lethargy, nausea, vomiting, tachycardia, hypotension, metabolic acidosis, and electrolyte disturbances (hyponatremia and hypocalcemia). Extracorporeal therapy is recommended for severe overdose (valproate level >1300 mg/l [9000 μmol/l], cerebral edema, or shock). Extracorporeal therapy can be considered for valproate concentrations above 900 mg/l (6250 μmol/l), coma or respiratory depression requiring ventilation, acute hyperammonemia, or pH less than 7.10. HD is preferred to hemoperfusion because it not only clears unbound drug but also reverses associated metabolic abnormalities.[25]

Tricyclic Antidepressant Drugs

Extracorporeal therapy is not likely to have any clinical benefit for patients who have experienced an overdose with TCA drugs.[26]

Thallium

Thallium (MW 204 Da) poisoning continues to be reported where it is used as a rodenticide and a contaminant of herbal and illicit drug products (see reference list in reference 27). It is absorbed extensively through almost all routes of exposure and is widely distributed across multiple body compartments. Toxicity is caused by thallium replacing potassium as a stimulator or inhibitor of a variety of intracellular electrochemical and enzymatic processes. Despite a lack of high-quality evidence and as a result of the severe toxicity of thallium and a lack of alternative therapies, extracorporeal therapy is strongly recommended.[27] Intermittent HD is preferable, but hemoperfusion and CRRT are valid alternatives.

Barbiturates

Although barbiturate overdose is less common, it is still a significant cause of fatal poisoning. It is recommended that extracorporeal therapy be restricted to cases of severe long-acting barbiturate poisoning with clinical features including prolonged coma, respiratory depression requiring ventilation, shock, and a failure to treat effectively with multiple-dose activated charcoal; intermittent HD is the preferred mode of therapy.[28]

Acetaminophen

There is a paucity of high-quality evidence for the extracorporeal removal of acetaminophen (MW 46 Da), although it may have a role in the rare cases when *N*-acetylcysteine has not been effective; intermittent HD is the preferred modality.[29]

Carbamazepine

Carbamazepine (MW 236 Da) is moderately well dialyzed, with intermittent HD being the favored modality for severe poisoning (coma, respiratory depression requiring ventilation, or carbamazepine levels that do not respond to standard therapy with activated charcoal). If HD is not available, hemoperfusion or CRRT can be considered.[30]

Phenytoin

Phenytoin (MW 252 Da) has a large volume of distribution and is extensively protein bound (90%) but dissociates easily and is amenable to extracorporeal removal. However, phenytoin poisoning rarely causes permanent organ damage or death, and so extracorporeal therapy is recommended only in very severe cases of poisoning that have been resistant to standard therapy.[31] Enteral absorption of phenytoin is slow and unpredictable, so vigilance should be maintained for the delayed effects of poisoning.

Digoxin

Digoxin (MW 781 Da) has variable absorption from the gut depending on the size of the ingestion. Although it is 20% to 30% protein bound, it also has a large volume of distribution and an effective antidote (digoxin immune Fab) so extracorporeal therapy is not useful in the management of overdose.[32]

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SELF-ASSESSMENT QUESTIONS

1. Which one of the following statements is *true* regarding ethylene glycol toxicity?
   - **A.** Ethylene glycol is metabolized to glycolic acid.
   - **B.** Ethylene glycol is metabolized to formic acid.
   - **C.** Ethylene glycol is metabolized by alcohol hydrogenase.
   - **D.** Urinalysis demonstrates uric acid crystals.
   - **E.** Ethylene glycol toxicity is associated with a normal anion gap
2. Which one of the following is not associated with a raised osmolar gap?
   - **A.** Ethylene glycol intoxication
   - **B.** Methanol intoxication
   - **C.** Isopropanol intoxication
   - **D.** Diabetic ketoacidosis
   - **E.** Acute kidney injury
3. Intermittent hemodialysis (HD) is not effective for removal of which of the following in overdose?
   - **A.** Lithium
   - **B.** Ethylene glycol
   - **C.** Metoprolol
   - **D.** Atenolol
   - **E.** Methanol
4. Which one of the following statements is true:
   - **A.** Hemoperfusion remains the 1st choice treatment for removal of theophyllines.
   - **B.** If endogenous clearance rates of toxins are < 10 ml/min/kg body weight, extracorporeal treatment should be considered.
   - **C.** Highly protein-bound toxins are not suitable for extracorporeal treatment.
   - **D.** When continuous veno-venous hemofiltration is used, solely, for poison removal, conventional doses used for patients with AKI should be utilized.
   - **E.** Toxin rebound after intermittent hemodialysis may be mitigated by frequent scheduling of treatment or adjunctive therapy with one of the continuous renal replacement therapies.

99

Plasma Exchange

Jeremy Levy

Over the last 10 years, it has become clearer how best to use plasma exchange (plasmapheresis) in the management of renal disease, but the quality of published data is relatively poor, with less than 1% of relevant literature in the form of randomized controlled trials (RCTs). Plasma exchange came into widespread clinical use after early reports of beneficial effects in Goodpasture disease in the mid-1970s. It is used to remove many large molecular weight (MW) substances from plasma, including pathogenic antibodies, cryoglobulins, and lipoproteins. Newer techniques allow more selective removal of plasma components, such as double-filtration plasma exchange, cryofiltration, and immunoadsorption with or without immobilized ligands. The most common renal indications recorded in the Canadian Apheresis Registry in 2014 (in order of frequency) were thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (TTP/HUS), renal transplantation (antibody-mediated rejection and for desensitization either for anti-ABO blood group antibodies or anti–human leukocyte antigen [HLA] antibodies), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, cryoglobulinemia, recurrent focal segmental glomerulosclerosis (FSGS), and anti–glomerular basement membrane (anti-GBM) antibody disease.

TECHNIQUES

Plasma exchange can be carried out either by centrifugal cell separators or (more commonly in renal units) with hollow-fiber plasma filters and standard hemodialysis (HD) equipment (Figs. 99.1 and 99.2). Centrifugal devices allow withdrawal of plasma from a bowl with either synchronous or intermittent return of blood cells to the patient.[1] There is no upper limit to the MW of proteins removed by this method. The bowls and circuits are single use and disposable and require relatively low blood flow rates (50 to 150 ml/min) that can be delivered through large-bore peripheral cannulae. Platelet counts can decrease by as much as 50%, with centrifugal devices, although this has improved with newer technologic approaches and is usually less than 10%. Membrane plasma filtration uses highly permeable hollow fibers with membrane pores 0.2 to 0.5 μm. Plasma readily passes through the membrane while the cells are simultaneously returned to the patient. All immunoglobulins will cross the membrane (immunoglobulin G [IgG] slightly more efficiently than IgM), and molecules up to 3 million d are cleared. Hemolysis can occur if transmembrane pressures are too high (a rare complication). The blood flow rates required for membrane plasma filtration are higher than for centrifugal cell separators (100 to 300 ml/min) and require central venous access or a fistula; there is no increase in rate of plasma filtration at blood flows greater than 300 ml/min, but there is an increased risk for hemolysis. Membrane exchange takes slightly longer than centrifugal techniques for the same plasma volume removal. Membranes used in plasma filters are polysulfone, polypropylene, cellulose diacetate, polymethylmethacrylate, and polyacrylonitrile.[1] It has been suggested that the adsorptive properties of the membrane for cytokines and other biomolecules may account for some of the beneficial effects of plasma filtration. There have been occasional reports of mild adverse reactions in patients taking angiotensin-converting enzyme inhibitors when plasma is filtered with ethylene vinyl alcohol or acrylic copolymer membranes. Reuse of plasma filters is not advised because of potential risks resulting from loss of filtration capacity and to staff from cleaning procedures, but performance data do not indicate a major loss of function during routine plasma exchange. For patients with severe renal failure, sequential HD and plasma exchange can easily be performed with plasma filtration.

Vascular access is usually achieved using standard central venous catheters, but existing arteriovenous fistulas (AVFs) can be used if available. Sometimes plasma exchange can be done using large-bore, short intravenous cannulas placed in the antecubital fossa, especially with centrifugal devices. Single-needle access using an AVF is also relatively easy to accommodate, especially for centrifugal plasma exchange, in which the blood removal and return can be asynchronous, but also for membrane filtration. Anticoagulation must be carefully managed in patients at higher bleeding risk (e.g., thrombotic microangiopathy [TMA], recent or ongoing pulmonary hemorrhage, or a recent renal biopsy). Citrate is used for anticoagulation with centrifugal plasma exchange and heparin for membrane plasma filtration; however, citrate is superior for patients at higher bleeding risk in view of its lack of systemic anticoagulation.[1] When heparin is used, higher doses may be needed than in HD as a result of increased losses during the procedure (heparin is protein bound). Bolus doses of unfractionated heparin of 2000 to 5000 U are given initially and then 500 to 2000 U/h. Anticoagulant is administered prefilter. Increasingly low molecular weight heparin (LMWH) is also used with a single bolus dose at initiation of exchange.

Both methods of plasma exchange require large volumes of colloid replacement. A single plasma volume exchange will lower plasma macromolecule levels by approximately 60%, and five exchanges over 5 to 10 days will clear 90% of the total body immunoglobulin (Fig. 99.3).[1,2] For most patients, this is achieved by removing 50 ml of plasma per kilogram body weight at each procedure (~4 liters for a 75-kg person). Daily plasma exchange more rapidly depletes total body load of immunoglobulins, but there is no good evidence that intensity of exchanges has a major effect on outcomes except in patients with HUS with poor prognostic markers (see later discussion). Indeed, alternate-day exchanges are of proven efficacy in ANCA-associated diseases. Replacement solely with crystalloid is contraindicated because of the need to maintain colloid oncotic pressure. Synthetic gelatin–based plasma expanders or hydroxyethyl starch (Hespan) can be used as part of a replacement regimen but have been reported to cause a coagulopathy in patients with sepsis and have a shorter half-life than

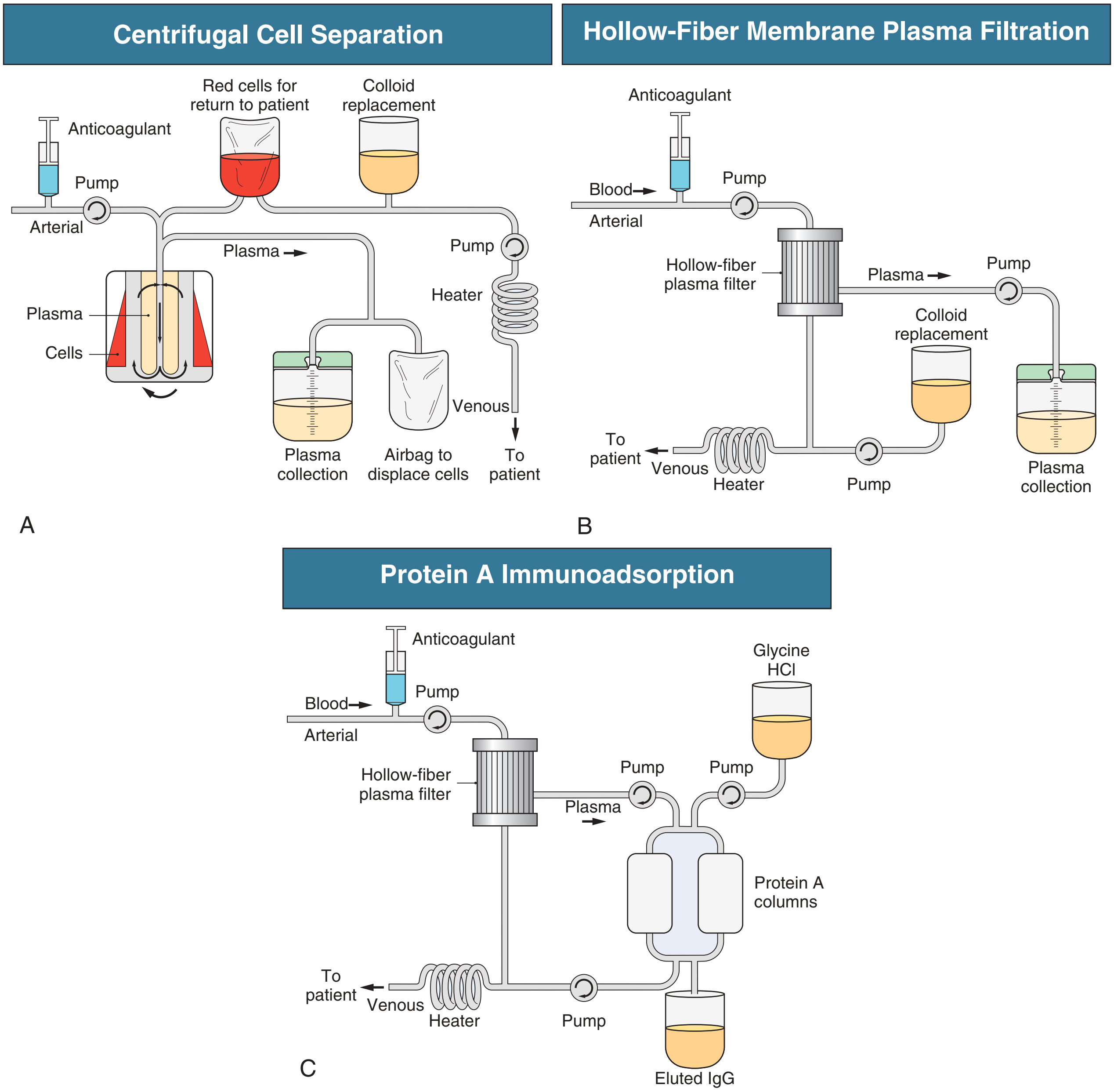
Centrifugal Cell Separation
Red cells for return to patient
Colloid replacement
Anticoagulant
Pump
Arterial
Plasma
Pump
Heater
Plasma
Cells
Venous
Plasma collection
Airbag to displace cells
To patient
A
Hollow-Fiber Membrane Plasma Filtration
Anticoagulant
Blood
Pump
Arterial
Hollow-fiber plasma filter
Plasma
Pump
Colloid replacement
To patient
Venous
Heater
Pump
Plasma collection
B
Protein A Immunoadsorption
Anticoagulant
Glycine HCl
Blood
Pump
Arterial
Hollow-fiber plasma filter
Pump
Pump
Plasma
Protein A columns
To patient
Venous
Heater
Pump
Eluted IgG
C

Fig. 99.1 **Plasma exchange and immunoadsorption techniques.** Techniques include centrifugal cell separation (A), hollow-fiber membrane plasma filtration (B), and protein A immunoadsorption (C). *IgG*, Immunoglobulin G.

human albumin, which is the main replacement fluid. The major disadvantage of albumin solutions is the lack of clotting factors, with the potential development of depletion coagulopathy after plasma exchange. Fresh-frozen plasma (FFP) should be given, usually in addition to human albumin solution, in patients at particular risk for bleeding. If partial replacement is with FFP, this should be given late during the exchange so the constituents are not removed by the ongoing plasma exchange. However, almost all the serious complications of plasma exchange (hypotension, anaphylaxis, citrate-induced paresthesia, urticaria) have been reported in patients receiving FFP rather than albumin (see later discussion).[1,3] Both human products carry a tiny risk for transmission of infectious diseases, especially viral. Standard regimens for plasma exchange are summarized in Table 99.1. Human albumin solution (4% to 5%) should be used for all exchanges except in TMAs (in which plasma should provide the total exchange), and FFP should form part of the exchange when bleeding risk is high (ongoing pulmonary hemorrhage or within 48 hours of biopsy or surgery). If fibrinogen levels decrease to below 1.25 to 1.5 g/l or prothrombin time is increased 2 to 3 seconds above normal, FFP should be administered (Table 99.2).

Double-filtration plasma exchange (or cascade filtration) uses membrane filtration to separate cells from plasma and then a secondary plasma filtration (pore size 0.01 to 0.03 μm) to remove plasma solutes based on molecular size. Most albumin is therefore returned to the patient, together with lower MW proteins, reducing the need for replacement fluids. Cryofiltration uses a similar principle but exposes the filtrate

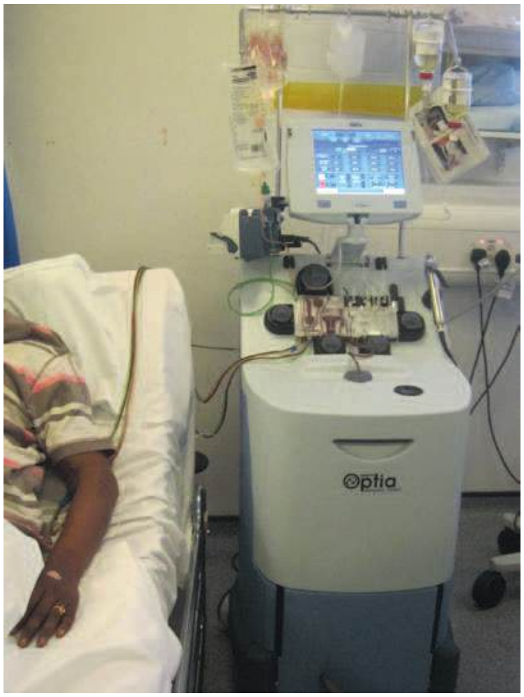

Fig. 99.2 A centrifugal cell separator in use for plasma exchange.

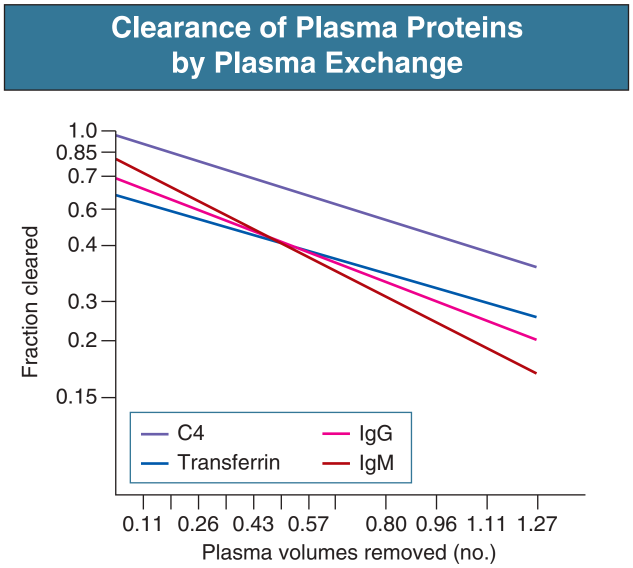

Fig. 99.3 Clearance of plasma proteins by plasma exchange. Clearance from the intravascular compartment varies with the plasma volume exchanged and among individual proteins. *IgG,* Immunoglobulin G; *IgM,* immunoglobulin M. (Modified from reference 2.)

TABLE 99.1 Practical Regimens for Plasma Exchange in Renal Disease

Indication	Anti–Glomerular Basement Membrane Antibody (anti-GBM) Disease	Small-Vessel Vasculitis	Cryoglobulinemia	Recurrent FSGS After Transplantation	HUS/TTP
Duration of treatment	Daily, at least 14 days until anti-GBM antibodies 20% of baseline	Daily or alternate daily, 7-10 days depending on clinical response	At least 7-10 days or until clinical response	Daily, at least 10 days initially, then continuing less frequently, often for months	Daily for 7-10 days or until platelet count 80-100 $\times 10^9$/l (sometimes needed twice daily)
Exchange volume	50 ml/kg each treatment	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease
Replacement fluid	Human albumin 5% (unless bleeding risk)	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease	Fresh-frozen plasma (FFP) or cryo-poor FFP
Additions to replacement fluid	20 ml 10% calcium gluconate (occasionally more), 3 ml 15% KCl if not dialysis dependent, heparin 2000-5000 U bolus, then 500-2000/h, (LMWH an alternative with bolus only) *or* citrate anticoagulation	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease	As for anti-GBM disease (may need more calcium because of increased volume of FFP-containing citrate)
Immunosuppression	See Chapter 24	See Chapter 25	See Chapter 21	See Chapter 29	See Chapter 29
Variations	FFP 5-8 ml/kg at end of exchange volume if hemorrhage risk (renal biopsy in last 48 h, lung hemorrhage, platelets <40 $\times 10^9$/l, fibrinogen <1.5 g/l); immunoadsorption may be as effective	As for anti-GBM disease Immunoadsorption may be as effective	As for anti-GBM disease	As for anti-GBM disease; may need to include replacement immunoglobulins if continuing long term; immunoadsorption may be as effective	

FSGS, Focal segmental glomerulosclerosis; *HCV,* hepatitis C virus; *HUS,* hemolytic-uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura.

TABLE 99.2 Investigations To Be Undertaken Before Every Plasma Exchange Session

Investigation	Action To Be taken
Platelet count	Caution with undertaking plasma exchange if platelet count less than 40 × 10^9/L unless disease itself associated with thrombocytopenia (e.g., aHUS/TTP), and use FFP as part of replacement fluid.
Plasma fibrinogen	If <150 mg/dl, should use FFP as part of exchange fluid.
Prothrombin time	If prolonged more than 2-3 seconds, use FFP as part of exchange fluids.
Serum calcium	If <2.1 mmol/l (<8.4 mg/dl), increase amount being provided with replacement albumin/FFP.
Serum potassium	Can be very variable depending on changing renal function in addition to plasma exchange treatment; adjust potassium replacement according to serum potassium.

aHUS, Atypical hemolytic-uremic syndrome; *FFP,* fresh-frozen plasma; *TTP,* thrombotic thrombocytopenic purpura.

to 4° C during the procedure, with the aim of precipitating cryoproteins. These techniques are not widely available.

Selective and specific immunoadsorption techniques are increasingly available. Protein A immunoadsorption has been used to remove immunoglobulin alone from plasma, without the need for replacement fluids and without depletion of clotting factors and complement (see Fig. 99.1C). Protein A selectively binds the Fc domains of immunoglobulin molecules, and the immunoadsorption columns can be repeatedly regenerated. Columns have been used for 1 year for a single patient on up to 30 occasions; however, the repeated acid stripping during regeneration reduces the efficacy of antibody binding. This technique has been used to treat conditions in which autoantibodies are thought to be important and usually in place of plasma exchange (e.g., Goodpasture disease, rheumatoid arthritis, lupus, or systemic vasculitis) and to remove anti-ABO or anti–HLA antibodies in highly sensitized transplant recipients. In general, the reported efficacy has been equal to that of plasma exchange, although if used over the long term, immunoadsorption can be much more cost-effective in single patients because there is no requirement for replacement albumin or plasma. Specific ligands also have been immobilized onto columns for more specific removal of potentially pathogenic serum factors; ligands used include anti–human IgG, C1q, phenylalanine, hydrophobic amino acids, acetylcholine receptor, β-adrenoreceptor peptides, and blood group–related oligosaccharides. Immunoadsorption of all varieties is not widely available because the initial column costs are high and few centers have much clinical experience. Costs of all other plasma exchange modalities are dominated by the costs of replacement albumin and plasma; equipment costs do not vary much among modalities, and all require skilled and trained nursing staff. Plasma filtration requires minimal extra support or training for dialysis nurses because the equipment is very similar to normal HD machines.

COMPLICATIONS

The complication rate of plasma exchange is not high.[3] The Swedish registry reported no fatalities during 20,485 procedures and an overall adverse incidence rate of only 4.3% of all exchanges (0.9% for severe adverse events) of which 27% were paresthesias, 19% transient hypotension, 13% urticaria, and 8% nausea.[4] The Canadian Apheresis Registry collected data on 144,432 apheresis procedures since 1981 and reported adverse events occurring in 12% of procedures (mostly minor) and overall in 40% of patients. Severe events occurred in only 0.4% of procedures. Three deaths were probably related directly to the procedure: one from a transfusion-related acute lung injury and two from complications from central venous catheters.[5] An overall complication rate of 1.4% has been reported in more than 15,000 treatments in patients receiving albumin and 20% in patients receiving FFP.[1,3,5,6] Plasma exchange by centrifugation had a lower risk for adverse events than by filtration.

Other complications directly attributable to plasma exchange include citrate-induced hypocalcemia (presenting with perioral tingling and paresthesias) and citrate-induced metabolic alkalosis. Citrate is usually present in FFP (up to 14% by volume) or is administered in the extracorporeal circuit as an anticoagulant; it binds free calcium in plasma. Symptomatic hypocalcemia can be averted by infusing 10 to 20 ml of 10% calcium gluconate during each plasma exchange. Alkalosis is rare and is caused by metabolism of citrate to bicarbonate and failure to excrete the latter in patients with renal impairment.

Plasma exchange predictably increases the risk for bleeding by depleting coagulation factors in patients receiving albumin as sole replacement colloid. Prothrombin time is increased by 30%, and partial thromboplastin time by 100% after a single plasma volume exchange. Patients at risk for bleeding (pulmonary hemorrhage, postbiopsy, postoperative) should receive FFP (300 to 600 ml) with replacement fluids. Dilutional hypokalemia is avoided by replacing potassium according to daily blood testing. An increased incidence of infection secondary to hypogammaglobulinemia has not been confirmed in recent series.[3-6] Sepsis related to intravenous access is the most common infectious complication of plasma exchange. Hypotension can occur for a variety of reasons related to extracorporeal circuits, sepsis, and allergic reactions, but also if saline is used for exchanges with a concomitant reduction in serum oncotic pressure during the procedure. Cascade filtration can lead to hemolysis (in up to 20% patients) but rarely necessitates transfusion.

MECHANISMS OF ACTION

The pathogenicity of autoantibodies in anti-GBM disease (Goodpasture disease) provided the impetus for development of plasma exchange therapy, but it is now clear that antibodies, although necessary, are not alone sufficient to cause the necrotizing glomerulonephritis (GN) in that disease. Plasma exchange, however, removes all large MW substances from the plasma in addition to antibodies, including complement components, immune complexes, endotoxin, lipoproteins, and von Willebrand factor (vWF) multimers. In animal studies, for example, complement depletion abrogates anti-GBM GN very effectively. Therefore plasma exchange may well have benefits in addition to clearance of autoantibodies.

The clearance of antibodies from patients is variable and depends on several factors, including the rate of equilibration of macromolecules between the intravascular and extravascular compartments. IgM antibodies are cleared more effectively than other classes of immunoglobulin because they are retained in the vascular compartment almost wholly. A rebound increase in antibody production will occur unless there is concomitant immunosuppression to prevent resynthesis.

Plasma exchange has been shown to remove immune complexes, which may have clinical significance in cryoglobulinemia and systemic lupus, and fibrinogen and complement components. There is no good evidence that removal of cytokines has any clinical significance. Plasma exchange reduces plasma viscosity, with consequent improved blood flow in the microvasculature. There is also some evidence for improvement in monocyte/macrophage function, alteration in lymphocyte function, and sensitization of antibody-producing cells to immune-suppressive drugs after plasma exchange.

INDICATIONS FOR PLASMA EXCHANGE

Evidence to support specific indications for plasma exchange is variable in quality. Direct comparison among RCTs can be unsatisfactory because of variations in dose and frequency of plasma exchange and in immunosuppressive and other adjunctive therapy. The American Society for Apheresis (ASFA) reviewed all indications for plasma exchange most recently updated in 2016 and summarized available trial data.[7,8] In this chapter, evidence from available randomized trials is discussed alongside observational data. The indications are summarized in Tables 99.3 and 99.4.

Anti–Glomerular Basement Membrane Antibody Disease (Goodpasture Disease)

Most patients can be depleted of pathogenic anti-GBM antibodies after 7 to 10 plasma volume exchanges if further antibody synthesis is inhibited by the concurrent use of cyclophosphamide and corticosteroids. Before plasmapheresis, the mortality from Goodpasture disease was higher than 90%, and only 11% of patients who were not dialysis-dependent at presentation survived with preserved renal function. The use of plasma exchange improved the outcome considerably: 70% to 90% of patients now survive. However, only 50% of survivors retain independent renal function and no more than 10% of those who are dialysis dependent at presentation. There has been only one small controlled trial of plasma exchange in the treatment of Goodpasture disease, which used a low intensity of plasma exchange.[7,9] A total of 17 patients were randomized to receive corticosteroids and cyclophosphamide, with or without plasma exchange. Only 2 of the 8 who received plasma exchange developed end-stage renal disease (ESRD) compared with 6 of the 9 who received drugs alone.

Long-term data from 71 patients with Goodpasture disease confirmed the benefit of a treatment regimen including plasma exchange because most patients with mild to moderate renal failure retained independent renal function over 10 to 25 years,[10] and renal recovery was possible even in some of those with the most severe renal disease. Very similar results were identified in the largest reported series from China. Combining all the available published data for patients with Goodpasture disease, 76% of patients presenting with serum creatinine below 5.5 to

TABLE 99.3 **Conditions for Which There Is Strong Evidence for the Benefit of Plasma Exchange**

Indication	Randomized Controlled Trials (No. Patients)	Controlled Trials (No. Patients)	Case Series (No. Patients)	Replacement Fluid	Comments
ANCA-associated systemic vasculitis	8 (300)	1 (26)	22 (347)	Albumin unless pulmonary hemorrhage or need to prevent coagulopathy	Proven benefit only in dialysis-dependent patients. Should consider daily exchanges in fulminant cases or with pulmonary hemorrhage.
Anti–glomerular basement membrane antibody disease	1 (17)	0	9 (468)	Albumin unless pulmonary hemorrhage or need to prevent coagulopathy	Minimum course 14 days to remove antibodies effectively. Especially beneficial in nonoliguric patients predialysis. Patients with creatinine >5.5 mg/dl (500 μmol/l) unlikely to benefit.
Cryoglobulinemia	1 (57) (and 1 using immunoadsorption; 17 patients)	0	24 (302)	Albumin	Long-term maintenance treatment needed in some patients. Ensure blood warmer on return lines or warm replacement fluids.
Thrombotic thrombocytopenic purpura	7 (301)	2 (133)	38 (1541)	Plasma or cryo-poor plasma	Daily. Often with corticosteroids. The only treatment that has improved mortality.
ABO-incompatible kidney transplantation	0	0	>21 (>750)	Albumin ± plasma (compatible with donor and recipient or AB)	Used pretransplant to reduce titers of antibodies and often continued for a few days after surgery to allow successful transplantation.
Antibody-mediated kidney transplant rejection	3 (61)	8 (342)	37 (727)	Albumin	Daily or alternate day. Usually with IVIG and sometimes enhanced immunosuppression
HLA desensitization for transplantation (in highly sensitized patients)	0	5 (441)	29 (466)	Albumin	Always in combination with immunosuppression and usually IVIG, and continued until cross-match negative. Usually five plasma exchanges are needed to reduce Ab levels sufficiently.

ANCA, Antineutrophil cytoplasmic antibody; *HLA,* human leukocyte antigen.

TABLE 99.4 Conditions for Which There Is Some Evidence for Plasma Exchange

Indication	Randomized Controlled Trial (No. of Patients)	Controlled Trials (No. of Patients)	Case Series (No. of Patients)	Replacement Fluid	Comments
Catastrophic antiphospholipid antibody syndrome	0	0	6 (109)	Plasma	Should be done daily. Combination of plasma exchange or IVIG, heparin, and corticosteroids (from registry data) gives best outcomes.
Recurrent FSGS after transplantation	0	3 (48)	49 (224)	Albumin	Sometimes in combination with rituximab. May need long-term maintenance treatment.
Atypical hemolytic-uremic syndrome	0	0	10 (200)	Plasma or cryo-poor plasma	Daily plasma exchange initially. Eculizumab preferred treatment if available.
Myeloma	5 (182)	0	8 (102)	Albumin	Daily or alternate day for 7-10 exchanges. Despite negative randomized trial in 2005, plasma exchange might be considered if high light-chain load, severe renal failure, and oliguria and light chains not depleted with urgent chemotherapy.
Rapidly progressive glomerulonephritis (may include patients with ANCA-associated disease in older literature)	7 (196)	0	21 (295)	Albumin	No good evidence for benefit in immune complex disease of any cause. Small case series of benefit in crescentic IgA vasculitis (Henoch-Schonlein purpura) with RPGN.
Scleroderma	0	3 (75)	7 (70)	Albumin	No good evidence for benefit, but some patients have reported improvement.
Systemic lupus (not nephritis)	1 (20)	1 (4)	14 (128)	Albumin	For cerebritis, lupus-associated TTP, severe hemolysis, or pulmonary hemorrhage.

ANCA, Antineutrophil cytoplasmic antibody; *FSGS,* focal segmental glomerulosclerosis; *IVIG,* intravenous immunoglobulin; *RPGN,* rapidly progressive glomerulonephritis; *TTP,* thrombotic thrombocytopenic purpura.

6.8 mg/dl (500 to 600 μmol/l) will retain renal function if treated with plasma exchange, in contrast to only 8% of those who are dialysis dependent at presentation. Diffuse alveolar hemorrhage, which occurs in up to 50% of patients and can be life threatening, is an independent indication for plasma exchange regardless of renal function.

Recommendation

All patients who are not dialysis-dependent at presentation should receive intensive plasma exchange with daily 4-liter exchanges initially for 14 days (regimen shown in Table 99.2). For dialysis-dependent patients, we recommend plasma exchange with immunosuppression only for those who have biopsy or clinical evidence of recent-onset disease. Pulmonary hemorrhage is an independent indication for plasma exchange. Treatment of Goodpasture disease is discussed further in Chapter 24.

Small-Vessel Vasculitis

The majority of patients with rapidly progressive glomerulonephritis (RPGN), other than anti-GBM disease, have small-vessel vasculitis with ANCA detectable in their serum, and there is increasing evidence that these autoantibodies are pathogenic. Plasma exchange was initially introduced in such patients because of the similarity of the histologic changes to those seen in Goodpasture disease and the supposition that removing ANCA itself may be of benefit. Several trials of plasma exchange in non–anti-GBM RPGN have been reported.[7,11] Most of the early trials included patients with a variety of diseases, used a low intensity of plasma exchange, and often excluded those with oligoanuria. These trials showed no overall benefit of plasma exchange in addition to conventional immunosuppression; however, those patients with the most severe disease did seem to benefit. Combining the results of the controlled trials, 31 of 42 (74%) dialysis-dependent patients treated with plasma exchange recovered renal function compared with only 8 of 25 (32%) treated with drugs alone. The most recent RCT (MEPEX Methylprednisolone or Plasma Exchange in severe ANCA-associated vasculitis) randomized 137 patients with ANCA-associated systemic vasculitis and serum creatinine above 5.5 mg/dl (500 μmol/l) to plasma exchange or intravenous methylprednisolone in addition to oral corticosteroids and cyclophosphamide.[11] Sixty-nine percent of patients recovered renal function when treated with plasma exchange compared with 49% of those receiving intravenous methylprednisolone, and significantly more patients were dialysis independent at the trial end-point, although this difference was not maintained at 3 years. MEPEX was the largest study in a meta-analysis of 387 patients, with creatinine levels ranging from 3.2 to 13.5 mg/dl. The addition of plasma exchange to standard immunosuppression in MEPEX was associated with reduced risk for ESRD or death. Patients with both ANCA and anti-GBM antibodies (so-called double-positive patients) and RPGN do not seem to respond well to plasma exchange and rarely, if ever, recover renal function.[12]

Recommendation

We perform plasma exchange in patients with small-vessel vasculitis who present with severe renal failure (serum creatinine >5.5 mg/dl [~500 μmol/l] or dialysis dependent) or pulmonary hemorrhage. The regimen is shown in Table 99.2.

Other Crescentic Glomerulonephritis

Crescent formation is a common histologic finding in a number of other patterns of GN, including postinfectious GN, GN associated with infective endocarditis, IgA nephropathy (IgAN), membranoproliferative glomerulonephritis (MPGN), and membranous nephropathy. Such patients were often included in studies of treatment of RPGN, and plasma exchange has been used in the treatment of a number of these conditions. Over 400 patients with such diseases have been treated with plasma exchange with no good evidence for any benefit in crescentic GN not caused by anti-GBM disease or vasculitis.[7,8] In crescentic IgAN, there are anecdotal reports of short-term benefit in patients with severe renal impairment, but longer term follow-up has proved disappointing. A single recent report showed some benefit of 5 to 10 plasma exchanges in preventing or reversing dialysis dependency in 12 patients with crescentic IgAN manifesting with RPGN, with measured decreases in circulating plasma IgA-IgG complexes.[13]

Recommendation

We reserve plasma exchange in IgAN and other GNs for patients with rapidly deteriorating renal function and extensive fresh crescents in the biopsy specimen.

Focal Segmental Glomerulosclerosis

Plasma exchange and protein A immunoadsorption have been used to treat patients with primary FSGS or recurrent disease after transplantation. The results have been less good in primary disease because less than 40% of patients achieve either partial or complete remission,[7,8,14] and we do not recommend plasma exchange in this setting. Plasma exchange for recurrent disease is discussed later and in Chapter 108.

Thrombotic Microangiopathies

In both HUS and TTP, endothelial activation leads to TMA, but through distinct mechanisms.

Infection-Associated Hemolytic-Uremic Syndrome

Infections leading to HUS are most recognized after enteropathogenic *Escherichia coli* from Shiga toxin production (Stx-associated HUS) and more recently described after *Streptococcus pneumoniae* (pHUS). The prognosis is generally good, especially in childhood. Most children will recover fully with supportive care and management of fluid and electrolyte imbalance and hypertension. Two controlled trials of plasma infusion (at least 10 ml/kg/day) in childhood HUS complicated by dialysis-dependent renal failure showed no clinical benefit (as determined by hypertension, renal dysfunction, and proteinuria) in either short- or medium-term follow-up.[15] There has been no study of plasma exchange in childhood Stx-associated HUS. Plasma exchange and infusion have not been subjected to any controlled trials in adult Stx-associated HUS, but uncontrolled observations suggest possible benefit.[7,16] The 2011 outbreak of enterohemorrhagic and Stx-producing *E. coli* O104:H4 in Europe led to 855 confirmed cases of HUS, but despite severe illness in many patients a retrospective analysis of 491 treated patients did not support any major benefit of plasma exchange in addition to intensive supportive care.[17]

Thrombotic Thrombocytopenic Purpura

Patients with TTP usually have a defective vWF cleaving protease (ADAMTS13), an enzyme that normally degrades large vWF multimers. The defect is typically due to an inherited deficiency or autoantibodies directed against the protease. Accumulation of vWF multimers leads to systemic platelet activation under conditions of high shear stress (the microcirculation) and thrombosis. The rationale for plasma infusion and plasma exchange in TTP is therefore to replenish vWF cleaving protease, to remove antibodies against the protease, and to remove the large vWF multimers from circulation. There are well-designed RCTs in the treatment of TTP.

The first prospective, controlled trial compared plasma infusion with plasma exchange (1 to 1.5 plasma volumes at least seven times in the first 9 days).[18] All patients received aspirin and dipyridamole. Of patients receiving plasma exchange, 47% had a platelet count exceeding 150×10^9 cells/l and no new neurologic features, compared with only 25% of those receiving plasma infusion over the first 2 weeks. At 6 months, survival was substantially better in those given plasma exchange (50% vs. 78%). More recent series using plasma exchange have reported mortality rates as low as 15%,[7] and there may be an association of reduced early mortality with more intensive plasma exchange. Renal impairment is not an independent predictor of poor outcome in TTP and does not in itself warrant more intensive therapy; clinical course does not correlate with ADAMTS13 activity. Fever, age older than 40 years, and hemoglobin below 9 g/dl have been associated with a worse outcome. Whether FFP or its cryosupernatant fraction is better as replacement fluid remains unclear.

TTP may also be induced by drugs, including ticlopidine, clopidogrel, mitomycin C, cyclosporine, tacrolimus, gemcitabine, and quinine, and the evidence for benefit of plasma exchange in this context is poor, with the exception of ticlopidine-induced TTP in which ADAMTS13 activity is severely depressed.[7]

Atypical Hemolytic Uremic Syndrome

The less common forms of HUS in which there is no clear diarrheal prodrome (atypical HUS [aHUS]) are now known to be commonly caused by mutations, polymorphisms, or acquired dysregulation of the complement pathway (including the development of autoantibodies), especially of factor H, factor I, and membrane cofactor protein, leading to uninhibited activation of complement. Other causes include infections or drugs that cause platelet or leukocyte activation and complement activation and consumption. Direct activation of endothelial cells also may be a cause. Plasma exchange and infusion have not been evaluated in controlled trials in aHUS, but uncontrolled series suggest benefit and current guidelines recommend early initiation of plasma exchange with FFP (see Chapter 29), both to remove potential complement inhibitors or autoantibody and to replace absent or defective complement regulators.[7] The introduction of the complement inhibitor eculizumab, a humanized anti-C5 monoclonal antibody, has revolutionized the treatment of aHUS and should now be the mainstay of management after urgently excluding other diagnoses and can replace plasma exchange. If eculizumab is not available, plasma exchange should be continued. TMA occurring after renal transplantation has also responded to plasma exchange.

Recommendation

We use plasma exchange in all adults with TTP or atypical HUS and perform all exchanges against FFP or cryo-poor FFP. In aHUS, plasma exchange continues until we can initiate eculizumab therapy.

Systemic Lupus

Plasma exchange has been used extensively in patients with lupus. Most studies have included patients with diverse patterns of disease, often with only mild renal involvement. A randomized, prospective trial could show no benefit of plasma exchange over conventional immunosuppression for renal, serologic, or clinical outcomes, both in the short and long term.[19] However, patients with crescentic lupus nephritis and those with the most severe renal dysfunction (dialysis dependency) were excluded. Anecdotal evidence suggests that plasma exchange may benefit patients with systemic lupus and crescentic GN, pulmonary hemorrhage, cerebral lupus, catastrophic antiphospholipid syndrome, severe antibody-induced hemolysis, lupus-associated TTP, or severe lupus unresponsive to conventional drugs or in patients for whom cytotoxic therapy has been withdrawn because of bone marrow suppression or other toxicity. Immunoadsorption may be more successful in the severe forms of lupus nephritis. A variety of techniques have been used, including standard protein A and antiimmunoglobulin absorption, and also phenylalanine, tryptophan, and dextran sulfate ligands, all of which bind immunoglobulin, rheumatoid factors, and immune complexes to varying degrees and all of which have been reported to induce remission in patients with severe disease after failure of conventional therapy.

Recommendation

We reserve plasma exchange for lupus patients with rapidly progressive renal failure and class IV lupus nephritis with crescents, for patients with severe neurologic involvement or severe hemolysis, for patients with myelosuppression who are thought unable to tolerate cyclophosphamide, and for those with catastrophic antiphospholipid syndrome or severe macrophage activation syndrome. The treatment of lupus is further discussed in Chapter 26.

Cryoglobulinemia

In type I cryoglobulinemia, usually associated with myeloma or lymphoma, a monoclonal immunoglobulin causes hyperviscosity and cryoprecipitation. Such antibodies are easily removed by plasma exchange, often with immediate clinical benefit. Cytotoxic agents are used simultaneously to inhibit further paraprotein production. There are no controlled trials of plasma exchange, but symptoms are closely related to the presence of the cryoimmunoglobulin, and hence treatment with plasma exchange appears effective.[7]

Patients with type II (mixed essential) cryoglobulinemia develop a monoclonal antibody (usually IgM) with specificity for a second, usually polyclonal, immunoglobulin. Type II cryoglobulins occur most commonly in association with hepatitis C virus (HCV) infection and lymphoma. The resulting immune complexes can be deposited in the microcirculation and are particularly associated with MPGN (see Chapter 21). Plasma exchange is effective at clearing the immune complexes, although the cryoglobulins often recur, and sustained benefit has not been clearly demonstrated. However, many of the acute features of cryoglobulinemia resolve with plasma exchange, particularly arthralgia, skin lesions, and digital necrosis, and patients with RPGN can recover renal function. Concomitant treatment with rituximab may prevent resynthesis of the cryoproteins, although some patients require long-term intermittent plasma exchange to control symptoms. Patients with HCV-associated cryoglobulinemia should now be treated with the newer antiviral agents, which are extremely effective in curing the viral infection, after which cryoglobulins usually disappear. A single RCT in 17 patients with HCV-associated cryoglobulinemia added immunoadsorption apheresis (with dextran sulfate) to antivirals and immunosuppression and showed significant clinical improvements, but this was from an era before the current antiviral agents.[20]

Cryofiltration apheresis (in which a normal plasma filter is used to separate plasma, which is then cooled to precipitate the cryoglobulin before return to the patient) selectively removes cryoglobulins, avoids large volumes of replacement fluids, and avoids deficiency of clotting factors, but needs to be combined with immunosuppression to prevent synthesis of further cryoglobulin. Few centers currently perform this technique, especially because of the widespread introduction of rituximab for cryoglobulinemia.

Myeloma

Plasma exchange almost certainly does not provide benefit in myeloma with either cast nephropathy or light-chain renal toxicity, and the most important therapy seems to be urgent initiation of chemotherapy, especially thalidomide, lenalidomide, or bortezomib. A large prospective, controlled trial randomized 97 patients with myeloma and progressive acute kidney injury (creatinine >200 µmol/l [2.3 mg/dl] with an increase >50 µmol/l over the previous 2 weeks despite conventional management) to receive plasma exchange (five to seven sessions of 50 ml/kg over 10 days) in addition to chemotherapy (vincristine, adriamycin, and dexamethasone [VAD] or melphalan and prednisolone).[21] This study showed no benefit of plasma exchange on mortality or recovery of renal function. However, patients had a wide degree of renal dysfunction and relatively few had a renal biopsy performed to confirm cast nephropathy. A retrospective review suggested that those with myeloma and high light-chain loads or severe renal failure may benefit if plasma exchange reduces light chains rapidly.[22] More recently a variety of studies in patients with renal disease and myeloma, especially using bortezomib-based regimens, have shown significant improvements even in patients with dialysis-requiring renal failure but without plasma exchange. An RCT of HD using novel membranes allowing the removal of large MW molecules and lengthy dialysis sessions (6 to 8 hours) failed to show any benefit (for survival or recovery of renal function) when added to modern chemotherapeutic regimens, which depleted light chains rapidly in the absence of plasma removal.

Recommendation

We no longer use plasma exchange in patients with myeloma but ensure effective chemotherapy is urgently initiated.

TRANSPLANTATION

Antibody-Mediated Rejection

A review of 157 patients included in five trials did not demonstrate any significant difference in the outcome of acute vascular rejection in patients treated with or without plasma exchange.[7,8] More recently, at least 11 trials including more than 400 patients with more clearly defined antibody-mediated rejection and case series of more than 700 patients have suggested that plasma exchange, combined with intravenous immunoglobulin (IVIG) and/or rituximab, but sometimes antithymocyte globulin, may effectively reverse 55% to 100% of such rejection episodes.[7]

There is no convincing evidence that plasma exchange has any role in the treatment of chronic rejection.

Anti–Human Leukocyte Antigen Antibodies

Highly sensitized patients with preformed anti-HLA antibodies have been treated before and after transplantation with plasma exchange or immunoadsorption to reduce cytotoxic antibody levels, often with high-dose IVIG.[7] Patients usually received intensive immunoadsorption or plasma exchange before transplantation to ensure a current negative crossmatch immediately before transplantation; some received longer term immunoadsorption or plasma exchange in combination with immunosuppressive therapies in the months preceding transplantation. Most recent studies have shown that donor-specific antibody titers of less than 1:32 are often depleted completely with preoperative plasma exchange, allowing successful renal transplantation. Such patients have an increased risk for antibody-mediated rejection—approximately 40%—but despite this, 90% have 1-year graft survival.

ABO-Incompatible Renal Transplantation

Plasma exchange is widely used to remove natural anti-A or anti-B blood group antibodies from the recipient before living donor transplantation from an ABO-incompatible donor. Various protocols are in use, but all rely on depletion of specific antibody over 2 to 5 days before transplantation by exchanging a single plasma volume for human albumin solution (in addition to routine immunosuppression, sometimes including rituximab and IVIG). Plasma exchange is sometimes continued for one or two sessions after transplantation or if antibody-mediated rejection occurs.[23] One-year graft survival rates of over 90% have been reported with such protocols, and although rejection episodes are more common than in ABO-compatible transplants, overall graft survival is similar. Patients with increasingly high antibody titers are being treated in this way. Immunoadsorption using synthetic A- or B-oligosaccharide epitopes linked to Sepharose has been developed, which specifically remove anti-A or anti-B antibodies, but any clinical benefit remains uncertain and the costs are high.

Recurrent Focal Segmental Glomerulosclerosis

Plasma exchange, double-filtration plasma exchange, and protein A immunoadsorption have been used to treat nephrotic syndrome after transplantation in patients with recurrent FSGS.[7,24,25] An incompletely defined circulating factor causing increased permeability of glomerular capillaries can be found in most patients with recurrent FSGS. There are no controlled trials of plasma treatments in recurrent FSGS, and most series are small. One study demonstrated an 82% reduction in urinary protein excretion in eight patients with recurrent nephrosis during plasma protein adsorption; however, the effect was transient and persisted for less than 2 months in seven of the eight patients.[24] Other investigators have obtained remissions (complete and partial) in up to 80% of patients and a significant reduction in graft loss resulting from recurrent disease compared with historic controls.[25] More intensive treatment regimens have led to more persistent remissions. All three apheresis modalities have been used prophylactically in patients deemed to be at high risk for recurrence, with variable success.

Recommendations

We recommend use of plasma exchange for patients with recurrent FSGS, initially daily for 7 to 10 days. If proteinuria is successfully reversed, this may need to be continued less frequently (weekly, then every other week, then monthly) for 2 to 3 days on each occasion. Management of recurrent FSGS is discussed further in Chapter 108.

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SELF-ASSESSMENT QUESTIONS

1. A patient with anti–glomerular basement membrane disease, serum creatinine 250 µmol/l, and pulmonary hemorrhage is being treated with plasma exchange and immunosuppression. Which complication can occur as a direct result of the plasma exchange?
   - **A.** Hypernatremia
   - **B.** Hyperviscosity
   - **C.** Hypocalcemia
   - **D.** Pulmonary embolism
   - **E.** Thrombocytosis
2. A 52-year-old woman presented with acute kidney injury and evidence of hemolysis and thrombocytopenia.
   Investigations:
   Hemoglobin: 86 g/l (115-165)
   White cell count: 4.2 × 10^9/l (4.0-11.0)
   Platelet count: 35 × 10^9/l (150-400)
   Serum creatinine: 238 µmol/l (60-110)

The results of remaining investigations are awaited. Which one of these diagnoses should lead to urgent initiation of plasma exchange?
   - **A.** Atypical hemolytic-uremic syndrome (HUS)
   - **B.** Infection-associated HUS
   - **C.** Myeloma
   - **D.** Scleroderma renal crisis
   - **E.** Systemic lupus
3. A 42-year-old man received a cadaveric kidney transplant under standard immunosuppression. Six weeks later his renal function deteriorated, an ultrasound scan was normal, and a kidney biopsy was performed. Which finding might lead to initiation of plasma exchange?
   - **A.** Antibody-mediated rejection
   - **B.** CD4-positive staining on the biopsy
   - **C.** Cyclosporine-induced microangiopathy
   - **D.** Recurrent membranous nephropathy
   - **E.** T cell–mediated cellular rejection

100

Immunologic Principles in Kidney Transplantation

Karl L. Womer

Important to an effective immune response is the ability of T cells to recognize a wide variety of nonself antigens, which allows for restrained immune activation and subsequent antigen-specific killing. This task is accomplished through the generation of a diverse repertoire of T cells in a single individual with specificity for an enormous number of potential foreign antigens presented as peptides on the surface of major histocompatibility complex (MHC) molecules. Variations in MHC structure among individuals increase the variety of peptides that can be presented to T cells, which protects the species as a whole by ensuring adequate T cell responses to a given foreign organism. Although slight, these MHC polymorphisms expressed in the donor kidney are recognized as foreign after kidney transplantation between nongenetically identical humans and induce alloresponses that in the absence of immunosuppression result in rejection of the allograft (see Box 100.1 for graft terminology). In this chapter, basic immunologic principles important to the field of kidney transplantation are reviewed.

ISCHEMIA/REPERFUSION INJURY

The immunologic responses after kidney transplantation occur in well-defined stages[1] (Fig. 100.1). Initial insults to the graft during donor organ procurement and subsequent transplantation into the recipient are referred to as ischemia/reperfusion injury (IRI). The pathogenesis of IRI involves biochemical, cellular, vascular endothelial, and tissue-specific factors, with inflammation as a common feature.[2] Acute ischemia leads to tissue damage and endothelial cell activation, which initiates the innate, or antigen-nonspecific, immune response. Innate immunity occurs rapidly, with limited specificity and without memory and includes both cellular elements (neutrophils, monocyte/macrophages, dendritic cells [DCs], and natural killer [NK] cells) as well as molecular components (pathogen-associated pattern recognition receptors [PRRs], complement proteins, cytokines, and chemokines [chemoattractant cytokines]).

PRRs expressed on innate immune cells enable them to recognize not only pathogen-associated molecular patterns but also endogenous markers of tissue injury or damage-associated molecular patterns (DAMPs) released by cells during IRI.[3] The sensing of DAMPs by PRRs results in release of cytokines, including tumor necrosis factor (TNF), interleukin (IL)-6, IL-1, type I interferons, chemokines, and the rapid expression of P-selectin (CD62P) by endothelial cells.[3] These events identify the transplant as a site of injury and inflammation, which stimulates the migration of donor-derived antigen-presenting cells (APCs) from the transplant to recipient lymphoid tissue and triggers the recruitment of inflammatory leukocytes into the graft. Neutrophil accumulation is the prime cellular mediator of microvascular plugging and local tissue destruction in IRI. In the next phase, monocyte/macrophage infiltration occurs and likely contributes to extension of early injury, as well as repair.[4]

These events contribute to delayed graft function and trigger the adaptive, or antigen-specific, phase of transplantation immunity (T cells and antibody-producing B cells) that can negatively affect long-term graft survival. NK cells likely also function as a bridge between innate and adaptive immunity in IRI, in part through bidirectional cross-talk between NK cells and DCs that plays a relevant role in the mechanisms leading to activation/maturation of DCs.[5] Likewise, although activation of the complement system plays an important role in IRI as a manifestation of the innate immune system, complement also regulates adaptive immune responses. T and B cells constitute the primary arms of the adaptive immune response, but they also play an important role in the acute and possibly healing phases of IRI.[2] These described immunologic events are not specific to allografts because they also occur in syngeneic grafts during IRI. However, innate immune responses alone are only rarely able to reject an allograft.

ANTIGEN PRESENTATION

Antigen-Presenting Cells

APCs are specialized cells capable of activating T cells. Antigen is endocytosed by APCs and then displayed by MHC molecules on their surface. T cells recognize and interact with the antigen:MHC complex to become activated. DCs, macrophages, and B cells are considered “professional APCs,” although DCs are the most potent at antigen presentation. Alloimmune responses are initiated by activation of APCs (mostly DCs) through innate immune recognition systems when there is a genetic difference between donor and recipient. DCs are highly versatile, determining whether the environment indicates that antigen should lead to an immune response or alternatively to tolerance.[6] In the graft and surrounding tissues after transplantation, DCs of either donor or host

BOX 100.1 Graft Terminology

Autograft (autologous graft): A graft from one part of the body to another. Examples include skin and vascular grafts. No rejection occurs.

Isograft (isogenic or syngeneic graft): A graft from one member of a species to a genetically identical member of the same species. Examples include grafts between identical twins and between members of the same inbred rodent strain. No rejection typically occurs.

Allograft (allogeneic graft): A graft between nonidentical members of the same species. Examples include grafts between unrelated or related nonidentical humans and between members of different inbred rodent strains. Rejection occurs by lymphocytes reactive to alloantigens on the graft (i.e., alloresponse).

Xenografts (xenogeneic grafts): A graft between members of different species. Examples include pig or baboon to human, and rat to mouse. Rejection occurs by lymphocytes reactive to xenoantigen on the graft (i.e., xenoresponse).

origin become activated and move to T cell areas of secondary lymphoid organs (SLOs).

The trafficking pattern of naïve T cells is restricted to SLOs, such as the lymph node and spleen, but also possibly to tertiary lymphoid structures formed in tissues after inflammation, including those in allografts.[7] They traverse from blood to lymphoid organs, where they pass through the T cell areas and become activated on encounter with donor antigen (alloantigen) presented by activated DCs in the context of MHC molecules. The movement of DCs and naïve T cells is coordinated to bring them into contact in the T cell areas of SLOs, which appears essential for effective priming.[8] Once activated, T cells leave SLOs via lymph vessels and enter the blood and peripheral tissues, particularly into sites of inflammation. B cells are activated when antigen engages their antigen receptors, initially in the border of T and B cell areas of SLOs, where helper T cell function is provided.[9]

Antigen-experienced memory cells may be activated by other APCs, such as graft endothelium.[10] Patients normally have no preexisting immunoreactivity to alloantigen, unless they have been exposed to alloantigen through pregnancy, blood transfusion, or prior transplantation. However, microbial antigens that cross-react with alloantigens (molecular or antigenic mimicry) may generate alloantigen-specific memory cells through a process termed *heterologous immunity.*[11]

T Cell Ontogeny and Major Histocompatibility Complex Specificity

Allografts induce alloimmune responses by the recognition of nonself antigens (e.g., MHC) from the graft by recipient T cells. During T cell ontogeny in embryogenesis, multilineage bone marrow precursors migrate to the thymus, where ultimate rearrangement of the T cell receptor (TCR) gene occurs, resulting in irrevocable T cell commitment. TCR gene rearrangement is random and ensures that a diverse repertoire of T cells exists to respond to the enormous number of potential foreign antigens.[12] The mature T cell repertoire is determined in the thymus by two processes, positive and negative selection. Positive selection depends on a certain degree of antigen-specific T cell affinity to self-MHC molecules expressed on thymic cortical epithelial cells. This process ensures that mature T cells will interact effectively with MHC to allow recognition of foreign antigen in the context of self-MHC. Negative selection occurs by deletion of T cells with excessively high affinity for self-peptide and MHC, thereby preventing release of high-affinity T cells with autoimmune potential.

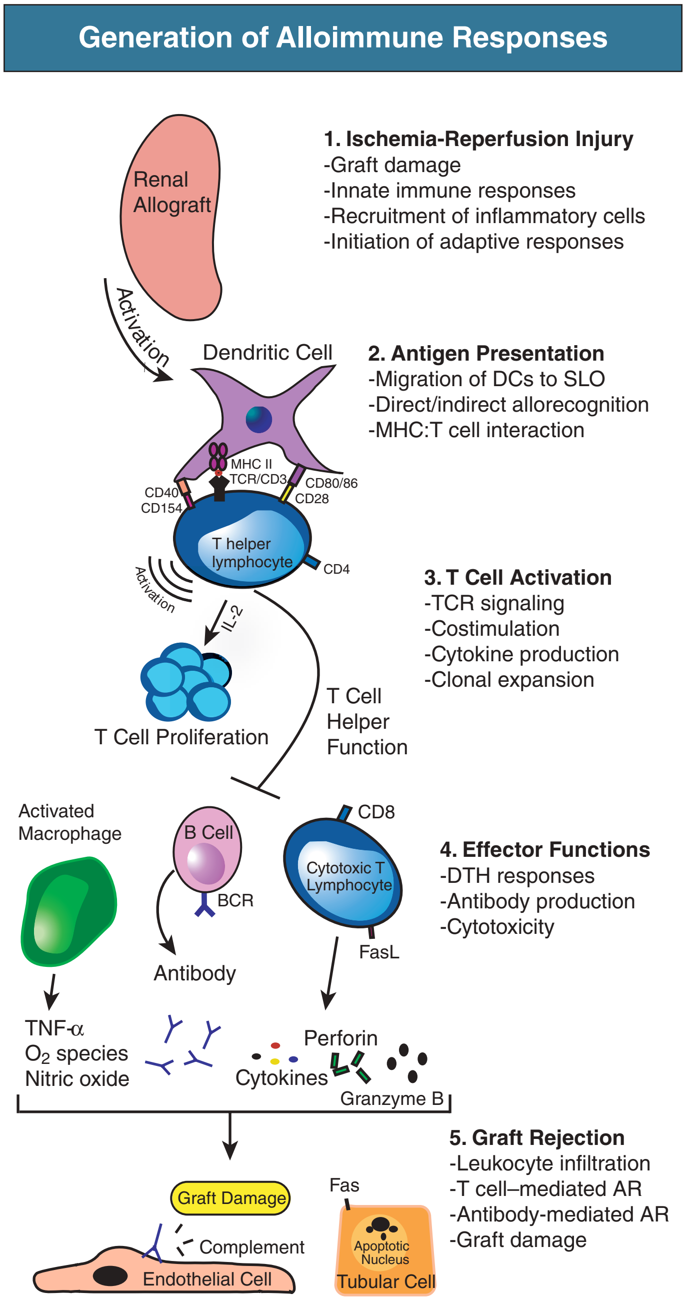
Generation of Alloimmune Responses
Renal Allograft
1. Ischemia-Reperfusion Injury
-Graft damage
-Innate immune responses
-Recruitment of inflammatory cells
-Initiation of adaptive responses
Activation
Dendritic Cell
2. Antigen Presentation
-Migration of DCs to SLO
-Direct/indirect allorecognition
-MHC:T cell interaction
MHC II
TCR/CD3
CD80/86
CD28
CD40
CD154
T helper lymphocyte
CD4
Activation
IL-2
3. T Cell Activation
-TCR signaling
-Costimulation
-Cytokine production
-Clonal expansion
T Cell Proliferation
T Cell Helper Function
Activated Macrophage
B Cell
BCR
CD8
Cytotoxic T Lymphocyte
4. Effector Functions
-DTH responses
-Antibody production
-Cytotoxicity
FasL
Antibody
TNF-α
O2 species
Nitric oxide
Perforin
Cytokines
Granzyme B
5. Graft Rejection
-Leukocyte infiltration
-T cell–mediated AR
-Antibody-mediated AR
-Graft damage
Fas
Graft Damage
Complement
Apoptotic Nucleus
Endothelial Cell
Tubular Cell

Fig. 100.1 Generation of alloimmune responses. Immunologic responses after renal transplantation represent a series of well-defined stages that result in rejection of the allograft in the absence of exogenous immunosuppression. Graft damage following ischemia/reperfusion injury during procurement and transplantation activates innate (antigen-nonspecific) immune responses, which recruit inflammatory cells and initiate adaptive (antigen-specific) immune responses. After activation, dendritic cells *(DCs)* of donor (direct pathway) or recipient (indirect pathway) origin migrate to secondary lymphoid organs *(SLO),* where they present alloantigen to T cells through major histocompatibility complex *(MHC)* structures on their cell surface. After T cell receptor *(TCR)* signaling and appropriate costimulation, T cells become activated to produce large amounts of cytokine and undergo clonal expansion. CD4 T cells provide help to B cells, CD8 T cells, and macrophages for the production of alloantibody, cellular cytotoxicity, and delayed-type hypersensitivity *(DTH)* responses, respectively. These effector functions result in destruction of the graft by acute rejection, which may be T cell- and/or antibody-mediated. *AR,* Acute rejection; *BCR,* B cell receptor; *IL-2,* interleukin 2; *TCR,* T cell receptor.

Mature T cells expressing their clone-specific TCRs exit the thymus as either CD4 or CD8 T cells. The TCRs of CD4 T cells (also called *T helper cells*) are selected to interact with class II MHC molecules, whereas the TCRs of CD8 T cells (precursors of cytotoxic T lymphocytes [CTLs]) interact with class I MHC molecules. A fundamental principle of immunology is that T cells do not recognize intact foreign proteins directly, but instead as peptides presented by self-MHC on APCs. However, allelic variation among MHC molecules from individual to individual is quite small, resulting in similarities between donor and recipient MHC structure. Thus unique to the transplant setting, recipient TCRs have a strong affinity for intact donor MHC molecules and can recognize them directly, which explains in large part the high proportion of T cells responding to alloantigen.[13] In fact, only 1/10^5 to 1/10^6 of T cells will respond to any given foreign antigen (e.g., peptide derived from tetanus toxin or influenza hemagglutinin). However, the frequency of T cells that respond to foreign MHC molecules (alloantigens) is 100-fold to 1000-fold higher (up to 5% to 10% of all T cells) because the thymus does not select for or against T cells to recognize the many MHC alleles not expressed by the graft recipient.[14]

Pathways of Allorecognition

Recipient T cells encounter alloantigen by either direct, semidirect, or indirect pathways of allorecognition (Fig. 100.2). As previously alluded to, direct antigen presentation involves recipient T cell recognition of donor MHC peptides in the peptide groove of intact donor MHC molecules on the surface of donor APCs. By this mechanism, donor APCs migrate from the graft to recipient lymphoid organs and activate alloreactive recipient T cells to initiate the alloimmune response. The best evidence of the potential importance of direct allorecognition to the alloresponse is the strong in vitro response generated in the mixed lymphocyte response, where lymphocytes are cultured with allogeneic APCs. It has been suggested that the direct pathway may be active only early after transplantation, when a large number of donor APCs are present in the allograft. However, direct antigen presentation also may occur later when recipient T cells recognize intact donor MHC molecules on cells of the graft (e.g., endothelium). Likewise, semidirect antigen presentation can occur through the transfer of intact donor MHC:peptide complexes contained in extracellular vesicles derived from the surface of donor APCs or from the graft to the surface of recipient APCs for presentation to recipient T cells, a process called *cross-dressing* or *cell nibbling*.[14] B cells also recognize intact donor MHC antigen via their B cell receptors.

Indirect antigen presentation is the physiologic mechanism of foreign antigen recognition. Foreign antigen is taken up by APCs, processed intracellularly, and then presented as peptides on MHC molecules. During indirect allorecognition after allotransplantation, donor MHC molecules and minor histocompatibility antigens (discussed in later section) are shed from the graft and processed by recipient APCs, where they are presented as peptides to recipient T cells in the context of recipient MHC molecules.[15] Donor MHC molecules are continually shed from the graft and presented by recipient APCs; thus indirect allorecognition may play a larger role in the late alloresponse, including during chronic rejection. However, the relative contribution of the direct, semidirect, and indirect allorecognition pathways to the alloresponse at different time points after transplantation remains the subject of debate.

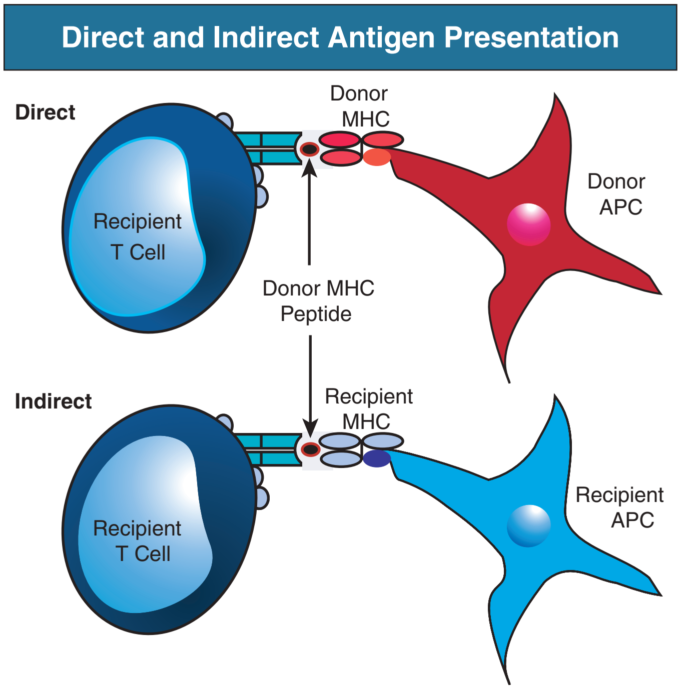

Fig. 100.2 Direct and indirect antigen presentation. In direct allorecognition, donor antigen *(shown in red)* is presented to recipient T cells as a peptide in the context of intact donor major histocompatibility complex *(MHC)* molecules on the surface of donor antigen-presenting cells *(APC)*. In indirect allorecognition, the donor antigen is processed by recipient APCs and presented as a peptide in the context of recipient MHC molecules.

Major Histocompatibility Complex

Class I and II MHC molecules are designed for presentation of antigen from different sources for different purposes (Fig. 100.3). The class I system is designed to sample cytosolic proteins to detect tumors or intracellular pathogens, such as virus and intracellular bacteria. Class I molecules are recognized by CD8 T cells and provide a surveillance mechanism to target infected or malignant cells for destruction by CTLs. The class II system is designed to sample extracellular proteins that have been taken up and processed by APCs. Class II molecules are recognized by CD4 T helper cells and allow for the generation of immune responses to invading pathogens that are phagocytosed by APCs. Cross-presentation is a process by which certain APCs take up, process, and present extracellular antigen on class I molecules to CD8 T cells.[16] This mechanism is necessary for immunity against tumors and viruses that do not infect APCs. MHC products also play other important roles, including the positive and negative selection of developing T cells described earlier, stimulation of naïve and memory T cells that is necessary for their survival (homeostatic proliferation), the induction of T cell tolerance and anergy (discussed later), and interaction with NK cells and other inhibitory/activating receptors.

The MHC gene locus (in humans, HLA) maps to the short arm of chromosome 6 and is divided into three regions: the class II region, the class III region, and the class I region. Only the class I and II regions encode proteins involved in antigen presentation. The key MHC genes are the class I genes (HLA-A, -B, and -C) and the class II genes (HLA-DP, -DQ, and -DR). The class I and II proteins share structural homology but are functionally different[17] (see Fig. 100.3).

Class I proteins are expressed on virtually all nucleated cells, although the amount expressed varies. Class II proteins have a more restricted cell distribution, generally limited to bone marrow–derived "professional" APCs, including DCs, B cells, macrophages, and Langerhans cells, but also other cells, including activated parenchymal and endothelial cells. Both class I and II antigens can be induced on a variety of cells by interferon (IFN)-γ in synergy with other cytokines during rejection episodes.

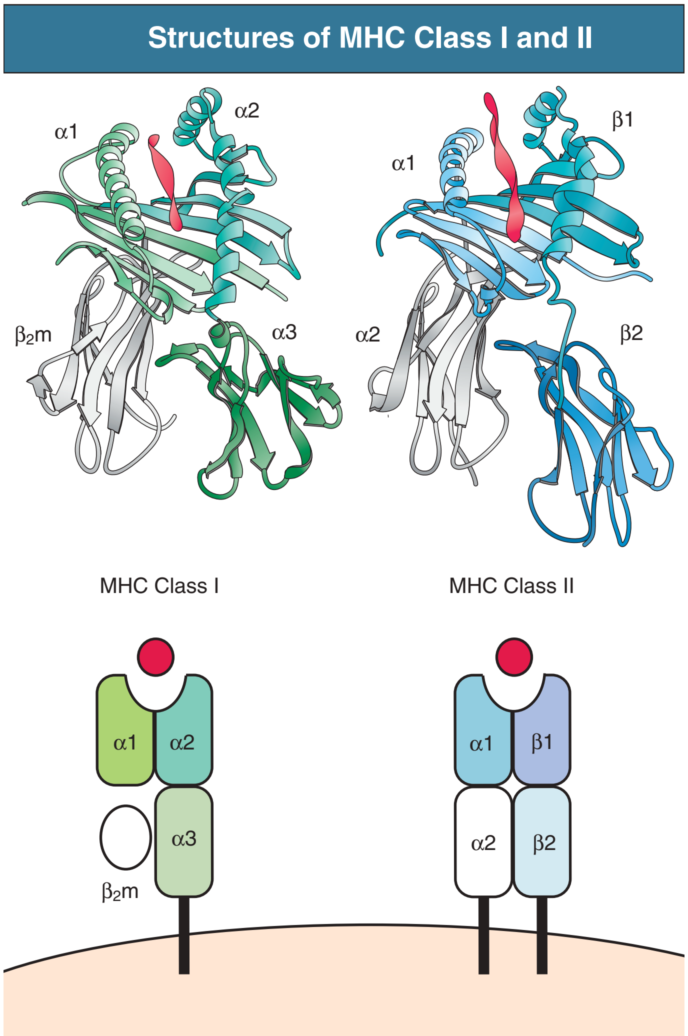

Fig. 100.3 Structures of major histocompatibility complex *(MHC)* **classes I and II.** MHC class I is composed of a heavy chain divided into α1, α2, and α3 domains noncovalently associated with β_2-microglobulin (β_2m). The α1 and α2 domains each form a long α helix and β sheet to make up the floor and walls of the peptide-binding groove *(peptide indicated by red ribbon).* MHC class II is a dimer composed of α and β chains. Each chain is divided into two domains, with α1 and β_1 domains forming the two α helices and β-pleated sheet that surround the peptide-binding groove.

Human Leukocyte Antigen Typing and Transplantation

MHC class I and II genes are highly polymorphic in the regions that encode the peptide-binding groove. These polymorphisms help ensure survival of the species by increasing the variety of peptides that can be presented to T cells.[18] However, these polymorphisms also predispose to allograft rejection because the antigen-presenting structures of one individual, though very similar, are still regarded as foreign by another nonidentical individual.

Originally, polymorphisms were defined by HLA serologic (antibody) typing using sera from multiparous women or persons who had received blood transfusions. The development of molecular biology techniques (polymerase chain reaction [PCR] sequencing) has allowed the analysis of the HLA allelic sequence diversity at the DNA level. By DNA typing, many more polymorphisms (alleles) have been identified: currently 3657 for HLA-A, 4459 for HLA-B, and 2208 for HLA-DR, with an increasing number of sequences added each year. An updated source for HLA alleles can be identified at www.ebi.ac.uk/imgt/hla.

Human Leukocyte Antigen Inheritance

HLA genes are inherited in a mendelian codominant fashion, meaning that a copy of each HLA gene (i.e., one haplotype) is inherited from each parent and expressed as antigens. HLA typing identifies the specific alleles carried by a person. The term *HLA matching* means assigning a donor kidney to a recipient with as few mismatches as possible. In kidney transplantation, efforts are made to match HLA-A, -B, and -DR genes and proteins. It can be predicted that siblings from the same set of parents will have a 25% chance of having zero mismatches, 50% chance of one haplotype mismatch, and 25% chance of two haplotype mismatches (Fig. 100.4).

Non–Major Histocompatibility Antigens

Minor histocompatibility antigens are normal proteins that are polymorphic within a given species. Even when a transplant donor and recipient are identical with regard to MHC genes, amino acid differences in these minor proteins can lead to rejection. Minor antigens are encoded by a large number of chromosomes and are presented only as peptides in the context of recipient MHC (indirect allorecognition). Minor antigens are responsible for the need for immunosuppression after donation between HLA matched but nonidentical twin siblings. The prototypic minor histocompatibility antigen, the male or H-Y antigen, is derived from a group of proteins encoded on the Y chromosome. Alloresponses to this antigen are responsible for rejection of male mouse skin grafts by otherwise identical female recipients and may explain observations of reduced long-term graft survival in human male-to-female donations.

MHC I–related chain A (MICA) antigens are surface glycoproteins with functions related to innate immunity. Exposure to allogeneic MICA during transplantation can elicit antibody formation.[19] ABO blood group glycolipids expressed on endothelial and red blood cells are other notable non-MHC antigens. Finally, immune responses to autoantigens have been associated with allograft damage.[20]

T CELL ACTIVATION

T cells are required for allograft rejection. Alloreactive T cells can be found in the naïve and memory T cell populations, but both require recognition of nonself MHC molecules to become activated. Reactions mediated by naïve T cells take longer to develop than those mediated by memory T cells, which can be generated more quickly and with higher numbers of cells (secondary response). During allograft rejection, both populations are activated simultaneously.

T Cell Receptor

Each T cell bears about 30,000 identical antigen-receptor molecules. Each receptor consists of two different polypeptide chains, termed the TCR α and β chains, which are linked by a disulfide bond. The genes encoding the TCR chains are members of the immunoglobulin supergene family, which are found on B, T, and NK cells. The α:β heterodimers are very similar in structure to the Fab fragment of an immunoglobulin molecule and account for antigen recognition by most T cells (Fig. 100.5). In contrast to the immunoglobulin receptors of B cells, TCRs do not recognize antigen in its native state, but instead recognize a composite ligand of a peptide bound to an MHC molecule. A minority of T cells bear an alternative, but structurally similar, receptor composed of a different polypeptide heterodimer (γ:δ).

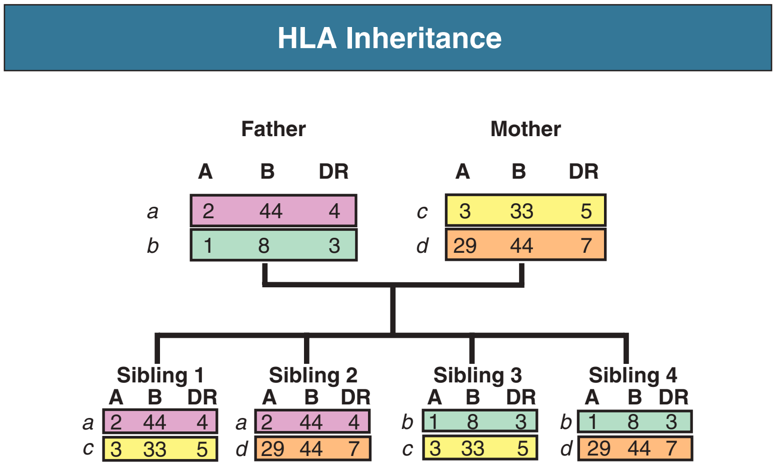

Fig. 100.4 Human leukocyte antigen (HLA) inheritance. HLA antigens are inherited and expressed in a mendelian codominant fashion, whereby one copy of each HLA gene called a *haplotype* (e.g., *a, b, c, d*) is inherited from each parent. Efforts are made to match both class I (HLA-*A* and -*B*) and class II (HLA-*DR*) antigens.

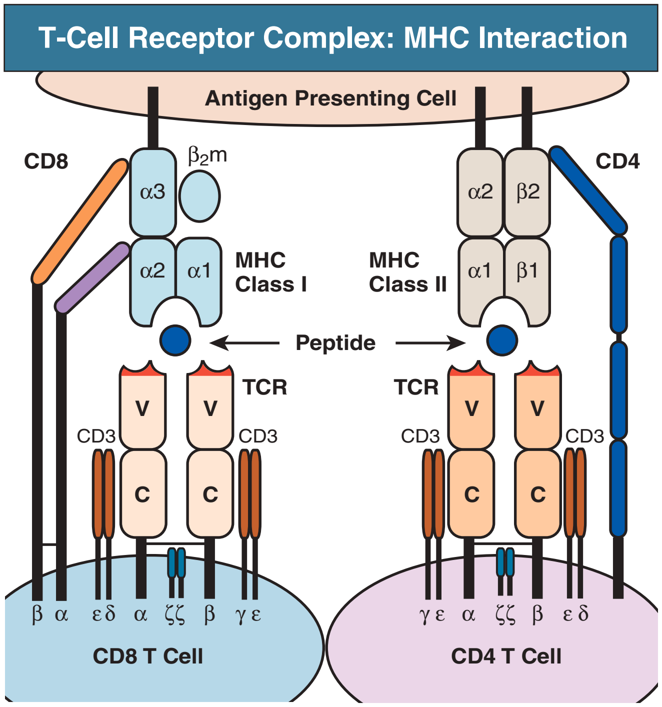

Fig. 100.5 T cell receptor complex: Major histocompatibility complex (MHC) interaction. Each T cell receptor *(TCR)* consists of an α and β chain linked by a disulfide bond. The α:β heterodimers are similar in structure to the Fab fragment of immunoglobulin molecules (Fig. 100.7), including variable *(V)* and constant *(C)* regions. Diversity in the T cell repertoire is encoded in the V domains of the α and β chains in three complementarity-determining regions (CDRs) that form the antigen binding site at the end of the TCR *(highlighted in red).* CD8 is a disulfide-linked α:β heterodimer or α:α homodimer, with each chain containing a single immunoglobulin-like domain linked to the membrane by a polypeptide chain. CD8 binds to the conserved region of the $\alpha3$ domain of the class I MHC molecule on antigen-presenting cells (APCs), but also interacts with the class I MHC $\alpha2$ domain probably through the α chain. CD4 is composed of four immunoglobulin-like domains and binds to a conserved site on the β_2 domain of the class II MHC molecule on APCs. Triggering of the TCR by antigen initiates a signaling cascade started by the signaling complex made up of CD3 γ, ε, and δ chains, as well as the ζ chain homodimer.

CD4 and CD8 Coreceptors

T cells fall into two major classes with different effector functions, distinguished by the expression of the cell-surface proteins CD4 and CD8 (Fig. 100.5). Both CD4 and CD8 have a cytoplasmic tail that can associate with signaling proteins important in T cell activation. CD4 and CD8 binding to MHC are required to make an effective response. Thus these molecules are called coreceptors.

T Cell Receptor Engagement of Antigen: Signal 1

The TCR α:β heterodimer recognizes and binds its peptide:MHC ligand[21] but cannot signal to the cell that antigen has bound. In the functional receptor complex, α:β heterodimers are associated with a complex of four other signaling chains (two ε, one δ, one γ) collectively called CD3 (see Fig. 100.5). Engagement of the TCR by MHC, along with the other required receptor engagements, initiates the signaling process from the CD3 complex, leading to cell proliferation and differentiation.[22]

T Cell Costimulation: Signal 2

Binding of the TCR:CD3 complex to the peptide:MHC complex on APCs delivers a signal that can induce the clonal expansion of naïve T cells only when the appropriate costimulatory signal is delivered (signal 2). CD8 T cells require a stronger costimulatory signal, and their clonal expansion is aided by CD4 T cells interacting with the same APC (i.e., T helper function). Costimulation is likely a checkpoint developed by the immune system to prevent the activation of self-reactive T cells that escaped negative selection in the thymus. Antigen binding to the TCR in the absence of costimulation not only fails to activate the T cell but also leads to a state called *anergy,* in which T cells become refractory to subsequent activation, or even undergo apoptosis (programmed cell death). Thus costimulation removes this inhibition and determines whether a T cell will proceed with clonal expansion and the development of effector functions. It is now clear that costimulatory molecules can provide positive or negative signals to T cells (Fig. 100.6). It is the integration of both positive and negative costimulatory signals during and after initial T cell activation, dictated by their temporal and spatial expression patterns, that ultimately determines the fate and functional status of the T cell response.[23]

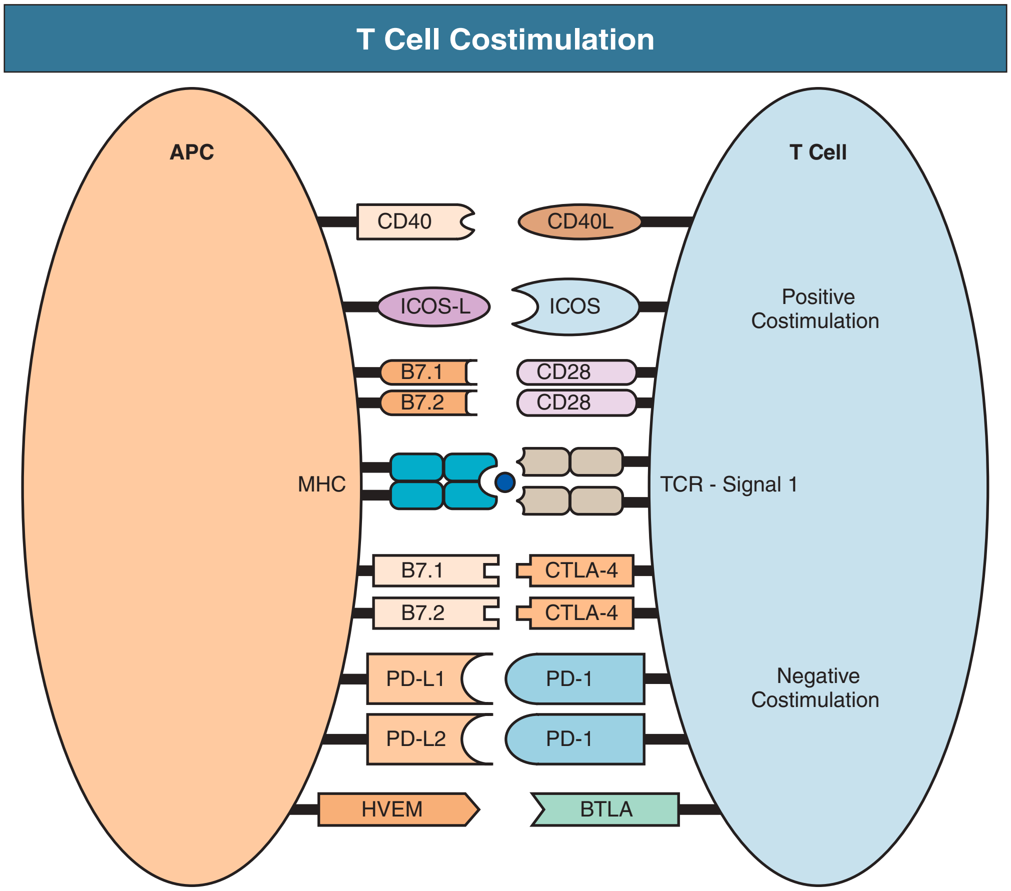

Fig. 100.6 T cell costimulation. Binding of the T cell receptor *(TCR):CD3* complex to the peptide:major histocompatibility complex on antigen-presenting cells *(APCs)* delivers a signal that can induce the clonal expansion of naïve T cells only when the appropriate costimulatory signal is delivered (Signal 2). CD28 and its ligands, B7.1 (CD80) and B7.2 (CD86), are the best-characterized costimulatory molecules and are members of the immunoglobulin superfamily. Ligation of CD28 by B7 molecules is required for clonal expansion of naïve CD4 T helper cells. Once activated, T cells express increased levels of CTLA-4 (CD152). CTLA-4 has an affinity 10 to 20 times greater than that of CD28 for B7 molecules and thus binds most or all of the B7 molecules, effectively shutting down the proliferative phase of the response. B and T lymphocyte attenuator *(BTLA)* and programmed death-1 (PD-1) are two other costimulatory molecules of the immunoglobulin superfamily that when engaged by their ligands (herpes virus entry mediator [HVEM] and PD-L1/PD-L2, respectively) provide inhibitory signals to T cells. Activated T cells express a number of proteins that contribute to sustaining or modifying the costimulatory signal to drive clonal expansion and differentiation. The inducible costimulatory molecule (ICOS) is a CD28 homologue, but unlike CD28 is not constitutively expressed on naïve T cells. Rather, ICOS is induced only after T cell activation. Engagement of ICOS by B7H enhances T cell proliferation, cytokine production, and survival. Costimulatory molecules of the tumor necrosis factor (TNF) and TNF-R superfamily include CD40 ligand (CD40L, CD154) on T cells and its receptor CD40 on APCs, such as B cells, DCs, macrophages, and endothelial cells. Binding of CD40 by CD40L, which is upregulated by CD28 signaling, transmits activating signals to the T cell but also activates the APCs to secrete proinflammatory molecules and to express B7 molecules, thus stimulating further T cell proliferation.

T Cell Clonal Expansion and Differentiation

In most instances, the number of T cells that react to a given antigen is quite small. Therefore effective immune responses require clonal expansion and differentiation of T cells. These processes are driven by cytokines, including IL-2, which acts on the T cell in an autocrine fashion or by paracrine secretion to neighboring T cells. Activated T cells produce the alpha subunit (CD25) of the IL-2 receptor (IL-2R), enabling a fully functional signaling receptor composed of α, β, and γ subunits that can bind IL-2 with high affinity, which in turn initiates another pathway mediated in part through the protein mammalian target of rapamycin (mTOR). New proteins are then translated, allowing the cell to progress from the G1 phase to the S phase of the cell cycle, resulting in proliferation. Table 100.1 lists selected cytokines involved in allograft rejection, their sources, and their effects.

CD4 and CD8 T cells have different roles during immune responses. CD4 T cells are both effectors and regulators and have heavy cytokine secretion. After prolonged stimulation, CD4 T cells tend to express groups (signatures) of several cytokines, probably depending on the local environment, nature of the antigen, and type and activation status of the APC. These different T helper (Th) subsets, each with unique transcription factor and cytokine signatures, are referred to as Th1,

TABLE 100.1 **Cytokines Involved in Allograft Rejection**

Cytokine	Source	Biologic Activity
IL-1	Macrophages, DCs, ECs, NK cells	Proinflammatory, adhesion molecule expression on ECs, NK cell function
IL-2	Activated T cells	T cell proliferation, CTL and NK cell function, Treg maintenance, immunoglobulin production by B cells, AICD of activated T cells
IL-4	Activated T cells	Activated T and B cell proliferation, Th2 differentiation, allergic responses, MHC II upregulation on B cells
IL-6	T cells, macrophages, ECs	Proinflammatory and antiinflammatory, acute-phase responses
IL-10	T cells, macrophages, DCs	Antiinflammatory, suppression of APC function, NK cell inhibition
IL-12	Macrophages, DCs	Proinflammatory, Th1 differentiation, NK cell and CTL activity, IFN-γ and TNF-α production by NK and T cells
IL-15	Epithelial cells, stromal cells, macrophages	NK cell proliferation, T cell proliferation, memory T cell survival
IL-17	T cells	Proinflammatory and allergic responses, Th17 function, cytokine production from many cell types
IFN-γ	Activated Th1 cells, CTLs, DCs, NK cells	MHC expression by EC, macrophage function, Th1 differentiation, Th2 suppression, adhesion and binding of T cells to ECs, NK cell activity
TGF-β	T and B cells, macrophages, platelets	Antiinflammatory, wound healing, fibrosis
TNF-α	Macrophages, T and B cells, ECs, NK cells	Proinflammatory, acute phase responses, cytotoxicity

AICD, Activation-induced cell death; *CTL,* cytotoxic T lymphocytes; *DC,* dendritic cells; *EC,* endothelial cells; *IL,* interleukin; *NK,* natural killer; *Treg,* regulatory T cells; *Th,* T helper (cell); *IFN-γ,* interferon-γ; *TNF-α,* tumor necrosis factor-α; *TGF-β,* transforming growth factor-β.

Th2, Th9, Th17, and Tfh (follicular help) populations. The Th1 clones produce IL-2, IFN-γ, and lymphotoxin, and Th2 clones produce IL-4, IL-5, and IL-10. Th1-derived cytokines are growth and maturation factors for CTLs (especially IL-2) and macrophages (particularly IFN-γ), whereas Th2-derived cytokines act similarly on B cells. Th2 cells also mediate B cell class switching to differentiation to Th9 cells requires TGF-beta and IL-4. These clones secrete IL-9 and recruit mast cells. T helper 17 (Th17) cells are a subset of T helper cells stimulated by TGF-β and a number of other cytokines and produce IL-17, IL-21, and IL-22.[24] Th17 cells and IL-17–producing CD8 T cells have the capacity to play a role in rejection, particularly in the absence of a Th1 response. Tfh cells are found in lymph nodes and are important for B cell maturation, possibly playing a role in antibody-mediated rejection. CD8 T cells are usually cytotoxic but can be divided into Tc1 and Tc2 subsets, in addition to IL-17–producing CD8 T cells.[3]

In addition to T cells that promote immune responses, there are populations that regulate or control immune responses termed *regulatory T cells* (Tregs). Tregs are thymus-derived T cells that can be induced in the periphery and exhibit sustained expression of the transcription factor, Foxp3.

Memory Cells

Although there is limited knowledge of how memory T cells are generated or maintained, these cells are an important component of the immune response to infectious pathogens. In clinical transplantation, previous sensitization to alloantigen with formation of memory cells is associated with increased risk for rejection and premature graft failure. Memory responses to alloantigen frequently occur at the time of blood transfusion, pregnancy, and transplantation. However, alloantigen memory responses can develop as a result of antigen cross-reactivity during response to infection (heterologous immunity), but also by normal proliferation in response to lymphopenia induced by leukocyte-depleting agents in transplant recipients.

The principle of immunologic memory is that the immune response to a previously encountered antigen is swifter and more effective than the response to a new antigen. Memory cells are more easily activated than naïve T cells, with lower requirement for costimulation, and in addition, produce more cytokines. Furthermore, there is an increase in antigen-specific T cell frequency after exposure to a given antigen. Finally, exposure to antigen leads to a refinement of the antibody repertoire, resulting in a more effective memory response. Effector memory T cells are specialized for quickly entering inflamed tissues because they can rapidly mature into effector T cells and secrete larger amounts of cytokines after restimulation. Central memory T cells likely remain in the SLOs and do not produce as much cytokine.[25] Memory cells are believed to persist after an initial immune response through expression of the antiapoptotic genes *Bcl-2* and *Bcl-xL,* which are induced primarily by IL-2 and CD28 stimulation, although IL-15 also may provide survival signals. Long-term memory cell survival is likely a function of periodic interactions with self-MHC:peptide complexes on APCs (i.e., homeostatic proliferation).

EFFECTOR FUNCTIONS

Once activated and expanded, T cells exert effector functions that result in destruction of graft tissue. Although T cells are essential for acute organ allograft rejection, the precise mechanisms by which they mediate graft injury are uncertain. CD4 T helper cells may release numerous cytokines that affect the alloimmune response. For example, they may promote delayed-type hypersensitivity (DTH) responses that involve stimulating production of nitric oxide, reactive oxygen species, and TNF-α by macrophages. T cell cytokines may act directly on parenchymal cells or indirectly through effects on the endothelium and vascular supply. TNF-α and TNF-β exert local cytotoxic effects on receptors on the graft, including endothelial cells (TNF-R1) and tubular cells (TNF-R2). IFN-γ, the prototypical Th1 cytokine, is released by both CD4 and CD8 T cells during rejection. IFN-γ induces MHC class II expression on endothelium and MHC class I expression on vascular endothelial cells, epithelial cells, and parenchymal cells in the graft. The precise role of class II expression by donor cells in the graft remains controversial because mouse kidney grafts lacking class II are rejected more vigorously. Although IFN-γ is strongly associated with rejection, it probably has other signaling roles that actually help stabilize the graft. As cytokine production by CD8 T cells is generally lower than that of

CD4 T cells, production of cytokines such as IL-2 by CD4 T cells provides help for the generation of CTLs from their CD8 T cell precursors. CD4 T cells may themselves become cytolytic T cells, by mechanisms similar to those used by CD8 CTLs (described later). CD4 T cells also provide help to B cells to enhance their production of alloantibodies. Finally, Tregs have important roles in suppressing immune responses and maintaining tolerance.

Cytologic T Lymphocyte Differentiation and Function

With rare exceptions, virtually all CTLs are MHC class I–restricted CD8 T cells. Activated CTLs possess two mechanisms to kill target cells that require cell-to-cell contact.[26] First, they release perforin and granzyme B from specialized lytic granules of most CTLs and NK cells. Perforin, like activated complement, has the ability to induce transmembrane pores. The granzyme B–perforin complex enters the cell through the mannose 6-phosphate receptor, and, after internalization, perforin allows granzyme B to enter the cell through the vesicle surface to induce programmed cell death through apoptosis.[27] A third cytotoxic protein, granulysin, also induces apoptosis in target cells. The second mechanism is by Fas/Fas ligand (FasL) interactions. Fas (CD95) is a member of the TNF-R family and is the surface mediator of a pathway that when activated by FasL on activated CTLs, induces the target cell to undergo apoptosis. Both pathways induce apoptosis through activation of the caspase cascade in target cells. As previously alluded to, CD8 CTLs also release several cytokines that exert direct cytotoxic effects, including IFN-γ, TNF-α, and TNF-β.[28] Effector CD4 T cells that can mediate class II–restricted cytotoxicity to minor antigens also have been detected.

Macrophage Activation

Macrophages are recruited to the graft in response to proinflammatory cytokines, such as IL-1 and IL-6. The activated macrophage is an important mediator of DTH responses, which leads to localized tissue destruction. Resting macrophages must be activated to exert full inflammatory and cytopathic effects. Th1 cells provide help for this activation by interaction of CD40L with CD40 on the macrophage and by production of IFN-γ, which sensitizes the macrophage to respond to IFN-γ. It is possible that T cell membrane–associated TNF-α and TNF-β can substitute for CD40L. CD8 T cells also produce IFN-γ and can activate macrophages. Production of TNF-α, oxygen radicals, and nitric oxide by activated macrophages are important for their cytopathic effects. Activated macrophages also can produce IL-12, which directs the differentiation of activated naïve CD4 T cells into Th1 effector cells. Macrophage activation is inhibited by cytokines such as transforming growth factor-β (TGF-β) and IL-10, many of which are produced by Th2 cells.

The Humoral Immune Response

The extracellular spaces of the body are protected by the humoral immune response, in which antibodies produced by B cells cause the destruction of extracellular microorganisms and prevent the spread of intracellular infections. Membrane-bound immunoglobulin on the B cell surface serves as the antigen receptor and is known as the *B cell receptor* (BCR) (Fig. 100.7). It is associated with antigen-nonspecific signaling molecules, Igα and Igβ. Immunoglobulin of the same specificity is then secreted as antibody by terminally differentiated B cells (i.e., plasma cells). B cells develop in the bone marrow and undergo sequential rearrangement of immunoglobulin gene segments to generate a diverse repertoire of antigen receptors that can interact with antigen in their environment. In a process similar to that for developing T cells in the thymus, immature B cells that are strongly self-reactive at this stage are inactivated by negative selection. In contrast to T cells, new B cells are continually produced in adulthood.

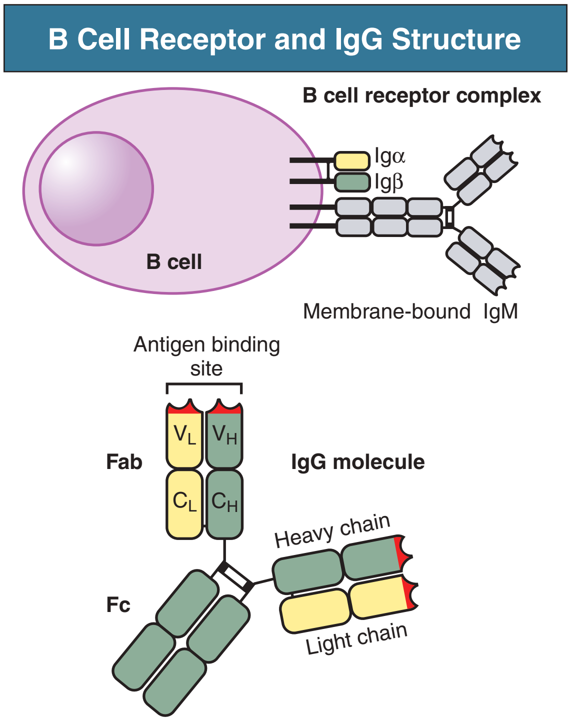

Fig. 100.7 B cell receptor and immunoglobulin G *(IgG)* structure. B cell surface membrane-bound immunoglobulin M *(IgM)* associated with antigen-nonspecific signaling molecules, Igα and Igβ, forms the B cell receptor complex. The IgG molecule is made up of four polypeptide chains, comprising two identical light (L) chains *(yellow)* and two identical heavy (H) chains *(green)*. Each of the four chains has a variable *(V)* region at its amino terminus (Fab portion), which contributes to the antigen binding site, and a constant *(C)* region (Fc portion), which determines the isotype. The V domains contain hypervariable regions that determine antigen specificity called *complementarity-determining regions (highlighted in red)*.

B cell activation requires binding of antigen to the BCR. Although some polysaccharides and polymeric proteins activate B cells directly, antibody responses to most proteins require both binding of the antigen to the BCR and interaction of the B cell with antigen-specific helper T cells. Helper T cells recognize peptide fragments derived from the antigen that are internalized and presented as peptide:MHC class II complexes on the B cell surface. Helper T cells stimulate B cells through the binding of CD40L with CD40 on B cells, through interaction of other TNF:TNF-R family ligands and by the directed release of cytokines. Although these helper T cells are generally of the Th2 subset, Th1 cells also can assist with B cell activation. Activated B cells also provide signals to T cells via B7 family molecules that promote their continued activation.

Secretion of antibodies, which bind pathogens or their toxic products, is the main effector function of B cells in adaptive immunity. The antibody molecule has two separate functions: one is to bind specifically to molecules from the pathogen that elicited the immune response, and the other is to recruit other cells and molecules to destroy the pathogen bound by the antibody. The five major classes of antibodies are IgM, IgD, IgG, IgA, and IgE. IgG is by far the most abundant immunoglobulin and has several subclasses (IgG1, 2, 3, and 4). The IgG molecule is made up of two identical light (L) and two identical heavy (H) chains that form a flexible Y-shaped structure (see Fig. 100.7). Each of the four chains has a variable (V) region at its amino terminus (Fab portion), which contributes to the antigen binding site, and a constant

(C) region (Fc portion), which determines the isotype. The V regions of a given antibody contain hypervariable segments that determine antigen specificity by forming a surface complementary to the antigen referred to as *complementarity-determining regions* (CDRs).

After appropriate activation and help from T cells, previously naïve B cells proliferate, secrete IgM, and then undergo differentiation into memory B cells or antibody-secreting plasma cells. During this process, the antibody isotype can change (to IgA, IgG, or IgE) in response to cytokines released by helper T cells, and the antigen-binding properties of the antibody can change by somatic hypermutation of the V region genes. T helper cells selectively activate higher affinity mutants, resulting in high-affinity plasma cells and memory B cells. Antibodies function in several different ways once bound to their target antigen. These mechanisms include fixation of complement, opsonization for phagocytosis by Fc receptor (FcR)-positive cells (including B lymphocytes, NK cells, macrophages, and neutrophils), opsonization for cell lysis by cells capable of antibody-dependent cellular cytotoxicity (NK cells, macrophages, neutrophils, and eosinophils), and induction of eosinophil degranulation.

Natural Killer Lymphocytes

NK cells are a subset of peripheral lymphocytes that share developmental and functional features with CD8 T lymphocytes.[29] Unlike T or B cells, NK cells do not possess a clonotypically distributed, antigen-specific cell surface receptor that is generated by gene recombination. Instead, NK cells use receptors that recognize the loss of HLA class I molecules on susceptible targets. Thus NK cells can recognize when self-MHC class I is absent, the so-called "missing self," which triggers their activation. Peripheral NK cells are mature, do not require costimulation and differentiation as with T cells, and immediately release cytotoxic granules and inflammatory cytokines such as TNF-α and IFN-γ on detection of relevant targets. Given the strong cytolytic function and potential for autoreactivity, NK cell activity is tightly regulated. Mechanisms of activation include cytokines, binding of antibody to FcRs, and binding of ligands to activating and inhibitory receptors. The role NK cells play during rejection is still being investigated.[30,31]

Termination of the Immune Response

Mechanisms are also in place to terminate the immune response. Once the source of antigen is destroyed, there are still preexisting effector cells that can cause antigen-specific tissue damage and must be deactivated. Several mechanisms accomplish this task. Once terminally mature, DCs switch cytokine production from IL-12 to IL-10, favoring the generation of regulatory mechanisms that suppress the function of effector T cells. As mentioned previously, induction of CTLA4 after T cell activation provides regulatory feedback to provide inhibitory signals to T cells that induce anergy. In the absence of continued cytokine production, T cells lack the necessary growth factors and undergo passive cell death. Finally, activated T cells undergo activation-induced cell death (AICD) by the expression of Fas and FasL on their surface. Engagement of Fas by its ligand triggers a death signal, leading to apoptosis of the cell. Although IL-2 is important for the clonal expansion of T cells, it is also essential for AICD, as well as the proliferation of Tregs, which are important in maintaining self-tolerance after removal of effector T cells.[32]

ALLOGRAFT REJECTION

Allograft rejection is defined as tissue injury produced by the effector mechanisms of the alloimmune response, leading to deterioration of graft function.[33] There are two types of rejection: T cell–mediated rejection (TCMR) and antibody-mediated rejection (AMR). Both types of rejection can be early or late, fulminant or indolent, and isolated or concomitant and can share pathologic features on biopsy.[3]

Recruitment of Cells into the Interstitium of Kidney Allografts

Allograft rejection is caused by several cellular elements of the immune system, including T cells, macrophages, B cells, plasma cells, eosinophils, and neutrophils. Although there are a variety of target cells in the graft, endothelial and tubular cells are particularly affected by these mediators. T cells serve as the main effectors and regulators of the alloimmune response, and macrophages serve as possible effectors but also aid in the removal of apoptotic cells. B cells and plasma cells serve in the production of alloantibodies, and neutrophils likely cause significant damage, particularly during AMR.

A three-step model has been proposed to explain the entry of cellular infiltrates into the allograft: tethering, adhesion, and transmigration. Table 100.2 lists several of the proteins involved in this process. The endothelium of postcapillary venules in the graft serves as the entry

TABLE 100.2 Proteins Involved in the Recruitment of Leukocytes into Allografts

Protein Type	Name	Ligand	Function
Selectins	CD62L (L-selectin) CD62L (P-selectin) CD62L (E-selectin)	Sialylated glycoproteins	Initial rolling of leukocytes on endothelium
Chemokines	MCP-1/CCL2	CCR2	Recruitment of monocytes, immature DCs, T cells, and NK cells
	MIP-1α/CCL3	CCR1	Recruitment of monocytes, immature DCs, T cells, and neutrophils
	RANTES/CCL5	CCR1, CCR4, CCR5	Recruitment of monocytes, DCs, T cells, NK cells, and neutrophils
	IL-8/CXCL8	CXCR1, CXCR2	Recruitment of neutrophils
	MIG/CXCL9	CXCR3	Recruitment of activated memory T cells
	IP-10/CXCl10	CXCR3	Recruitment of activated memory T cells
	Lymphotactin/XCL1	XCR1	Recruitment of T cells
Immunoglobulin superfamily	CD54/ICAM-1	LFA-1	Tight adhesion of leukocytes to endothelium
	CD102/ICAM-2	LFA-1	Tight adhesion of leukocytes to endothelium (not as strong as ICAM-1)
	CD50/ICAM-3		
	CD106/VCAM-1	VLA-4	Rolling and tight adhesion of leukocytes to endothelium
	CD31/PECAM-1	CD31	Extravasation of leukocytes across endothelium

DCs, Dendritic cells; *ICAM,* intercellular adhesion molecule; *LFA-1,* leukocyte function–associated antigen 1; *NK,* natural killer; *PECAM,* platelet endothelial cell adhesion molecule; *VCAM,* vascular cell adhesion molecule; *VLA-4,* very late antigen-4.

point of recipient leukocytes from the bloodstream. Selectins cause leukocytes to roll along the vessel wall, a process called *tethering*. Leukocytes slowed by selectins come into more prolonged contact with the endothelium and are stimulated by chemokines. As chemokines bind to receptors on leukocytes, they activate the adhesion function of integrins.

The best characterized integrin, LFA-1, is expressed on most leukocytes. The ligands for LFA-1, including intercellular adhesion molecule (ICAM)-1, -2, and -3 (immunoglobulin superfamily gene members), are expressed weakly on resting endothelium, but are induced by activation with cytokines, such as IL-1 and TNF-α. Likewise, LFA-1 transitions to a high-affinity state for ICAM, resulting in tight adhesion of the leukocyte to the endothelium. This adhesion contributes to antigen recognition, and, through a process called *haptotaxis,* leukocytes are induced to move along the vessel wall by an adhesion gradient.

Transmigration is the final step in the process of cellular entry into the allograft. Rapidly after integrin engagement of their ligands, leukocytes flatten and then undergo diapedesis through gaps between endothelial cells. Leukocyte secretion of proteases degrades the basement membrane, allowing their escape from the vessel. Once in the interstitium, secretion of matrix metalloproteinases allows leukocytes to digest extracellular matrix to move through the tissue on a chemokine gradient by a process called chemotaxis. Once confronted with foreign antigen in the allograft, previously activated T cells are capable of releasing proinflammatory cytokines (helper T cells) or directly killing foreign cells (cytotoxic T cells).

Acute T Cell–Mediated Rejection

Tubulitis, invasion of the tubular epithelium by infiltrating T cells and myeloid cells of the monocyte, macrophage, and DC series, is a characteristic feature of acute TCMR (Fig. 100.8). Deterioration of renal function during TCMR correlates with tubulitis and arterial inflammation (endothelialitis), which is much less common. The precise mechanisms by which T cells orchestrate damage to the allograft are not clear. CTLs can kill target cells by release of cytotoxic molecules (perforin, granzyme B, and granulysin) or engagement of Fas on target cells by FasL. Human gene expression studies show an increase in mRNA for CTL-associated transcripts, including granzyme B, perforin, and FasL, as well as T-bet, a master transcription factor for effector Th1 lymphocytes, during rejection episodes. Moreover, lymphocytes expressing mRNA and perforin

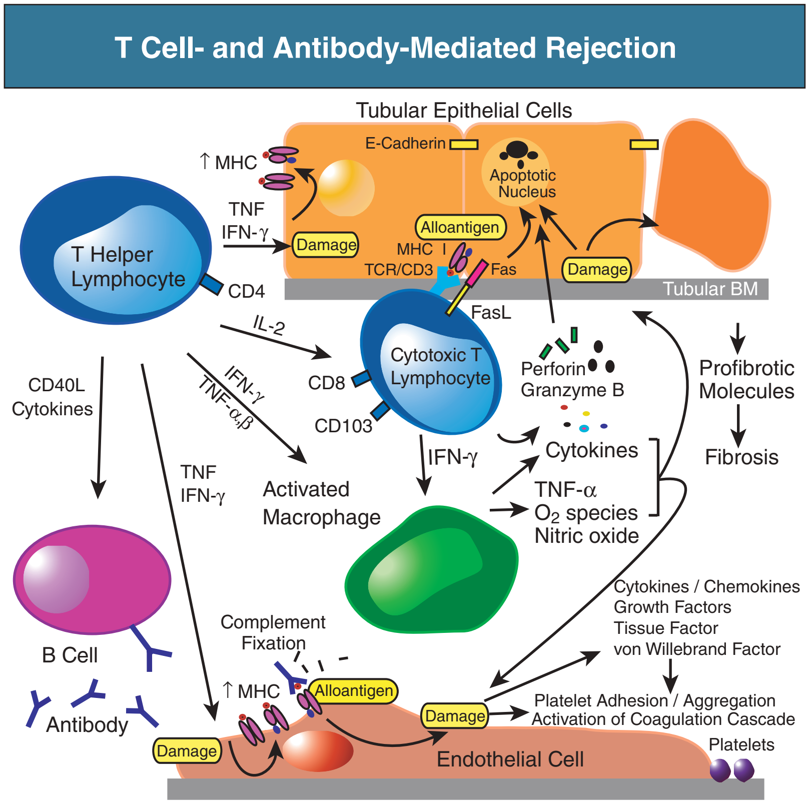
T Cell- and Antibody-Mediated Rejection
Tubular Epithelial Cells
E-Cadherin
↑ MHC
Apoptotic Nucleus
TNF
IFN-γ
Damage
Alloantigen
MHC I
TCR/CD3
Fas
Damage
Tubular BM
T Helper Lymphocyte
CD4
FasL
IL-2
Cytotoxic T Lymphocyte
CD8
CD103
Perforin
Granzyme B
Profibrotic Molecules
Fibrosis
CD40L
Cytokines
IFN-γ
TNF-α,β
IFN-γ
Cytokines
TNF
IFN-γ
Activated Macrophage
TNF-α
O2 species
Nitric oxide
B Cell
Cytokines / Chemokines
Growth Factors
Tissue Factor
von Willebrand Factor
Complement Fixation
↑ MHC
Alloantigen
Antibody
Damage
Damage
Platelet Adhesion / Aggregation
Activation of Coagulation Cascade
Platelets
Endothelial Cell

Fig. 100.8 **T cell–mediated and antibody-mediated rejection.** CD4 T cells induce epithelial and endothelial cell damage directly by secretion of cytokines but also indirectly by activation of cytotoxic T lymphocytes (CTLs) and macrophages. CTLs may cause apoptosis by releasing cytolytic granules containing granzymes and perforin or by exposure of Fas ligand (FasL) on the T cell surface. The integrin component CD103 is postulated to help retain T cells in epithelial layers by binding to E-cadherin, expressed most strongly in the distal nephron. Macrophages induce local tissue damage through secretion of cytokines, oxygen species, and nitric oxide (delayed-type hypersensitivity response). CD4 T cells secrete cytokines, which induce upregulation of major histocompatibility complex *(MHC)* molecules on epithelial and endothelial cells. CD4 T cells also provide help to B cells for production of alloantibody by engagement of CD40L and production of cytokines. Antigraft antibody is usually directed at MHC molecules, followed by activation of complement. Damaged endothelial cells secrete factors that activate coagulation systems and result in formation of microthrombi. Exposure of tubular cells and glomerular capillary loops to alloimmunity over time results in interstitial fibrosis, tubular atrophy, and glomerulosclerosis. *IFN,* Interferon; *TCR,* T cell receptor; *TFN,* tumor necrosis factor.

protein are closely associated with tubular epithelial cells. Some studies suggest that tubulitis may involve a specific subset of CTLs expressing the integrin CD103, which binds to its ligand E–cadherin on epithelial cells, resulting in retention of T cells in the tubules.

Most experimental evidence with perforin/granzyme, Fas/FasL, and CD103 knockouts indicates that any one of these individual cytolytic pathways is dispensable because acute rejection still occurs with these deficiencies in fully mismatched combinations.[34] These studies argue against cytoxicity as a primary mechanism to explain graft epithelial cell deterioration. Likewise, CD103:E-cadherin interactions may not be responsible for creating the lesions of tubulitis, but rather may reflect damaged cells that lose the ability to exclude inflammatory cells. Thus tubulitis may not be the cause of tubular cell deterioration but instead a sign that is has occurred.

T cells may mediate rejection instead through the secretion of cytokines, either through their direct effects or through their ability to activate macrophages to organize a DTH response.[35] DTH responses involve the release of reactive oxygen species, proteolytic enzymes, eicosanoids, and other products. These products may act directly on tubular epithelium and interstitial matrix or indirectly via effects on endothelium and the vascular supply.

Endarteritis is detected in a minority of biopsy specimens taken for acute TCMR and often responds only to anti–T cell therapies, arguing for a pathogenic role for T cells. Endarteritis is not always associated with interstitial inflammation, arguing for a T cell pathway distinct from that of tubulointerstitial rejection. Glomerulitis is an occasional feature of acute TCMR, and cells are typically a mixture of T cells and macrophages. Why the glomerulus becomes the target in only a minority of cases is not currently known. Foxp3 + CD4 Tregs are concentrated in tubules during rejection, although their role during TCMR continues to be debated.

Acute Antibody-Mediated Rejection

Acute AMR may occur with or without a component of TCMR (see Fig. 100.8). Although typically a response to donor HLA antigens expressed on endothelial cells, AMR can occur to non-HLA antigens. Examples include ABO blood group antigens and the putative endothelial alloantigens, as suggested by the rare occurrence of AMR in HLA-matched nonidentical sibling grafts. Autoantibodies also have been implicated, including to angiotensin II type 1 receptors. The kidney typically shows an accumulation of T cells, neutrophils, and monocytes in peritubular and glomerular capillaries (microvascular inflammation), although the infiltrate can be quite sparse.[36] Tubulitis is generally minimal, unless a component of TCMR is present. Foxp3 + Tregs are more rare in the AMR infiltrate than that of TCMR,[37] perhaps relevant to the poorer prognosis. Hyperacute rejection, which is due to the presence of preformed antidonor HLA antibody in sensitized recipients or of antibodies to mismatched ABO blood group loci, is a form of AMR that can result in immediate graft failure. This type of AMR is rare now that crossmatching practices and/or desensitization protocols are routinely employed by transplant centers.

Alloantibodies are cytotoxic through their ability to activate complement. Only the classical pathway has been shown to participate in acute or chronic AMR. C4d is an inactive fragment of C4b, an activation product of the classical pathway. C4b (and C4d) contains an occult sulfhydryl group that forms a covalent thioester bond with nearby proteins bound in the tissue after activation by immunoglobulin and C1. No functional role for C4d is known, but it remains in the tissue for several days after immunoglobulin and C1 have been released. C4d deposition is strongly associated with circulating antibody to donor HLA class I or II antigens and is currently the best single marker of complement-fixing circulating antibodies to the endothelium.

The acute effects of complement include chemoattraction of neutrophils and macrophages via C3a and C5a, vasospasm through the release of prostaglandin E2 from macrophages, and edema through the release of histamine from mast cells. C3a and C5a increase endothelial adhesion molecules and various cytokines and chemokines.[38] The membrane attack complex, C5b-9, causes lysis of endothelial cells. Alloantibodies also may induce cell damage through complement-independent pathways by recruitment of leukocytes with Fc receptors (CD16 most common), including NK cells and macrophages (antibody-dependent cellular cytotoxicity).[39]

A common feature of all types of AMR is the presence of microthrombi. As a result of antibody-mediated damage, von Willebrand factor is released from the endothelium, leading to platelet aggregation.[40] Animal models indicate that clotting activation is a direct consequence of complement fixation. Activation of endothelial protease-activated receptors by coagulation proteases, including thrombin, leads to the secretion of many proinflammatory cytokines.[41]

The current diagnostic criteria for acute/active AMR are: histologic evidence of acute tissue injury (in the absence of other possible causes), immunopathologic evidence of current/recent antibody interaction with vascular endothelium (e.g., C4d staining or microvascular inflammation), and evidence of circulating antibody reactive to the donor (HLA or other antigen).

Chronic Rejection

Late allograft dysfunction is due to both alloimmune mechanisms (i.e., chronic rejection) and alloimmune-independent mechanisms, including hypertension, calcineurin inhibitor toxicity, and recurrent disease.[42] Chronic rejection may occur by either cellular or humoral mechanisms, or both. Histologic features characteristic of chronic rejection are transplant glomerulopathy, peritubular capillaropathy (see later), transplant arteriopathy, and, less specifically, tubular atrophy and interstitial fibrosis.

Transplant glomerulopathy is defined by the widespread duplication or multilamination of the glomerular basement membrane (GBM), sometimes accompanied by mesangial expansion and accumulation of mononuclear cells in glomerular capillaries. GBM duplication may be caused by insults to the allograft glomerulus, including recurrent or de novo immune complex glomerular disease and thrombotic microangiopathy. However, it is believed that chronic antibody-mediated injury predominates, because the majority of cases of transplant glomerulopathy are associated with circulating antibody to donor class II MHC antigens (sometimes class I antigens), and approximately 30% to 50% of these cases have C4d deposition in the peritubular capillaries (PTCs).[43] Absence of C4d deposition in the remainder of cases may represent intermittent antibody involvement or antibodies directed at non-MHC antigens that do not fix complement.

Multilamination of peritubular capillaries can be demonstrated by electron microscopy (peritubular capillaropathy). Repeated episodes of antibody-mediated injury to the endothelium may result in repair mechanisms characterized by duplication of the basement membrane. What leads to episodic antibody injury is unknown, but fluctuating donor-specific antibody levels are observed in some patients. Neointimal thickening can be observed in either C4d positive or negative chronic rejection. Known as *transplant arteriopathy,* this lesion is characterized by thickening of the arterial intima. Macrophages and T cells may sometimes be demonstrated within the thickened intima, providing evidence of cell-mediated immunologic activity. Although not specific for rejection, interstitial fibrosis with tubular atrophy is another important histologic feature of chronically rejected allografts.

The current criteria for chronic active AMR are histologic evidence of chronic injury (in the absence of other possible causes), immunopathologic evidence of antibody action (e.g., C4d staining), and evidence of circulating antibody reactive to the donor (HLA or other antigen).[36] The first event in chronic AMR is alloantibody production (stage I), followed by antibody interaction with alloantigens resulting in the deposition of C4d in the PTCs and glomeruli (stage II), followed by pathologic changes (stage III), and finally graft dysfunction (stage IV). Although the factors promoting progression from stage 1 to stage IV are not currently understood, the hypothesized stages provide a useful organizing structure for ongoing clinical trials designed to intervene in the earlier stages (I or II).

TRANSPLANTATION TOLERANCE

Transplantation tolerance is a state characterized by the absence of a destructive immune response in the recipient toward a well-functioning donor allograft, with a fully intact immune system and no exogenous immunosuppression.[44,45] As with self-tolerance, transplantation tolerance is achieved through control of T cell reactivity by both central and peripheral mechanisms. Central tolerance involves thymic deletional mechanisms that eliminate T cells with reactivity against self-antigens (or donor antigens in the case of transplantation tolerance) and positive selection of T cells without such reactivity. In experimental transplant models, central tolerance is achieved by elimination of the preexisting mature T cell population by irradiation and/or cytotoxic agents, followed by infusion of donor hematopoietic progenitor cells. Reconstituted donor antigen "reeducates" the thymus to delete developing T cells with antidonor reactivity, leading to a state of chimerism, in which both donor and recipient cells coexist. Translating this approach to the clinical setting, however, requires a functional thymus, which may not be present in the adult human.

Peripheral tolerance mechanisms include deletion, anergy, and regulation. With self-tolerance, these mechanisms prevent deleterious autoimmune responses from T cells that escape central deletion. Various approaches to induce peripheral transplant tolerance with the goal of inhibiting deleterious alloimmune responses are currently under investigation, including costimulatory blockade, pharmacologic manipulation of DCs, and the induction of donor antigen-specific Tregs. A hurdle to the development of clinical tolerance strategies is the lack of reproducible immune monitoring assays for tolerance, which would determine when immunosuppressive medications could be safely withdrawn. Although transplantation tolerance is not yet a clinical reality, progress in the field is being made.[46,47]

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is *not* true regarding human leukocyte antigen (HLA) genes?
   - **A.** HLA genes are inherited in a mendelian codominant fashion.
   - **B.** It is predicted that siblings from the same parents will have a 50% chance of having zero HLA mismatches.
   - **C.** In kidney transplantation, efforts are made to match HLA-A, -B, and -DR genes.
   - **D.** One haplotype of HLA genes is inherited from each parent.
2. Which of the following is *true* regarding allograft rejection?
   - **A.** Chronic rejection may occur by either cellular or humoral mechanisms.
   - **B.** Acute antibody-mediated rejection may occur with or without a component of cellular-mediated rejection.
   - **C.** Tubulitis is a characteristic feature of acute cellular-mediated rejection.
   - **D.** All of the above.
   - **E.** None of the above.
3. Sensitization to an alloantigen can occur during which of the following conditions?
   - **A.** Pregnancy
   - **B.** Blood transfusion
   - **C.** Transplantation
   - **D.** Infection
   - **E.** All of the above
   - **F.** None of the above
4. Which of the following is *not* true regarding alloantigen presentation to T cells?
   - **A.** T cells recognize alloantigen via direct or indirect pathways.
   - **B.** Class II major histocompatibility complex (MHC) molecules are recognized by CD4 T cells.
   - **C.** The MHC class I system is designed to present extracellular proteins taken up and processed by antigen presenting-cells.
   - **D.** T cells recognize alloantigen as peptides presented by MHC molecules.

101

Immunosuppressive Medications in Kidney Transplantation

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Much of the success of kidney transplantation is a result of advances in immunosuppressive medications used during the induction and maintenance phases and for treatment of acute rejection.[1] The term *maintenance immunosuppression* is usually used to describe drug regimens consisting of small-molecule agents that are administered to stable kidney transplant recipients. Increasingly, physicians outside specialist transplant centers are involved in the care of stable kidney transplant recipients. In contrast, biologic agents that are used as induction immunosuppression before the maintenance stage or for the treatment of acute rejection episodes are usually managed by specialist transplant physicians.

SMALL-MOLECULE DRUGS

Corticosteroids

Corticosteroids have been a cornerstone of transplant immunosuppression for the past 50 years, both as maintenance immunosuppression and for treatment of acute rejection.

Mechanism of Action

Corticosteroids suppress production of numerous cytokines and vasoactive substances, including interleukin (IL)-1, IL-2, tumor necrosis factor-α (TNF-α), major histocompatibility complex class II, chemokines, and proteases. Corticosteroids also cause neutrophilia (often with a left shift), but neutrophil chemotaxis and adhesion are inhibited. They also affect nonhematopoietic cells, including endogenous renal cells. Corticosteroids act as agonists of glucocorticoid receptors but at higher doses have receptor-independent effects. Corticosteroid receptors (CRs) belong to a family of ligand-regulated transcription factors called *nuclear receptors* and are normally present in the cytoplasm in an inactive complex with heat shock proteins. The binding of corticosteroids to the CRs dissociates heat shock protein and forms the active corticosteroid-CR complex, which migrates to the nucleus and dimerizes on palindromic DNA sequences in many genes; this action is called the *corticosteroid response element.* The binding of CR in the promoter region of the target genes can lead to either induction or suppression of gene transcripts (e.g., of cytokines). CRs also exert effects by interacting directly with other transcription factors independent of DNA binding. Corticosteroids influence immune responses by regulation of the transcription factors activator protein 1 (AP-1) and nuclear factor-κB (NF-κB). Normally, NF-κB is present as an inactive complex with inhibitor of nuclear factor κB (IκB), but it can be released by IκB kinase. Corticosteroids limit inflammation by stimulating IκB, which then competes with the IκB–NF-κB complex for degradation by IκB kinase. Corticosteroids also stimulate lipocortin, which inhibits phospholipase A_2, thereby inhibiting production of leukotrienes and prostaglandins. Also, recent animal data suggest that there may be direct corticosteroid effects on renal glomerular cells separate from its immunosuppressive effects.[2] The net effect of corticosteroids involves immunosuppressive effects on cytokines, adhesion molecules, apoptosis, and inflammatory cells, as well as possible direct effects on renal glomerular cells.

Pharmacokinetics

The major corticosteroids used are oral prednisone (or prednisolone) and intravenous methylprednisolone. The oral agents have good bioavailability and short pharmacokinetic half-lives (60 to 180 minutes) but long biologic half-lives (18 to 36 hours). Corticosteroids are eliminated by hepatic conjugation and are excreted by the kidneys as inactive metabolites. Coadministration of inducers of cytochrome P-450 enzymes that metabolize corticosteroids (e.g., phenytoin, rifampin) decrease corticosteroid half-life, whereas concomitant use of P-450 3A4 inhibitors (e.g., ketoconazole) has the opposite effect. Because corticosteroid levels are not routinely monitored, dosage adjustment during concurrent therapy with these medications is problematic. For treatment of acute rejection, pulse doses of 250 to 1000 mg of methylprednisolone are typically used.

Side Effects

Side effects of corticosteroid therapy are common and associated with significant morbidity, particularly cataracts, osteoporosis, and avascular necrosis of the femoral head (Table 101.1). Other side effects include hypertension, increased appetite with weight gain, hyperglycemia, hyperlipidemia, cushingoid features, psychiatric disturbances, sleep disorders, peptic ulcer disease, pancreatitis, colonic perforation, growth retardation, and myopathy. Infection risk is also increased and is excessive if high-dose pulse therapy is prolonged. Interestingly, corticosteroids are not associated with an increased incidence of malignancy. Although corticosteroids are generally considered safe in pregnancy, fetal adrenal suppression has been reported. Rapid corticosteroid reduction protocols with low maintenance doses (5 to 10 mg/day of prednisone) can improve corticosteroid tolerability by ameliorating many of these side effects. In clinical trials of kidney transplant recipients, low-dose maintenance corticosteroids were still associated with lipid abnormalities and weight gain, but they were not associated with more infections or new-onset diabetes.[3,4]

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs), including cyclosporine and tacrolimus, are fungus-derived lipid-soluble small molecules that are the mainstays of current maintenance immunosuppression. Considerable variability exists in their pharmacokinetics, interactions, and side effect profiles, which raises the question of which agent to use in the individual patient. Cyclosporine is a cyclic, lipophilic undecapeptide with several *N*-methylated amino acids, which may explain its resistance to

TABLE 101.1 Side Effects of Small-Molecule Immunosuppressive Medications

	Cyclosporine	**Tacrolimus**	**Mycophenolate**	**Azathioprine**	**Corticosteroids**	**mTOR Inhibitors**	**Leflunomide**
Renal	Nephrotoxicity, type 4 RTA, HTN, diuretic resistance, hyperkalemia, hypomagnesemia, hypophosphatemia	Nephrotoxicity, type 4 RTA, HTN, diuretic resistance, hyperkalemia, hypomagnesemia, hypophosphatemia			HTN, hypokalemia, diuretic resistance	Synergistic nephrotoxicity with CNIs, delayed recovery from ATN, proteinuria, hypokalemia, HTN	
Gastrointestinal		Diarrhea, abdominal pain	Diarrhea, nausea and vomiting, gastritis, esophagitis, oral and colonic ulcers	Nausea and vomiting, hepatotoxicity, pancreatitis	Peptic ulcers, gastritis, esophagitis, diarrhea, colonic perforation	Diarrhea	Nausea, diarrhea, hepatitis
Hematologic	Thrombotic microangiopathy	Thrombotic microangiopathy	Anemia, leukopenia, thrombocytopenia	Anemia, leukopenia, thrombocytopenia	Leukocytosis, polycythemia	Thrombotic microangiopathy, anemia, thrombocytopenia	Anemia, leukopenia
Metabolic	Hyperlipidemia, hyperuricemia, gout, glucose intolerance	New-onset diabetes			Hyperlipidemia, hyperuricemia, hyperglycemia, osteoporosis, avascular necrosis, increased appetite and weight gain	Hyperlipidemia	
Dermatologic	Gingival hyperplasia, coarsened facial features	Alopecia			Hirsutism, acne, cushingoid facies, buffalo hump	Impaired wound healing, oral ulcers	Alopecia Rash
Neurologic	Encephalopathy, insomnia, myopathy, tremors	Encephalopathy, insomnia, myopathy, tremors	Progressive multifocal leukoencephalopathy		Psychosis, insomnia, myopathy	Reflex sympathetic dystrophy	
Other	Edema	Myocardial hypertrophy	Viral infections, pulmonary edema in elderly		Cataracts	Lymphocele, interstitial pneumonitis, rash, edema	

ATN, Acute tubular necrosis; *CNIs,* calcineurin inhibitors; *HTN,* hypertension; *mTOR,* mammalian target of rapamycin; *RTA,* renal tubular acidosis.

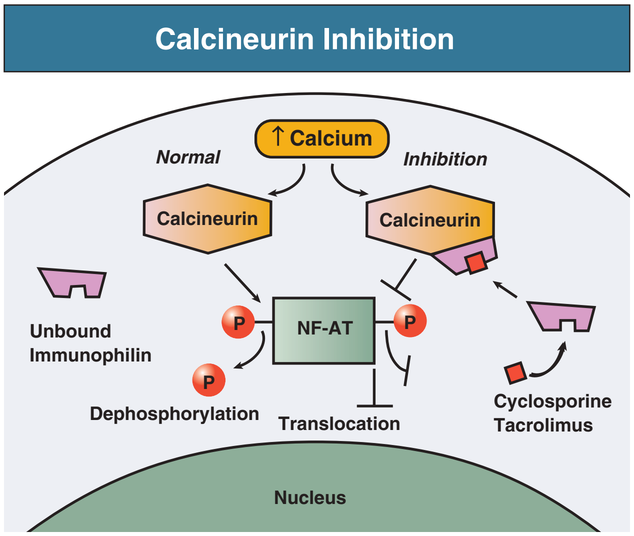

Fig. 101.1 Calcineurin inhibition. During normal T cell activation, calcium release activates calcineurin's phosphatase activity, causing dephosphorylation of the transcription factor, nuclear factor of activated T cells *(NF-AT),* and subsequent translocation to the nucleus. Cyclosporine and tacrolimus form a complex with immunophilins (cyclophilin or FK-binding protein 12, respectively), which bind calcineurin and sterically inhibit the phosphatase activity, preventing dephosphorylation and nuclear translocation of NF-AT.

inactivation in the gastrointestinal (GI) tract. Tacrolimus is a macrolide lactone antibiotic.

Mechanism of Action

CNIs exert their effect by binding to cytoplasmic proteins called *immunophilins* (Fig. 101.1). Cyclosporine binds to cyclophilin, and tacrolimus binds to FK-binding protein 12 (FKBP12).[5] Such binding enhances immunophilin affinity for and subsequent inhibition of calcineurin, which is a calmodulin-activated serine phosphatase important for dephosphorylation of inactive nuclear factor of activated T cells (NF-AT). Nuclear translocation of dephosphorylated (active) NF-AT, in association with other transcription factors, initiates downstream events leading to T cell activation. The tacrolimus-FKBP12 complex inhibits calcineurin with greater molar potency than the corresponding cyclosporine complex. Cyclosporine and tacrolimus can interfere with activation of calcineurin on substrates other than NF-AT, which likely explains many of their side effects. Treatment with CNIs also causes upregulation of the cytokine transforming growth factor-β (TGF-β), which has significant immunosuppressive properties but also promotes production of matrix proteins and tissue fibrosis. CNIs also can suppress the immune response by calcineurin-independent pathways, likely by blocking intracellular signaling pathways specific for T cells. The ability of these agents to interfere with two distinct mechanisms of T cell activation contributes to their highly specific immunosuppressive properties.

Pharmacokinetics, Monitoring, and Drug Interactions

After a dose of CNI, there is an initial absorptive phase, during which blood concentrations reach a peak level (C_{max}).[6] Typically, C_{max} occurs during the first 2 to 3 hours after the dose and corresponds to the time of maximum calcineurin inhibition. Drug levels then fall because of metabolism (also known as the *elimination phase*) until they are at the trough level (C_0) immediately before the next dose. The total drug exposure throughout the period from one dose until the next is the area under the concentration-time curve (AUC; Fig. 101.2).

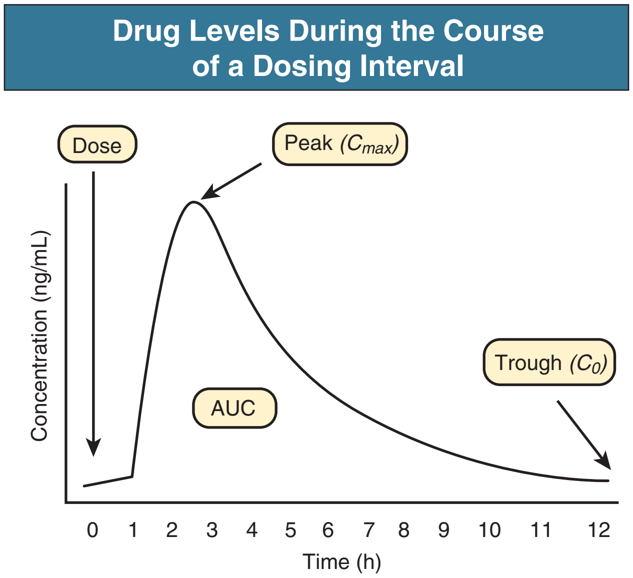

Fig. 101.2 Drug levels during a dosing interval. The drug concentration is lowest just before the dose is taken *(C_0),* then rises to a peak concentration at a certain time after the dose *(C_{max}).* The area under the concentration-time curve *(AUC)* describes total drug exposure during the entire administration interval.

For both CNIs, most of the interpatient and intrapatient variability occurs in the absorption rather than in the elimination phase. The oil-based formulation of cyclosporine requires solubilization in bile and is plagued by highly variable and unpredictable bioavailability. The microemulsion preparation of cyclosporine (modified) has enhanced bioavailability and less dependence on bile secretion. In blood, cyclosporine resides primarily in erythrocytes (60% to 70%) and leukocytes, with some binding to lipoproteins and, to a lesser extent, other plasma proteins. Cyclosporine is metabolized primarily by CYP3A4, a member of the cytochrome P450 superfamily. Metabolism occurs mostly in the liver. Interindividual differences in CYP3A4 activity and the large number of exogenous and endogenous substances capable of altering its function and expression explain the wide variation in clearance rates. One factor is the multidrug resistance 1 gene product, P-glycoprotein, which is variably expressed in the intestine and reduces the absorption of several xenobiotics, including CNIs, by transport out of intestinal epithelial cells. The average half-life of cyclosporine is about 19 hours, with excretion primarily in bile. Generic formulations of modified cyclosporine exist, although they may not have identical pharmacokinetics and therefore may not be readily interchangeable.

The absorption of tacrolimus, like that of cyclosporine, is highly variable, with bioavailability ranging from 5% to 67%. Absorption is not bile dependent but does depend on GI transit time and is affected by the presence or absence of food and the lipid content of food. Clearance appears to be faster in children, necessitating higher or more frequent dosing. African Americans and Latin Americans also require higher doses than Whites to achieve equivalent therapeutic levels, likely because of differences in subtypes of CYP3A, such as CYP3A5.[7] Similarly, higher tacrolimus dose requirements were reported for non-White Brazilian transplant recipients as well as Black transplant recipients in the United Kingdom.[8,9]

In blood, tacrolimus distributes primarily to erythrocytes, with whole-blood concentrations 10 to 30 times higher than in plasma. In contrast to cyclosporine, no lipoprotein binding occurs. Tacrolimus has 20- to 30-fold higher potency than cyclosporine on a molecular weight basis. Like cyclosporine, metabolism occurs through the CYP3A4 system,

BOX 101.1 Drugs and Other Substances That Interact With Calcineurin Inhibitors

Increase Blood Levels (P450-3A4 and/or P-Glycoprotein Inhibitors)

- Ketoconazole
- Fluconazole
- Itraconazole
- Voriconazole
- Erythromycin
- Clarithromycin
- Diltiazem
- Verapamil
- Nicardipine
- Cimetidine
- Methylprednisolone
- Metronidazole
- Ezetimibe
- Metoclopramide
- Fluvoxamine
- Human immunodeficiency virus (HIV) protease inhibitors
- Lovastatin
- Atorvastatin
- Simvastatin

- Grapefruit juice
- Chamomile
- Wild cherry

Decrease Blood Levels (P450-3A4 and/or P-Glycoprotein Inducers)

- Rifampin
- Rifabutin
- Phenytoin
- Carbamazepine
- Phenobarbital
- Caspofungin

- St. John's wort

with pharmacokinetics also affected by intestinal P-glycoprotein. Both CNIs are generally administered twice daily, but daily formulations for tacrolimus are also available in many countries. Because of the narrow therapeutic index for CNIs, the variability of concentrations among patients after a dose, and the potential for drug interactions, monitoring of drug levels is required to ensure both safety and adequacy.

Both cyclosporine and tacrolimus bind to cells and plasma components (primarily lipoproteins for cyclosporine and albumin for tacrolimus) and therefore must be assayed in whole blood. Four assays are currently used to monitor levels of CNIs in the blood: high-performance liquid chromatography (HPLC), monoclonal radioimmunoassay (RIA), monoclonal and polyclonal fluorescent polarization immunoassays, and the specific enzyme-multiplied immunoassay. Cyclosporine trough levels measured by HPLC or RIA are comparable because both measure only the parent compound. However, these concentrations are one-third lower compared with techniques that detect the parent compound plus its metabolites.

Given the complementary influence of both CYP3A4 and P-glycoprotein on the pharmacokinetic profiles of CNIs, it is assumed that CNI-drug interactions on both CYP3A4 and P-glycoprotein have similar complementary effects on CNI pharmacokinetics. Drugs that competitively inhibit CYP3A4 activity, such as ketoconazole, usually also inhibit P-glycoprotein, thereby increasing the bioavailability of CNIs, with potential for toxicity. Likewise, drugs such as phenytoin that increase CYP3A4 levels tend to upregulate P-glycoprotein, decreasing overall bioavailability. In this case the likelihood of rejection increases. Despite similar drug interactions, the age-related and ethnic differences in pharmacokinetics between the two CNIs are likely to influence the degree and importance of such interactions. Common interactions are presented in Box 101.1.

Side Effects

Cyclosporine and tacrolimus have similarities and differences in their toxicity profiles (see Table 101.1). Both can cause nephrotoxicity, hyperkalemia, hypomagnesemia and hypophosphatemia (secondary to urinary loss), type 4 renal tubular acidosis, hypertension, diabetes, and neurotoxicity. Gingival hyperplasia, hirsutism, hypertension, hyperuricemia, and hyperlipidemia, are more common with cyclosporine, whereas tremor and glucose intolerance are more common with tacrolimus. Cyclosporine also may be associated with coarsening of facial features, especially in children, and bone pain responsive to calcium channel blockers. Tacrolimus, especially in combination with mycophenolate mofetil (MMF), has been suspected of inducing more BK virus nephropathy. The most common and vexing problem with CNIs is nephrotoxicity, with its importance evident from heart and liver transplant recipients, in whom CNIs were associated with progression to end-stage renal disease. Both reversible hemodynamic and irreversible structural components underlie the nephrotoxicity of CNIs. Reversible vasoconstriction is caused by direct vascular effects but is also due to activation of the renin-angiotensin system (RAS), endothelin, thromboxane, and the sympathetic nervous system. Over time, chronic renal injury occurs characterized by afferent arterial hyalinosis and tubulointerstitial fibrosis, presumably as the result of prolonged renal vasoconstriction with ischemia. Experimentally, chronic cyclosporine nephropathy is exacerbated by sodium restriction and volume depletion, which stimulates the RAS, and can be ameliorated by angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Cyclosporine toxicity and to a lesser extent tacrolimus toxicity are potentiated in combination with mammalian target of rapamycin (mTOR) inhibitors such as sirolimus and everolimus. Finally, CNIs can cause thrombotic microangiopathy (TMA), probably by direct endothelial cell injury and dysfunction.

Mycophenolate

MMF and enteric-coated mycophenolate sodium (EC-MPS) are important components of immunosuppressive regimens that are associated with some of the most successful outcomes in kidney transplantation.[10] Because of its well-documented efficacy and acceptable side effect profile, MMF is by far the most frequently used antiproliferative agent and is commonly used in combination with CNIs.

Mechanism of Action

The immunosuppressive effects of mycophenolate are likely mediated through the active metabolite mycophenolic acid (MPA). MMF is a morpholinoethyl ester of MPA, a potent reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), isoform 2. EC-MPS is a salt that combines an acid—MPA—with a base—sodium. The enteric coating delays MPS release so that the MPA is absorbed in the small intestine rather than in the stomach. MPA noncompetitively inhibits IMPDH, which is the rate-limiting enzyme in the de novo synthesis of guanosine monophosphate (GMP). Inhibition of IMPDH creates a relative deficiency of GMP and a relative excess of adenosine monophosphate (AMP). GMP and AMP levels act as a control on de novo purine biosynthesis; therefore MPA, by inhibiting IMPDH, blocks de novo purine synthesis, which selectively interferes with proliferative responses of T and B cells. Some other cell types such as GI epithelial cells use the de novo pathway. Thus MPA may inhibit replication of GI epithelial cells, leading to the disruption of fluid absorption and diarrhea. However, most other cell types depend primarily on the alternative pathway for DNA synthesis and cell division and thus are relatively spared from toxicity.

Pharmacokinetics

MMF, being a prodrug of MPA, is absorbed rapidly and completely from the GI tract and undergoes extensive presystemic deesterification to become MPA, the active form. Food intake can delay the rate of MMF absorption but does not affect the extent. However, coadministration of antacids or cholestyramine decreases absorption by approximately 20% and 40%, respectively. EC-MPS has shown bioavailability equivalence as well as similar efficacy to that of MMF despite reaching higher levels with the use of proton pump inhibitors. MPA undergoes enterohepatic circulation, and its plasma concentration shows a secondary peak at 6 to 12 hours after intravenous or oral administration. The mean contribution of enterohepatic circulation to the overall AUC of MPA is 37% (range 10% to 61%). Most MPA is metabolized in the liver through a phase II glucuronidation process.

The major metabolite of MPA is the pharmacologically inactive 7-*O*-glucuronide metabolite (MPAG), although two other metabolites, MPA-acylglucuronide (AcMPAG) and MPA-phenyl-glucoside (glucoside-MPA), are isolated from the plasma of renal transplant patients. AcMPAG has shown in vitro pharmacologic activity (inhibition of IMPDH) as well as proinflammatory effects and potentially is responsible for the GI toxicity of MPA. The glucuronide metabolites are excreted into the bile, a process mediated by the multidrug resistance–related protein 2 (MRPR2), then undergo deglucuronidation back to MPA by enzymes that are produced by colonic bacteria. Blockade of MRPR2 by an inhibitor, such as cyclosporine but not tacrolimus, decreases the biliary excretion of MPAG and increases plasma MPAG levels. This eventually leads to lower plasma levels of MPA because the glucuronide metabolites no longer can be reabsorbed as MPA by enterohepatic cycling. Thus tacrolimus-treated patients have higher exposure to MPA than cyclosporine-treated patients. The ultimate elimination pathway for the glucuronide metabolites is through the kidney, and more than 95% of an administered dose eventually is found in the urine as glucuronide metabolites. For the most part, MMF and EC-MPS have been used in a fixed-dose regimen. However, studies have established a strong association of MPA AUC and its pharmacologic effects, specifically prevention of acute rejection. Furthermore, considerable interpatient variability is found in MPA AUC and trough concentrations in patients who receive a fixed dose of MMF. These data lend support to efforts to evaluate the role of therapeutic drug monitoring in increasing the therapeutic potential and minimizing adverse effects of MMF and EC-MPS.

Side Effects

MMF and EC-MPS have similar side effect profiles, including GI toxicity, bone marrow suppression, and increased infections, especially those of viral cause (see Table 101.1). GI disturbances include oral ulcerations, esophagitis, gastritis, nausea, vomiting, diarrhea, and colonic ulcers. Diarrhea and leukopenia frequently necessitate a dose reduction that could precipitate a rejection. Because the metabolites of MPA appear to play a major role in the GI disturbances associated with MMF, there is little rationale for enteric coating of the prodrug to reduce these symptoms. In fact, randomized controlled trials (RCTs) have found no significant difference in GI adverse events between MMF and EC-MPS.[11,12] MMF is not routinely used during pregnancy because of its teratogenicity in experimental animal models and clinical reports of major fetal malformations.

Azathioprine

The use of azathioprine has decreased dramatically in kidney transplantation since the introduction of MMF. Azathioprine is metabolized in the liver to 6-mercaptopurine and further converted to the active metabolite thioinosinic acid by hypoxanthine-guanine phosphoribosyltransferase. Because allopurinol (a xanthine oxidase inhibitor) increases levels of thioinosinic acid and can lead to life-threatening bone marrow suppression, the dose of azathioprine must be substantially reduced or azathioprine substituted with another agent—commonly MMF—in patients taking concurrent allopurinol. Azathioprine suppresses the proliferation of activated T and B cells and reduces the number of circulating monocytes by arresting the cell cycle of promyelocytes in the bone marrow. The antiproliferative effect is mediated by the metabolites of azathioprine, including 6-mercaptopurine, 6-thiouric acid, 6-methylmercaptopurine, and 6-thioguanine. These compounds are incorporated into replicating DNA and halt replication. They also block the de novo pathway of purine synthesis by formation of thioinosinic acid; this effect confers specificity of action on lymphocytes that lack a salvage pathway for purine synthesis. The major side effect of azathioprine is bone marrow suppression, leading to leukopenia, thrombocytopenia, and anemia (see Table 101.1) with potential life-threatening complications arising from the concurrent use of azathioprine and xanthine oxidase inhibitors such as allopurinol. The mean cell volume is commonly increased in patients taking azathioprine, and red cell aplasia occasionally can occur. The hematologic side effects are dose related and usually reversible on dose reduction or temporary discontinuation of the drug. Other common side effects are increased risk for malignancy (especially of skin cancers), hepatotoxicity, pancreatitis, and hair loss.

Mammalian Target of Rapamycin Inhibitors

mTOR inhibitors are proliferation signal inhibitors with immunosuppressive activity. Sirolimus, also known as *rapamycin,* was the first mTOR inhibitor used in transplantation and is a macrolide product of a soil fungus discovered on Easter Island.[13] Everolimus is a rapamycin analogue with a similar mechanism of action, immunosuppressive properties, and side effect profile. Although initially used in drug regimens with the intent of minimizing exposure to CNIs with its known side effects, the mTOR inhibitors have been associated with their own set of toxicities that have prevented their widespread use.

Mechanism of Action

Sirolimus has a structural similarity to tacrolimus and binds to immunophilin FK-binding protein 12 (FKBP12). The affinity of sirolimus for FKBP12 is higher than that of everolimus. mTOR inhibitors do not inhibit calcineurin or the calcium-dependent activation of cytokine genes but instead inhibit cytokine receptor–mediated signal transduction and cell proliferation that block lymphocyte responses to cytokines and growth factors. The sirolimus-FKBP12 or everolimus-FKBP12 complex binds with high affinity to the kinase enzyme mTOR, which is a serine-threonine kinase of the phosphatidylinositol 3–kinase pathway that acts during costimulatory and cytokine-driven pathways. mTOR inhibits a translation repressor protein (4E-BP1) and activates a ribosomal enzyme (p70-S6 kinase), both of which are important for translation of the mRNAs for certain proteins needed for progression from the G1 phase to the S phase of DNA synthesis. mTOR has been identified as the principal controller of cell growth and proliferation. The sirolimus-FKBP12 complex inhibits mTOR-mediated signal transduction pathways by blocking postreceptor immune responses to costimulatory signal 2 during G0 to G1 transition and to cytokine signaling during G1 progression. It also inhibits IL-2– and IL-4–dependent proliferation of T and B cells, leading to suppression of new ribosomal protein synthesis and arrest of the G1-S phase of the cell cycle. Proliferation of nonimmune cells, such as fibroblasts, endothelial cells, hepatocytes, and smooth muscle cells, is also impaired by inhibition of the growth factor–mediated responses (e.g., basic fibroblast growth factor, platelet-derived growth factor, vascular endothelial cell growth factor, and TGF-β). In addition, mTOR contributes to several protein synthesis pathways that could be involved in oncogenesis.

Pharmacokinetics

The oral bioavailability of sirolimus is poor (10% to 16%), with significant interindividual and intraindividual variability. Peak concentrations occur approximately 1 to 2 hours after an oral dose, and sirolimus distributes extensively into tissues, including blood cells. The oral bioavailability of everolimus is higher than that of sirolimus. High-fat meals increase sirolimus levels while decreasing everolimus levels. Because sirolimus has a relatively long half-life (~62 hours), it is reasonable to wait 1 week (~three half-lives to achieve steady state) before monitoring sirolimus blood levels after initiation or dose adjustment. Sirolimus is metabolized by the P-450 3A4 isoenzyme and P-glycoprotein system and thus has interactions similar to those described for CNIs (see Box 101.1).

When an mTOR inhibitor is administered simultaneously with cyclosporine, the C_{max} and AUC for both compounds are increased. Also, cyclosporine clearance may be reduced during concurrent therapy. Because of the risk for acute CNI nephrotoxicity, it is recommended that concurrent CNI and mTOR inhibitor therapy be avoided.

Side Effects

The mTOR inhibitors have a wide variety of toxicities (see Table 101.1). The most common adverse effects associated with sirolimus are dose-dependent hypertriglyceridemia, anemia, thrombocytopenia, and leukopenia. Other adverse effects include impaired wound healing and dehiscence, formation of lymphoceles, oral ulcers, reduced testosterone levels, diarrhea, and pneumonitis. Although not inherently nephrotoxic, the mTOR inhibitors result in renal graft damage through several mechanisms. When used in combination with full-dose cyclosporine (and probably tacrolimus), sirolimus potentiates CNI-induced nephrotoxicity. In patients with renal impairment, sirolimus is associated with marked yet potentially reversible proteinuria and worsening of established proteinuria. Sirolimus also can cause delayed recovery from acute tubular necrosis. Finally, cases of TMA have been reported, and there is concern that higher doses of sirolimus may inhibit endothelial cell growth. Interestingly, sirolimus-based regimens have been associated with a reduced incidence of post-transplantation malignancy. Some physicians regard sirolimus as the preferred immunosuppressive agent in transplant patients who develop malignancy, but this is based on data limited to kidney transplant recipients with squamous cell skin cancer.[14,15] Sirolimus is not routinely used during pregnancy because of its teratogenicity in animal models, although successful pregnancies have been reported.

Dihydroorotate Dehydrogenase Inhibitors

Leflunomide and its derivative FK778 are pyrimidine synthesis inhibitors with immunosuppressive as well as antiproliferative effects. These agents inhibit dihydroorotate dehydrogenase, which is a key rate-limiting enzyme in de novo pyrimidine synthesis. Unlike other cell types, activated lymphocytes expand their pyrimidine pool by nearly eightfold during proliferation, whereas purine pools increase only twofold. Thus inhibition of dihydroorotate dehydrogenase prevents lymphocytes from accumulating sufficient pyrimidines to support DNA synthesis. Leflunomide tablets are 80% bioavailable. After oral administration, leflunomide is metabolized to teriflunomide, which is responsible for essentially all of the activity in vivo and is monitored during therapy. Metabolism occurs in the liver, with excretion in the urine and bile. Because of its very long half-life (~2 weeks), a loading dose of 100 mg for 3 days is generally used to reach steady-state levels quickly. Side effects include GI symptoms, alopecia, bone marrow suppression, severe hepatitis, interstitial lung disease, peripheral neuropathy, and life-threatening skin reactions. Leflunomide use is not safe during pregnancy, and unless female leflunomide users receive cholestyramine therapy to eliminate the drug from the body, pregnancy must be avoided for 2 years after discontinuation. Additionally, male-mediated teratogenicity is a concern with leflunomide, so males wishing to father a child should undergo an accelerated leflunomide elimination procedure. Although it is not approved for use in kidney transplantation, leflunomide has been assigned orphan drug status for the prevention of rejection in solid organ transplantation, largely because of modest antiviral activity in vitro against BK virus and cytomegalovirus. However, the efficacy and safety of leflunomide have not been completely assessed in well-controlled studies. Furthermore, the manufacturers of FK778 discontinued development because of a lack of benefit over current options with regard to prevention of rejection and treatment of BK virus nephropathy.

BIOLOGIC AGENTS

Biologic agents in the form of polyclonal antibodies and monoclonal antibodies (mAbs) are frequently used in kidney transplantation either as induction therapy or for the treatment of rejection. Polyclonal antibodies are derived from horses or rabbits; historically, mAbs have been murine in origin. However, because foreign proteins can elicit an immune response, there has been an attempt to replace murine monoclonal products with humanized or chimeric mAbs (Fig. 101.3). Humanized antibodies are produced by merging the DNA that encodes the antigen-binding portion of a monoclonal mouse antibody with human antibody–producing DNA. Mouse hybridomas are then used to express this DNA to produce hybrid antibodies that are not as immunogenic as the murine variety. Chimeric antibodies use the same strategy but for the entire variable region and thus are more immunogenic than humanized antibodies. Polyclonal antibodies and mAbs can be depleting agents or immune modulators.

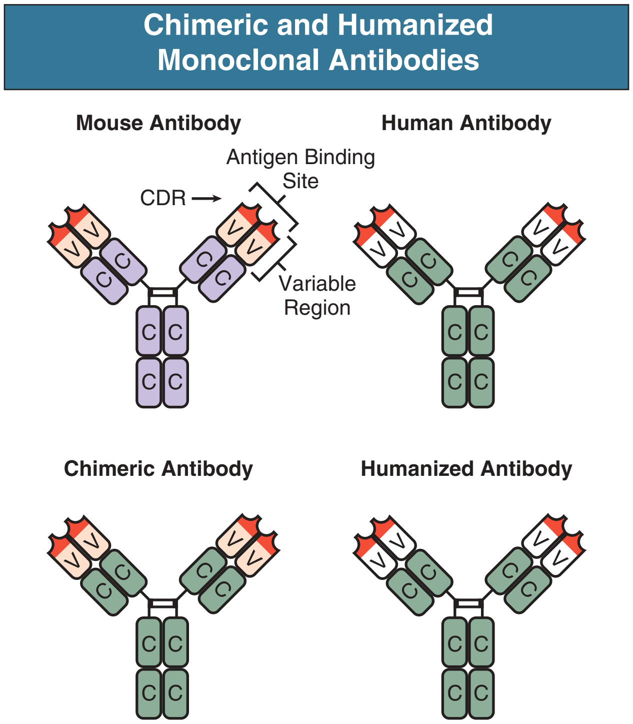

Fig. 101.3 Chimeric and humanized antibodies. Chimeric antibodies consist of human constant *(C)* regions and mouse variable *(V)* regions. A chimeric antibody therefore retains the antigen binding site of the mouse antibody but with fewer amino acid sequences foreign to the human immune system than a standard mouse antibody. Humanized monoclonal antibodies retain only the minimum necessary parts of the mouse antibody for antigen binding, the complementarity-determining region *(CDR, highlighted in red)*, and therefore are even less immunogenic in the human host.

Polyclonal Antilymphocyte Sera

Polyclonal antilymphocyte agents are produced by immunizing animals with human thymus–derived lymphoid cells. Although rabbit antithymocyte globulin (ATG) is currently the preferred preparation, equine preparations historically have been used. Most regimens involve daily intravenous administration of ATG for 4 to 7 days either as induction therapy or for treatment of corticosteroid-resistant rejection. ATG contains antibodies that react against a variety of targets, including red blood cells, neutrophils, dendritic cells, and platelets. ATG binds to multiple epitopes on the surface of T cells and induces a rapid lymphocytopenia by several mechanisms, including complement-dependent cytolysis, cell-dependent phagocytosis, and apoptosis. ATG is a potent immunosuppressive, and T- and B-lymphocyte counts can remain depressed up to 24 hours after administration. The lack of specificity coupled with marked immunosuppression increases the risk for infection and malignant neoplasms. Because polyclonal agents are xenogeneic proteins, they may elicit a number of side effects, including fever and chills. The initial lysis and activation of T cells that follow ATG administration may generate significant side effects after the first dose with the release of TNF-α, interferon-γ (IFN-γ), and other cytokines. Less commonly, ATG can induce a serum sickness–like syndrome and, rarely, acute respiratory distress syndrome.

Humanized Monoclonal Anti-CD52 Antibody

Alemtuzumab is a humanized IgG1 mAb directed against CD52, a glycoprotein found on circulating T and B cells, monocytes, macrophages, natural killer cells, and granulocytes. Alemtuzumab was originally approved for the treatment of B cell chronic lymphocytic leukemia, but it has been used off label as an induction agent in renal transplantation. Treatment results in a rapid and effective depletion of peripheral and central lymphoid cells, which may take months to return to pretransplantation levels. Side effects of alemtuzumab include first-dose reactions, neutropenia, anemia, and rarely, pancytopenia and autoimmunity (e.g., hemolytic anemia, thrombocytopenia, and hyperthyroidism). The risks for immunodeficiency complications such as infection and malignant neoplasia with alemtuzumab are still not clear, and additional controlled trials are necessary to establish dosing, safety, and efficacy.

Monoclonal Anti-CD25 Antibody

The alpha subunit of the IL-2 receptor (CD25) is upregulated on activated T cells and leads to the expression of high-affinity IL-2 receptors. The engagement of IL-2 receptors by IL-2 triggers the activated T cell to undergo proliferation. Basiliximab is a chimeric mAb with a specificity for CD25; it induces relatively mild immunosuppression and is used as an induction agent to prevent rejection but not to treat established rejection.[16,17] Although the exact mechanism of action is not fully understood, it is clear that significant depletion of T cells does not play a major role. Saturation of the IL-2 receptor alpha subunit persists for up to 25 to 35 days after treatment with basiliximab. Although saturation is important as a determinant of minimal blood concentrations, it is not predictive of rejection. No major side effects have been associated with anti-CD25 induction compared with transplant recipients receiving no anti-CD25 induction.

B Cell–Depleting Monoclonal Anti-CD20 Antibody

Rituximab is an engineered chimeric mAb that contains murine heavy- and light-chain variable regions directed against CD20 plus a human IgG1 constant region.[18] The CD20 antigen, a transmembrane protein, is found on immature and mature B cells and on malignant B cells. CD20 mediates proliferation and differentiation of B cells. Rituximab directly inhibits B cell proliferation and induces apoptosis and lysis by complement-dependent cytotoxicity, antibody-dependent cell cytotoxicity, and activation of tyrosine kinases as a direct effect of the antibody binding to its CD20 ligand. Rapid and sustained depletion of circulating and tissue-based B cells occurs after intravenous administration, and recovery does not begin until approximately 6 months after treatment. Although plasma cells are usually CD20 negative, many are short lived and require replacement from CD20-positive precursor cells. In addition, CD20-positive B cells can act as secondary antigen-presenting cells (APCs), thereby enhancing T cell responses. Thus by targeting CD20 on precursor B cells, rituximab decreases the production of activated B cells and limits their antibody production as well as antigen presentation capability. Most adverse events are first-infusion effects, such as fevers and chills, and are generally of mild severity, becoming less frequent with subsequent infusions. Viral infections, including reactivation of hepatitis B virus and JC virus have been reported, although it is not known whether these events are specific to the agent or instead reflect the overall state of immunosuppression. Antichimeric antibodies develop in some patients, but their true incidence and therapeutic significance are uncertain. Rituximab has been used in kidney transplantation to treat antibody-mediated rejection, as well as in combination with intravenous immunoglobulin (IVIG) to reduce high-titer anti–human leukocyte antigen (anti-HLA) antibodies in highly sensitized patients awaiting renal transplantation.[19] Rituximab is also used as induction therapy after desensitization therapy for ABO blood group–incompatible and high-risk positive crossmatch kidney transplantation. Finally, rituximab is often used to treat post-transplantation lymphoproliferative disease.

Intravenous Immunoglobulin

IVIG products are known to have powerful immunomodulatory effects in inflammatory and autoimmune conditions. The mode of action of IVIG is not well understood. In renal transplantation, the most important effect appears to be a reduction of alloantibodies through inhibition of antibody production and increased catabolism of circulating antibodies. Additional potential mechanisms include inhibition of complement-mediated injury, inhibition of inflammatory cytokine generation, and neutralization of circulating antibodies by antiidiotypes. Side effects related to IVIG administration include minor self-limited reactions, such as flushing, chills, headache, myalgia, and arthralgia. Rarely, anaphylactic reactions may occur. Delayed reactions include severe headache and aseptic meningitis, which respond to analgesics. More recently, severe thrombotic events have been linked to the administration of IVIG products. Osmotic injury of the proximal tubular epithelium can occur after administration of sucrose-containing IVIG preparations. This tubular injury is self-limited and can be minimized or avoided by use of sucrose-free preparations. In combination with plasma exchange, IVIG appears to offer significant benefits in the desensitization of positive-crossmatch and ABO-incompatible patients to allow successful transplantation as well as in the treatment of antibody-mediated rejection. Alone or in combination with rituximab, IVIG has been successful in the desensitization of highly sensitized wait-listed patients to increase the chances of finding a compatible donor.

Belatacept

Costimulation blockade is an immunosuppression alternative for kidney transplant recipients. Belatacept, a first-in-class costimulation blocker, is a fusion protein that binds to CD80 and CD86 on APCs to prevent T cell activation and proliferation (Fig. 101.4). The drug affects the CD28 pathway as well as the cytotoxic T-lymphocyte antigen 4 (CTLA-4) pathway, the latter being required for the function of T regulatory cells (Tregs) and tolerance of transplanted tissue. Belatacept was initially

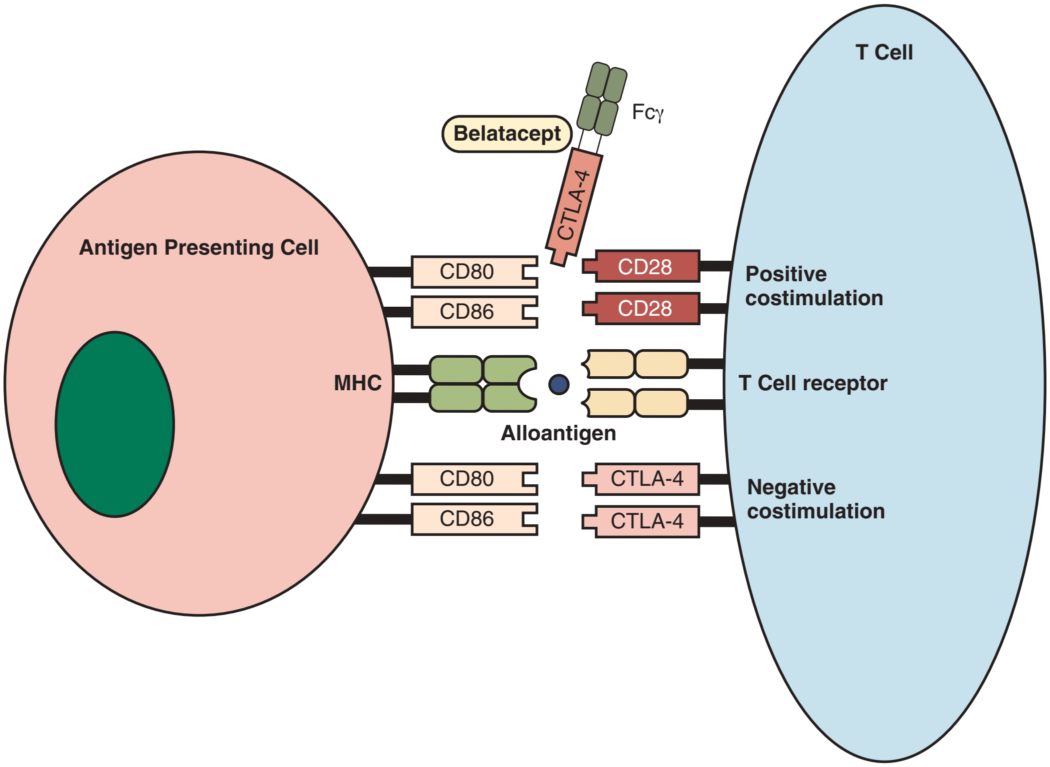

Fig. 101.4 Costimulation blockade. Lymphocyte T cell activation requires two signals with the first signal mediated by the major histocompatibility complex (MHC) and the T cell receptor, and the second signal (positive costimulation) mediated by CD80/CD86 on the antigen-presenting cell *(APC)* and *CD28* on the T cell. Negative costimulation is mediated by the cytotoxic T lymphocyte–associated protein 4 *(CTLA-4)* on activated T cells that binds to *CD80/CD86* on the APC and suppresses T cell responses (negative costimulation). Belatacept is a CTLA-4 fusion protein that binds CD80/CD86 and blocks positive costimulation via the CD28 pathway, thus preventing T cell activation.

approved by the U.S. Food and Drug Administration for de novo kidney transplantation only in Epstein-Barr virus (EBV)-seropositive adult patients because of concerns that administering belatacept might increase the risk for early post-transplant lymphoproliferative disorder (PTLD) in EBV-seronegative patients. Also, it has been used off label for conversion from CNIs after renal transplantation. Common side effects include anemia, leukopenia, and GI symptoms, as well as hypokalemia or hyperkalemia. Rare but serious side effects include progressive multifocal leukodystrophy and PTLD.

In the phase III BENEFIT trial, belatacept showed significantly better glomerular filtration rate (GFR) despite higher rates of early acute rejection compared with cyclosporine.[20] Belatacept-treated patients also had better blood pressure and lipid control compared with cyclosporine controls. The 7-year follow-up data showed that the composite endpoint of graft and patient survival was better with belatacept, but the individual graft survival and patient survival were separately not statistically different compared with cyclosporine.[21] Belatacept continued to show better 7-year renal function with no increased risk for late PTLD in EBV seropositive patients.

Other studies looked at patients who were not included in the BENEFIT trial. The BENEFIT-EXT trial included patients who received a kidney transplant from an expanded criteria donor, donation after cardiac death donor, or a donor with long cold ischemia time.[22] This trial also found that patient and graft survival with belatacept were not inferior, but unlike in the BENEFIT trial, the acute rejection rate and GFR were similar between belatacept and cyclosporine. More recently a retrospective study of the Scientific Registry of Transplant Recipients database compared the 1-year outcomes between belatacept and tacrolimus.[23] Similar to the BENEFIT trial, this study showed no difference in graft survival, but better renal function despite a greater risk for acute rejection was seen with belatacept compared with tacrolimus. Also, a lower risk for new-onset diabetes after transplantation was observed with belatacept. In summary, belatacept seems to better preserve GFR and have a better metabolic profile compared with CNIs, but it is unclear whether more acute rejection early on might affect long-term renal graft survival.

Other Agents Used in Transplantation

Bortezomib

Bortezomib is an antineoplastic agent originally approved for the treatment of plasma cell dyscrasias such as multiple myeloma and several types of lymphomas. It inhibits proteasomes, which are enzyme complexes that regulate protein homeostasis. Specifically, bortezomib reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest, and apoptosis. It targets mature rapidly proliferating antibody-producing plasma cells, but also interferes with T cell function and interleukin and TNF production. Bortezomib has been used off label for both primary and refractory antibody-mediated rejection, experimental desensitization protocols, and induction immunosuppression in patients who are highly sensitized with HLA antibodies.[24-26] Also, the BORTEJECT study is an ongoing phase 2 RCT investigating the impact bortezomib might have on treating late antibody-mediated rejection.[27] Bortezomib is administered intravenously and is metabolized by the liver. GI symptoms are common, but thrombocytopenia and peripheral neuropathy limit its use. Herpes zoster prophylaxis is required.

Eculizumab

Eculizumab is a humanized monoclonal antibody directed against complement protein C5 that prevents cleavage into C5a and C5b, thus blocking the subsequent formation of the terminal complex C5b-9 or membrane attack complex. Eculizumab prevents antibody-dependent complement-mediated cytotoxicity; therefore it has been used as an off label treatment for antibody-mediated rejection. However, because of its experimental use and extreme cost, eculizumab is usually reserved as a rescue therapy for allografts resistant to other antirejection therapies. Preliminary data using eculizumab in acute antibody-mediated rejection appears promising, but its role in treating chronic antibody-mediated rejection remains unproven.[28-30] As a result of increased incidence of meningococcal infections associated with eculizumab, meningococcal vaccine and antibiotic prophylaxis are required before starting therapy.

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SELF-ASSESSMENT QUESTIONS

1. What is the most common and vexing problem with cyclosporine and tacrolimus in kidney transplantation?
   - **A.** Nephrotoxicity
   - **B.** Hypertension
   - **C.** Thrombotic microangiopathy (TMA)
   - **D.** Alopecia
2. Belatacept offers patients a non-CNI alternative to maintenance immunosuppression and works by which mechanism of action?
   - **A.** Blocks complement C5 cleavage
   - **B.** Blocks CD25 on the IL-2 receptor
   - **C.** Blocks CD28 mediated costimulation of T cells
   - **D.** Inhibits B cell proliferation by targeting CD20
3. Which immunosuppressive agent has been associated with teratogenicity in experimental animals and major fetal malformations?
   - **A.** Tacrolimus
   - **B.** Azathioprine
   - **C.** Corticosteroids
   - **D.** Mycophenolate
4. The following agents commonly have been used in the treatment of acute rejection *except:*
   - **A.** Antithymocyte globulin
   - **B.** Basiliximab
   - **C.** Rituximab
   - **D.** Intravenous immunoglobulins

102

Evaluation and Preoperative Management of Kidney Transplant Recipient and Donor

William R. Mulley, John Kanellis

Kidney transplantation provides superior long-term outcomes compared with dialysis, in both quantity and quality of life, although the benefit gained varies among individuals.[1] The better outcomes associated with transplantation coupled with the shortage of available organs has led to an expansion of donor criteria and an increasing tendency for centers to accept marginal donor kidneys. In this chapter, we review current recommendations for the evaluation and preoperative management of both the kidney transplant recipient and the donor.

RECIPIENT EVALUATION

Many transplant centers now accept patients who were previously excluded from transplantation, such as those with human immunodeficiency virus (HIV) infection, obesity, and diabetes. This is because of the availability of newer treatment options for some conditions, a greater understanding of the impact of these conditions on patients and graft survival, and changing societal attitudes regarding equality of access to transplantation. Some absolute contraindications to transplantation remain (Box 102.1), including current infection or malignancy, noncompliance or substance abuse, and any condition likely to severely limit life expectancy (<1 to 2 years).[2-4]

Whereas the application of guidelines for transplant suitability may be relatively straightforward for patients with a single comorbidity, it is not as simple for those with multiple medical conditions, who represent a growing group of potential transplant recipients. Determination of suitability in such patients often requires input from specialists in a variety of medical and surgical disciplines along with allied health professionals. The final decision needs to be made by clinician and patient together after full discussion of the likely risks and benefits followed by regular reassessment of suitability while the patient awaits transplantation.

A summary of guidelines published by national and international transplantation associations[2-4] is presented in Box 102.2. Some of the important areas to consider in evaluating the transplant recipient are discussed here.

Cardiovascular Disease

Cardiovascular disease is common in patients with end-stage renal disease (ESRD) and is a major cause of death in transplant recipients. Hence, cardiovascular evaluation is critical in the evaluation of the potential transplant recipient.

Coronary Heart Disease and Left Ventricular Dysfunction

Chronic kidney disease (CKD) is a major risk factor for coronary heart disease (CHD). However, the vascular lesion, clinical features, and response to treatment may be quite different in patients with ESRD compared with the normal population. The role of pretransplantation screening and intervention for CHD is controversial. However, given the high incidence of cardiac events in the peritransplantation period and its major contribution to post-transplantation mortality, we favor aggressive evaluation and intervention in at-risk patients while avoiding unnecessary tests and procedures in low-risk candidates. Patients may be stratified into risk groups on the basis of history and examination, resting electrocardiography, and chest radiography. Further evaluation is unnecessary in asymptomatic patients without risk factors because of a very low incidence of coronary events.[5] Further investigation is recommended in patients with abnormal test results or significant risk factors, such as previous cardiac ischemic events, diabetes, smoking, age older than 50 years, hypertension, prolonged dialysis duration (>2 years), or a family history of CHD.[2-4]

Symptomatic patients should proceed directly to coronary angiography; noninvasive functional testing should be used to evaluate the need for angiography in asymptomatic patients.[5,6] Exercise echocardiography or myocardial perfusion scintigraphy are preferred; however, pharmacologically driven testing may be necessary if exercise is not impossible. Whereas a normal result does not exclude CHD, both testing modalities have negative predictive values for myocardial infarction or cardiac death in excess of 90% in patients with renal failure.[7] If significant CHD is identified, treatment before transplantation is required. Treatment consists of medical management, including aggressive risk factor modification, angioplasty, and stenting or coronary artery bypass grafting in patients with significant stenoses.[5,6] A suggested approach is presented in Fig. 102.1.

In patients with clinical or radiologic evidence of left ventricular dysfunction, transthoracic echocardiography should be performed to assess the severity and nature of the dysfunction. A cause should be sought and treated when possible. Severe left ventricular dysfunction may improve significantly after transplantation, so is not an absolute contraindication to transplantation. However, because it is associated with reduced post-transplantation survival it represents a contraindication in patients with significant comorbidities, unless combined heart and kidney transplantation is appropriate.[2-4]

Cerebrovascular Disease

Patients with a history of recent transient ischemic attack or stroke are at greatest risk for recurrence early after the primary event; and because stroke after transplantation is associated with a high rate of mortality,[8] a waiting time of 6 months is recommended. Meanwhile, aggressive risk factor modification is required to limit the likelihood of further stroke. Risk factors for de novo stroke post-transplantation include

BOX 102.1 Contraindications to Renal Transplantation

Current Absolute Contraindications to Transplantation

- Active sepsis
- Current uncontrolled malignancy
- Uncontrolled psychosis
- Active drug dependence
- Any medical condition with a severely shortened life expectancy (<1 to 2 years)
- Positive T cell CDC crossmatch

Historical Contraindications to Transplantation*

- HIV infection
- Hepatitis B and C infection
- Obesity
- Mood disorders
- Age older than 60 years
- Previous malignancy
- Blood group incompatibility

*These conditions are now acceptable under certain circumstances (see text).
CDC, Complement-dependent cytotoxicity; *HIV,* human immunodeficiency virus.

BOX 102.2 Recipient Evaluation Checklist

History and Examination

- Cause of renal failure and risk for recurrence
- Sensitization (transfusion, pregnancy, previous transplant)
- Past and current infections (TB, hepatitis, HIV)
- Immunization (especially hepatitis B)
- Malignancy
- Cardiovascular risks (smoking, hypertension, diabetes)
- Pulmonary, gastrointestinal disease
- Genitourinary tract
- Psychiatric, psychological history
- Surgical issues (weight, iliac vessels, abdomen, previous surgery)

Laboratory and Radiologic Investigations

- Viral serology (HIV, CMV, EBV, hepatitis B and C)
- Liver function tests
- Bone-related issues (PTH, calcium, phosphate)
- Chest radiograph
- Electrocardiogram
- Prostate-specific antigen (for men older than 50 to 60 years)
- Mammogram or breast ultrasound (women older than 50 years or with family history of breast cancer)
- Pap smear (sexually active women)

Immunologic Investigations

- ABO blood group and HLA typing
- Screening for HLA antibodies and autoreactive antibodies
- Crossmatching

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HIV,* human immunodeficiency virus; *HLA,* human leukocyte antigen; *PTH,* parathyroid hormone; *TB,* tuberculosis.

older age, diabetes, and atrial fibrillation, although transplantation is associated with a reduced risk for stroke relative to remaining on the waiting list or maintenance dialysis. Routine testing for cerebrovascular disease is not advocated in asymptomatic patients except for those with a carotid bruit who should proceed to carotid endarterectomy if a significant stenosis is found. Patients with polycystic kidney disease with additional risks for cerebral aneurysm rupture (e.g., personal or family history of cerebral hemorrhage) should be evaluated for cerebral aneurysm before transplantation. Risk for cerebral aneurysm in polycystic kidney disease is discussed further in Chapter 44.

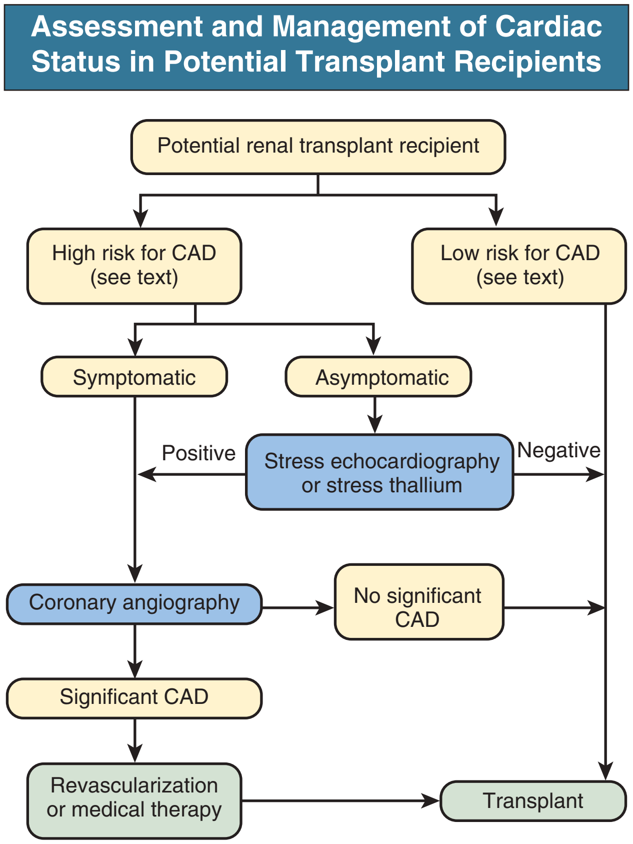
Assessment and Management of Cardiac Status in Potential Transplant Recipients
Potential renal transplant recipient
High risk for CAD (see text)
Low risk for CAD (see text)
Symptomatic
Asymptomatic
Positive
Stress echocardiography or stress thallium
Negative
Coronary angiography
No significant CAD
Significant CAD
Revascularization or medical therapy
Transplant

Fig. 102.1 Assessment and management of coronary artery disease in potential transplant recipients. *CAD,* Coronary artery disease.

Peripheral Vascular Disease

Asymptomatic patients with strong femoral and peripheral pulses generally require no further investigation. Patients with diabetes, history of claudication, or reduced pulses require vascular imaging beginning with Doppler ultrasound. Significant disease involving the iliac vessels may make transplantation difficult or impossible and may worsen ischemia in the distal leg. Although it is not an absolute contraindication to transplantation, peripheral vascular disease is associated with increased mortality and should be considered in conjunction with the patient's other comorbidities.

Cancer

Cancer is a major cause of death in renal transplant recipients. Further increases in the incidence of malignancy are likely with increased graft survival and acceptance of older recipients. The incidence of malignancy is also increased in transplant recipients compared with the general population.[9] However, the effect of transplantation on different types of cancer is not uniform, nor is the effect of different immunosuppressive agents.[10] Some cancers, such as nonmelanoma skin cancers (61% to 82% at 20 years) and lymphoma, have a markedly increased incidence in transplant recipients compared with the general population, in contrast to breast and prostate adenocarcinoma, which are not as substantially increased. In patients with previous malignancy, guidelines for

BOX 102.3 Guidelines for Transplantation in Patients With Previous Malignancy

Usual Wait Time of 2 Years

- Most cancers

No Wait Time Necessary

- Incidental renal carcinoma
- In situ carcinoma
- Focal neoplasm (defined as a localized tumor without metastases)
- Low-grade bladder cancer
- Basal cell skin cancer

Wait Time of More Than 2 Years May Be Necessary

- Melanoma
- Breast cancer
- Colorectal cancer
- Uterine cancer

BOX 102.4 Screening Tests for Occult Infection

Routine Serology

- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis B virus
- Hepatitis C virus
- HIV

Where Indicated, Tests for the Following Conditions and Infections

- HTLV
- Human herpesvirus 8
- Malaria
- Schistosomiasis
- *Strongyloides stercoralis*
- *Trypanosoma cruzi*
- Tuberculosis

Other Routine Investigations

- Chest radiograph
- Urine culture

HIV, Human immunodeficiency virus; *HTLV,* human T-lymphotropic virus.

recommended waiting time are based on the likelihood of recurrence after transplantation (Box 102.3). In general, the longer the cancer-free interval before transplantation, the smaller the recurrence risk. For most malignancies, a period of 2 to 5 years is recommended.[2-4] There are several exceptions. A longer waiting time (≥5 years) is recommended for breast cancer with nodal involvement, melanoma, and colorectal cancer worse than Dukes stage B1; no waiting time is thought necessary for nonmelanocytic skin cancers confined to the skin, in situ cancers of bladder and cervix, focal microscopic low-grade prostate cancer, and small (<7 cm) incidentally discovered and surgically removed renal cell carcinomas. Given the heterogeneity of malignant neoplasms, waiting periods before transplantation need to be individualized, taking into account the patient's other comorbidities.

Chest radiography is performed as part of the routine assessment. Although extensive screening of all potential recipients is not warranted, potential recipients should be evaluated for breast, cervical, prostate, and colorectal cancer. More comprehensive and targeted evaluation is recommended in patients with a strong family history or suggestive clinical features of malignancy or conditions associated with an increased risk for malignant disease, such as renal imaging in patients with acquired cystic disease of the kidney for possible renal cell carcinoma.[2,3]

Infectious Complications

All patients are screened for previous exposure to Epstein-Barr virus and cytomegalovirus (CMV) to assess the risk for infection, either primary or reactivation. This guides the appropriate use of prophylactic antiviral agents. For example, patients who are negative for CMV immunoglobulin G (IgG) who receive a kidney from a CMV-positive donor are at the highest risk for infection and may benefit from prolonged prophylaxis compared with the lower risk CMV-negative donor to a CMV-negative recipient (see Chapter 105). Screening for other infections should be tailored to geographical location; a guide for screening is presented in Box 102.4. All potential recipients should be immunized against hepatitis B virus (HBV). Immunization against encapsulated organisms (pneumococci, *Hemophilus influenzae,* and meningococci) should be considered in patients at high risk for antibody-mediated rejection in case rescue therapy (e.g., splenectomy) or complement inhibition with eculizumab is required.

Since the introduction of highly active antiretroviral therapy centers experienced in managing HIV infection and transplantation have reported excellent patient and graft survival in carefully selected recipients.[11] In the absence of an acquired immunodeficiency syndrome (AIDS)-defining illness, patients with sustained CD4 counts above 200/ml and undetectable HIV viral loads can be considered for transplantation.[2] Patients with HBV infection may be considered for renal transplantation if there is no evidence of active viral replication (HBV DNA or HBV early antigen [HBeAg] negative), advanced liver disease or cirrhosis (as determined by liver biopsy), or hepatocellular carcinoma.[2-4] Immunosuppression can increase HBV replication; hence, treatment before transplantation is indicated in patients with active disease, and although data to support prophylactic antiviral therapy after transplantation are scarce, treatments such as entecavir are commonly used while immunosuppression is at its highest (initial 12 to 24 months). Early reports suggest that mortality may be increased in HBV-positive patients after transplantation compared with HBV-negative recipients.[12] The significance of these findings is unclear in the current era with more effective treatment options and if only patients with inactive disease undergo transplantation. Frank disclosure of possible risks involved is recommended.[2-4]

Patients with hepatitis C should be assessed by measurement of hepatitis C virus (HCV) viral load and a liver biopsy. In patients without cirrhosis, transplantation should not be delayed by treatment because direct-acting antivirals can be safely used to treat HCV after transplantation[13] and mortality in HCV-positive patients is reduced by transplantation compared with remaining on dialysis.[14] With informed consent, HCV-positive patients may receive a kidney from an HCV-positive donor because any possible increased risk for the latter is offset by a significantly reduced waiting time. Patients with HBV and HCV infection should be screened every 12 months for hepatocellular carcinoma by liver ultrasound and serum α-fetoprotein. Those with cirrhosis may be considered for combined kidney-liver transplantation.

Patients at high risk for tuberculosis (TB) reactivation after transplantation (previous TB, abnormal chest radiograph, or positive tuberculin skin test result; residence in an endemic area) who have not been previously treated should receive prophylactic isoniazid after transplantation (see Chapter 105). Interferon-γ (IFN-γ) ELISPOT assays may replace or supplement the tuberculin skin test because they appear more sensitive for detecting latent TB infection.[15] The need to evaluate patients for TB is determined by the likelihood of previous exposure.

Previous graft loss caused by polyoma (BK) viral nephropathy is not a contraindication to repeated transplantation. Waiting for serum and urine BK polymerase chain reaction test results to become negative appears to be preferable,[16] whereas the value of graft nephrectomy before repeated transplantation is unclear. Vigilant evaluation for recurrence is recommended.[4]

Obesity

Transplantation in obese patients (body mass index [BMI] >30 kg/m^2) generally improves survival compared with matched waiting list controls, but inferior outcomes for patient and graft survival, delayed graft function and wound healing, and infective complications have been reported compared with nonobese patients, particularly those with a BMI above 36 kg/m^2.[17,18] The association of obesity with reduced graft and patient survival is less marked after adjustment for comorbidities.[19] Nevertheless, the overweight or obese patient is more likely to develop new-onset diabetes after transplantation, which can adversely affect graft and patient survival, so such individuals should be advised to lose weight before transplantation.

Recurrent Disease

The risk for disease recurrence should be discussed as part of the informed consent process, particularly in primary renal diseases with a high risk for recurrence (e.g., focal segmental glomerulosclerosis).[20] Recurrent disease accounts for more than 5% of graft loss[20] and becomes an increasingly important cause of graft dysfunction with increasing time post-transplantation. The risks and management of recurrent disease are discussed in Chapter 108.

Gastrointestinal Disease

Screening for gastrointestinal disease is not warranted in the asymptomatic patient.[3,4] Patients with active acute or chronic pancreatitis should not undergo transplantation until they have been clear of symptoms for 12 months. Patients with active peptic ulcer disease should be treated before transplantation with proton pump inhibitors, and this should be continued to prevent ulceration after transplantation. Patients with symptomatic diverticular disease require colonoscopy and potential colonic resection in severe cases before transplantation because they are at increased risk for perforation on immunosuppressive medications.[3] Whereas symptomatic cholecystitis should be treated surgically before transplantation, asymptomatic cholelithiasis does not require surgery before transplantation because cholecystectomy after transplantation is required in less than 10% of these patients and results in no increased mortality or morbidity compared with pretransplantation cholecystectomy and has no deleterious effects on graft function.[21]

Genitourinary Disorders

Screening for genitourinary tract disorders before transplantation is indicated in those with a history or renal ultrasound suggestive of urinary obstruction, especially in children, in whom urologic problems are a major cause of ESRD. If obstruction is found, urologic assessment, which may include voiding cystourethrography and urodynamic studies, is indicated to determine the best course of action to ensure bladder emptying and limit bladder pressures after transplantation; this may involve bladder augmentation, urinary diversion, or self-catheterization.

Native nephrectomy before transplantation should be considered in patients with recurrent or persistent renal sepsis, particularly in the setting of nephrolithiasis. Very large polycystic kidneys may need to be removed to accommodate the transplant kidney. Whether previous grafts should be removed before repeated transplantation is controversial. Nephrectomy of a failed graft is commonly performed on withdrawal of immunosuppression in patients with early graft failure (<12 months) to alleviate symptoms such as pain, fever, and weight loss.[22] Other indications include graft sepsis and allowance of room for the new graft. However, unless there is a convincing reason to remove the graft, it is generally left in situ. In these circumstances the patient may need to stay on minimal immunosuppression, such as prednisolone for 3 to 6 months, to minimize graft tenderness and inflammation. Graft nephrectomy may be associated with an increased risk for human leukocyte antigen (HLA) sensitization,[22] but this is not a universal finding. Another advantage of leaving the previous transplant in situ is preservation of any residual renal function and urine output.

Pulmonary Disease

Initial assessment by physical examination and chest radiography is indicated for all potential recipients; pulmonary function tests or computed tomographic (CT) scanning are performed if clinically indicated. Guidelines suggest that patients with a short life expectancy associated with pulmonary disease, such as cor pulmonale, uncontrolled asthma, and severe obstructive lung disease (FEV_1 <25% of predicted or Po_2 <60 mm Hg [8 kPa] on room air), or those needing home oxygen should be excluded from transplantation.[4] Many centers require patients to cease smoking before acceptance because smokers have an increased risk for death and graft loss. Cessation of smoking demonstrates positive lifestyle behavior and good adherence, suggesting these factors will optimal after transplantation.

Psychosocial Issues

Psychosocial issues can have a major impact on transplant outcomes. Patients should be evaluated by a health professional experienced in judging capacity to consent and assessing likely adherence with a transplant medication regimen. Adherence with the post-transplantation treatment regimen is vital to minimize premature graft loss. Predicting adherence can be challenging and may be based on pretransplantation adherence, such as to dialysis management regimens. Transplantation should not proceed if medical, psychiatric, psychological, and social work assessment suggests that adherence is unlikely.[2-4]

Cognitive impairment is not an absolute contraindication to transplantation if appropriate supports and proxy arrangements are in place. Patients with psychiatric illnesses, including depression, bipolar affective disorder, and psychosis, require assessment by a psychiatrist to determine transplant suitability and devise a management plan to cope with possible consequences of immunosuppressive medications such as corticosteroids.[2-4] Drug and alcohol addiction should be addressed with rehabilitation and demonstrated abstinence before the patient is listed for transplantation.

Presence of Multiple Comorbidities

Increasingly, patients with multiple comorbidities are referred for consideration of transplantation. Each morbidity in itself often is not an absolute contraindication, but taken together they may mean the patient has significantly reduced overall survival prospects. Controversially, some societies have suggested that patients must have specified long-term survival prospects—for example, an 80% chance of surviving 5 years—to be accepted for transplantation from a deceased donor. In addition, risk calculators have been devised based on registry data to allow such predictions (e.g., https://optn.transplant.hrsa.gov/resources/allocation-calculators/epts-calculator/.[23]

Reevaluation of Patients on the Waiting List

Patients may wait several years on the transplant list before an opportunity to undergo transplantation. It is vital that when their opportunity

BOX 102.5 Potential Recipient Re-Evaluation While Awaiting Transplantation

- Stress echocardiogram or thallium scan
- Angiography if indicated (see Fig. 102.1)

Cancer Surveillance Relevant to Age, Sex, and Risk Factors

- Prostate-specific antigen
- Mammography
- Pap smear
- Colonoscopy if indicated
- Skin cancer check

Comorbidity Reassessment

- Viral hepatitis
- Liver function tests
- α-Fetoprotein
- Liver ultrasound
- HIV
- CD4 count
- AIDS-defining illness
- Other (see discussion of individual organ systems)

Cardiac reevaluation every 1 to 2 years depending on risk factors (e.g., diabetes).

comes, they are still suitable candidates. A targeted reassessment of waiting list patients therefore should be conducted at regular intervals (Box 102.5). General measures, such as cancer screening (e.g., skin, prostate, breast, and cervical), should be continued as indicated. Reassessment of cardiac status is advocated based on risk. Diabetic and other high-risk patients should be reassessed every 1 to 2 years.[5] The value of reassessing low-risk patients is more questionable, but given that CKD is a strong risk factor for cardiac disease, repeated stress testing by exercise or pharmacologically driven echocardiography or myocardial perfusion scintigraphy at least every 3 years seems appropriate. Patients with preexisting medical conditions (e.g., HIV infection or viral hepatitis) require regular specialist reviews, with any issues arising brought to the attention of the transplant team. Surgical reassessment may be needed in patients with peripheral vascular disease, if patients gain weight, or if a complication such as peritonitis occurs while the patient awaits transplantation. Patients should be temporarily removed from the waiting list if they develop a serious infection or other illness until it is resolved.

DONOR EVALUATION

Donor kidneys can be obtained from both deceased and living donors.

Deceased Donors

Classification of the Deceased Donor

Deceased donors can be classified as either heart-beating donors with loss of brainstem function (donation after brain death [DBD]) or non–heart beating donors (donation after cardiac death [DCD]). In recent years the proportion of DCD donors has been increasing in many countries as a result of policies aiming to maximize the opportunities for donation.[24]

DBD donors can be further divided into standard criteria donors (SCDs) and expanded-criteria donors (ECDs). The definition of ECD varies; in the United States, for example, it refers to heart-beating donors older than 60 years or 50 to 59 years old with two or three of the following criteria: a history of hypertension, elevated serum creatinine at donation (>1.5 mg/dl or 130 μmol/l), or death from a cerebrovascular accident. In some jurisdictions, the term *marginal donor* is loosely used to describe donors who are less than optimal for some reason such as significant underlying disease (hypertension, diabetes, vascular disease, renal impairment) or advanced age (older than 65 years). In recent years the United Network for Organ Sharing (UNOS) in the United States has adapted a new system for classifying and allocating kidneys using a quality index.[25] The Kidney Donor Risk Index (KDRI) is a score that combines various donor factors, including clinical parameters to summarize the perceived quality of deceased donor kidneys relative to other deceased donor kidneys. Factors in the calculation include age, creatinine, mode of death, donor pathway (brain death vs. circulatory death), history of hypertension or diabetes, race (African American) and risk for HCV infection. A raw index score is converted to a percentile producing the Kidney Donor Profile Index (KDPI), rating from 0 (best) to 100 (worst).

BOX 102.6 Classification of Donation After Cardiac Death Donors

As per Maastricht classification[23] (also known as non–heart-beating donors)

Uncontrolled

Category I: Dead on Arrival to Hospital

Cause of death is usually obvious (e.g., severe head injury), and no resuscitation is given.

Category II: Unsuccessful Resuscitation

The patient is brought to the emergency department while being resuscitated, but this is not effective. Alternatively, cardiac arrest occurs in hospital and the patient cannot be resuscitated.

Controlled

Category III: Awaiting Cardiac Arrest

Severe brain injury without brain death. Patients are usually ventilator dependent. Cardiac arrest occurs once support is withdrawn.

Category IV: Cardiac Arrest While Brain Dead

Patient suffers cardiac arrest after being declared brain dead. Alternatively, this occurs during brain death testing and the patient is not successfully resuscitated.

Category V: Unexpected Cardiac Arrest in a Critically Ill Patient

Example: Unsuccessful resuscitation after unexpected cardiac arrest in intensive care.

From reference 45.

The Maastricht classification defines donors after cardiac death as controlled or uncontrolled (Box 102.6).[26] Controlled donors are those who experience cardiac arrest after withdrawal of support or after brain death. Uncontrolled donors are those who are deceased on arrival to the hospital or who had unsuccessful cardiopulmonary resuscitation. From a practical point of view, a system that uses controlled donors is easier to implement than one using uncontrolled donors. This is largely related to factors surrounding ethical considerations and the consent process involving relatives of the donor.

The survival of kidneys from expanded-criteria donors and from some categories of DCD donors is generally inferior to that of kidneys retrieved from standard criteria donors.[26] Many matching schemes attempt to allocate these less ideal grafts to recipients who are predicted to have a lower than average overall survival, but practice varies considerably across countries.

Evaluation of the Deceased Donor

In most circumstances, organ donor coordinators screen potential deceased donors after referral from intensive care units (ICUs) or emergency departments (EDs). Patient records are assessed and relatives are interviewed about important aspects of the clinical history. The assessment focuses on general health (including history of infections and cancer), social history (especially drug use and sexual history), and laboratory evidence of renal impairment or other diseases (Box 102.7).

BOX 102.7 Deceased Donor Evaluation Checklist

Medical History

- Hypertension, diabetes
- Malignancy
- Infections: Past and current (TB, hepatitis, HIV)
- Transfusions
- Trauma
- Surgical history
- Hospitalizations

Social History

- Intravenous drug use
- Alcohol, smoking
- Sexual behavior
- Tattoos, acupuncture
- Overseas travel
- Incarceration

Examination

- Blood pressure
- Cardiac, vascular
- Lymphadenopathy
- Abdominal

Laboratory and Technical

- Serum creatinine
- Urinalysis, urine culture
- Liver function tests
- Coagulation profile, complete blood count
- Blood culture
- *Virology, depending on geographical region: Antibodies to CMV, EBV, HSV-1 and HSV-2; HHV-6, HHV-7, HHV-8; HCV, HBV (including HBsAg, anti-HBcAg, IgG, and IgM), HIV, West Nile virus, rabies, HTLV-1
- Parasites, depending on geographical region: Malaria, babesiosis, toxoplasmosis, Chagas disease, syphilis
- Fungi in appropriate regions: *Coccidioides, Histoplasma*
- Tuberculosis (depending on geographical region)
- Chest radiograph
- Electrocardiogram
- Biopsy if there is concern for chronic kidney disease

Operating Room Evaluation

- Intraabdominal examination to detect occult malignancy

*Choice of virologic investigations according to local risks.
Macroscopic appearance of kidneys
CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HBcAg,* hepatitis B core antigen; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HHV,* human herpesvirus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *HTLV,* human T cell lymphotropic virus; *TB,* tuberculosis.

Patients with sepsis, acute hepatitis, or HIV infection are excluded from donation, as are those with a history of malignancy. Nonmelanoma skin cancers do not lead to exclusion, nor do primary brain tumors unless they are of a high grade or the donor has received chemotherapy or had a craniotomy or cerebral shunt inserted.[27] In some centers, donors potentially carrying HBV or HCV are accepted only for recipients who are seropositive for these viruses. The risk for an unknown donor malignant neoplasm is approximately 1.3%; however, the risk for transmitting a donor malignant neoplasm is lower at approximately 0.2%.[28]

Evaluation of renal function is determined by history, urinalysis, and serum creatinine concentration. In some patients a biopsy (often performed at retrieval) may provide useful information, particularly with ECDs or donors with a high KDPI. Serum creatinine concentration at admission should be in the near-normal range (estimated glomerular filtration rate [eGFR] >60 ml/min/1.73 m^2), but a temporary decline in renal function is acceptable if function is expected to recover. Proteinuria (>0.5 g/day) may indicate structural renal damage and is a valid reason for nonacceptance.

The use of kidneys from very small donors varies among centers. Donors younger than 5 or 6 years are generally associated with high risk for failure, especially from vascular thrombosis.[29] For this reason, some centers occasionally transplant two kidneys in the one recipient en bloc, using the aorta and inferior vena cava as conduits.[30]

Deceased Donor Management Before Transplantation

In the brain-dead donor, maintenance of adequate blood pressure (BP) and oxygenation are important to prevent warm ischemic renal injury. The use of pressor agents, volume resuscitation, and other conditioning strategies is complex and has been the subject of several guideline documents (see the Intensive Care Society website, www.ics.ac.uk). In this category of donor, the kidneys are generally not subject to significant warm ischemia at the time of organ retrieval unless the donor experiences prolonged hemodynamic compromise.

In DCD, once death is certified and deemed irreversible, either rapid surgical exposure of the great vessels with cooling of the organs followed by prompt retrieval is required, or, alternatively, the kidneys are cooled in situ by insertion of perfusion catheters through the femoral vessels (see also Chapter 103). Surgical retrieval can then take place after the following occur, as required: family counseling, donor assessment, or relocation from one hospital area to another (e.g., from the ICU or ED, to the operating theater). DCD is inevitably associated with warm ischemic renal injury. This is responsible for the higher rate of delayed graft function that is seen in this group. The need for dialysis after transplantation is approximately 50% but varies from 30% to 90%, depending on the Maastricht category of donor.[26]

Living Donors

Live kidney donation is currently accepted in most countries based on the demand for deceased donor organs—which far outweighs the supply—as well as the apparent very low level of risk to the majority of healthy donors.[31] Added to this are the detrimental effects for the recipient of waiting on dialysis and the excellent, generally superior results obtained through use of living donors.

Living donors may be related, unrelated, altruistic, or part of a donor exchange or list-exchange program. In many countries with well-established transplant programs, half or more of all transplants are now performed with living donors. In Japan, Brazil, and the Middle East, more than 80% of transplants use living donors. The superior outcomes of transplantation from living donors compared with that from deceased donors has supported the development of living donor paired exchange, in which living donors who are incompatible with their intended recipients are exchanged between recipients. Another

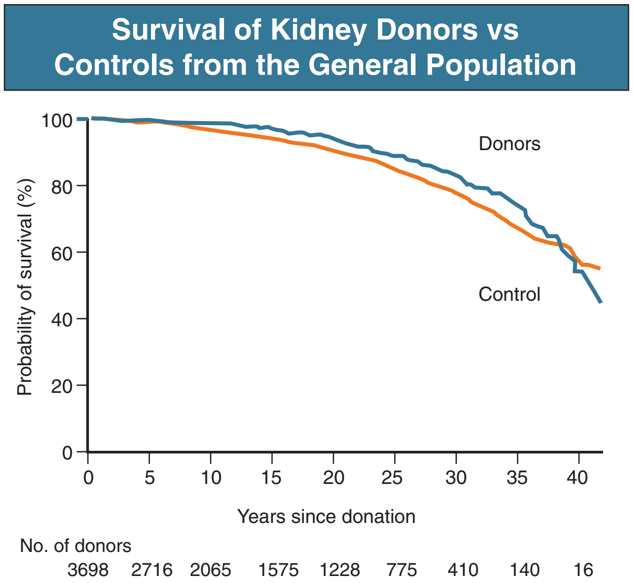

Fig. 102.2 Survival of living kidney donors. The survival of living related donors is similar to the survival among controls from the general population. Error bars at 5-year intervals indicate 95% confidence intervals for the probability of survival among kidney donors. (Modified with permission from reference 31.)

approach is living donor–deceased donor exchange, in which the donor donates to the wait list in exchange for the intended recipient receiving priority on the list.[33]

In some countries, either a state-organized or a free-market system results in the purchase of living donor kidneys; this is a highly controversial area.[33] The Declaration of Istanbul and the World Health Organization both condemn the exploitation of living donors who are vulnerable (illiterate, impoverished, undocumented immigrants, prisoners, and political or economic refugees).[34]

In recent times, many centers have extended their selection of donors to include patients who are mildly hypertensive, overweight, or hyperlipidemic or who have other abnormalities (such as isolated microhematuria or previous nephrolithiasis).[35] Whereas donation appears to be safe in the short to medium term for most of these patients, longer term medical or psychological risks have not been adequately assessed.

Mortality and Morbidity

Mortality related to living donation is a catastrophic and unexpected event (Chapter 104). Registry data and institutional surveys suggest the perioperative risk for donor death is approximately 3 in 10,000.[4,36] In the longer term, survival of donors appears to be similar to that of controls in the general population (Fig. 102.2).

Case series report that physical and psychological function in living donors is higher than the community norm. Physical issues reported by donors after donation frequently include a temporary decrease from baseline in energy; some note a longer time to full recovery than anticipated and incision pain (after open nephrectomy) that lasts longer than expected. Psychological factors usually include an improved relationship with the recipient, an improved self-image, and frequently a positive effect on the donor's life. Longer-term psychological morbidity appears minimal; however, some series have reported an association with anxiety, depression, or other psychological issues in a small proportion of the patients.[37] Even though most donors have a positive experience, a small number for a variety of reasons regret the decision to donate (0% to 5%).[38] Psychological evaluation before donation is therefore extremely important, as is the need to provide support and counseling after donation. This issue is particularly important when the transplant does not go as well as anticipated.

BOX 102.8 Living Donor Evaluation Checklist: History and Examination

History
- Hypertension
- Diabetes (including gestational)
- Infections
- Cancer (including skin lesions)
- Vascular disease
- Renal calculi
- Gout
- Urinary tract
- Family history
- Medications (including NSAIDs, herbs)
- Smoking
- Illicit and intravenous drug use
- Sexual history
- Vocation, sport interests
- Level of physical activity, exercise
- Psychiatric history, psychological factors
- Willingness to donate
- Relationship with recipient

Examination
- Blood pressure
- Weight and height, BMI
- Joints, skin
- Cancer (including skin lesions, breast)
- Lymph nodes
- Vascular disease
- Heart and lungs
- Abdomen

BMI, Body mass index; *NSAIDs,* nonsteroidal antiinflammatory drugs.

Evaluation of the Living Donor

Several groups have developed guidelines for the evaluation of the living donor, including Kidney Disease: Improving Global Outcomes (KDIGO), the Amsterdam forum[39] and consensus guidelines published by several U.S. transplant centers.[40] An outline of the usual donor evaluation is shown in Boxes 102.8 and 102.9. It includes a thorough history and examination, blood and urine screening tests, chest radiography, electrocardiography, age and family history, electrocardiography, cardiac stress test, and radiographic assessment of the kidneys and vessels. An assessment of relevant anatomy may be achieved by CT angiography or magnetic resonance angiography, depending on the center. Renal arteriography is not usually necessary, given the anatomic detail available from noninvasive techniques.

Assessment of Renal Function

Most centers use GFR of 80 ml/min/1.73 m^2 as the lower limit for donors. It is accepted that this threshold may be too low for donors younger than 40 years and too high for donors older than 60 to 65 years. An alternative approach is to consider the age-specific GFR and accept donors only if they fall within the average for this age-range. This method has been recommended by the British Transplantation Society (guidelines available at www.bts.org.uk) and is presented in Fig. 102.3. An alternative approach uses the life expectancy of the donor.[41] Based on these calculations, a 30-year-old donor would require a GFR of

BOX 102.9 Living Donor Evaluation Checklist: Investigations

Laboratory and Radiologic Investigations

- Urinalysis (blood, protein)
- Urine microscopy and culture (blood, organisms)
- Serum electrolytes, urea, and creatinine
- Liver function tests
- Full blood examination
- Fasting blood glucose and/or oral glucose tolerance test
- Fasting lipids
- 24-Hour urine, creatinine clearance, or GFR measurement by iothalamate, Cr-EDTA, DTPA clearance, 24-hour urine protein, or protein excretion by other methods (e.g., protein-creatinine ratio)
- Serum uric acid, calcium, phosphate
- Viral screening: HBV, HCV, HIV, CMV, EBV serology
- Syphilis screening (RPR)
- TB screening (PPD)
- Electrocardiogram
- Chest radiograph
- Females: Pap smear, mammography (according to age and family history)
- Males: Prostate-specific antigen (according to age and family history)
- Additional cardiac investigations (where indicated by age, history, risk factors)
  - Stress test
  - Echocardiography
  - Ambulatory blood pressure

Renal Imaging (According to Local Expertise)

- Computed tomographic angiography
- Magnetic resonance imaging angiography
- Catheter angiography

CMV, Cytomegalovirus; *Cr-EDTA,* chromium-labeled ethylenediaminetetraacetic acid; *DTPA,* diethylenetriaminepentaacetic acid; *EBV,* Epstein-Barr virus; *GFR,* glomerular filtration rate; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *PPD,* purified protein derivative test; *RPR,* rapid plasmin reagent; *TB,* tuberculosis.

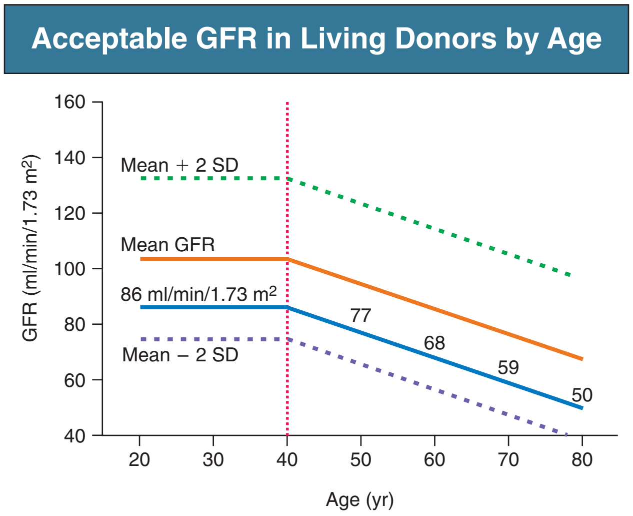

Fig. 102.3 **Acceptable glomerular filtration rate *(GFR)* in living donors by age.** Diagram explaining the minimum acceptable age-associated GFR in living donor candidates. The *solid orange line* shows the variation with age of mean GFR. The *outer dashed lines* show the +2 and –2 population standard deviation (SD) limits. GFR is constant up to the age of 40 years and then declines at the rate of 9 ml/min/1.73 m^2 per decade. The reference plot is based on an analysis of data for 428 living renal transplant donors who had chromium-51–labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA) GFR measurements. The *solid blue line* shows the acceptable lowest GFR for young adults, declining to 50 ml/min/1.73 m^2 at age 80 years. For transplant donors with preoperative GFR values above the solid blue line, the GFR of the remaining kidney will still be above 37. 5 ml/min/1.73 m^2 at age 80 years. (Modified with permission from the revised British Transplantation Society/Renal Association U.K. guidelines for living donor kidney transplantation, available at www.bts.org.uk/.)

123 ml/min/1.73 m^2; the required GFR for a 70-year-old person would be 68 ml/min/1.73 m^2.

Hypertension and Proteinuria in the Living Donor

Donation may be acceptable for some hypertensive individuals if BP is well controlled, GFR is as expected for donation and age, and there are no features of end-organ involvement from hypertension.[39,40] The evaluation for hypertension should include BP measurements on three separate occasions. Borderline elevated levels should be further evaluated with ambulatory BP monitoring. If elevated BP is detected and the prospective donor is still under consideration, echocardiography (looking for left ventricular hypertrophy), ophthalmologic evaluation (looking for hypertensive retinal changes), and assessment for microalbuminuria (suggesting hypertensive renal damage) should be undertaken. The prospective donor should be excluded if any of these features are present.

KDIGO recommends using the ratio of albumin to creatinine from a random urine sample with confirmation using an albumin excretion rate (AER) to assess donors for significant albuminuria (www.kdigo.org/guidelines/).[42] An acceptable AER is less than 30 mg/day, with 30 to 100 mg/day requiring an individualized approach. An AER greater than 100 mg/day should exclude potential donors. Previous recommendations referred mostly to total urinary protein excretion rather than albuminuria, with a level of 300 mg/day being used as the cut-off for exclusion. These newer recommendations are more consistent with our improved understanding of the early changes seen with underlying renal and systemic microvascular pathology signifying an increased cardiovascular risk.

Obesity and Abnormal Glucose Tolerance in the Living Donor

Although many centers accept obese living donors, several issues must be addressed. These include the impact of obesity on perioperative complications, future renal function, and cardiovascular health. In one study, obese (BMI >30) patients had an increased rate of proteinuria and renal impairment 10 to 20 years after nephrectomy.[43] Obese individuals may therefore be more prone to development of renal disease after donation, but this issue has not been carefully studied.

Future risk for diabetes is another important consideration. In addition to close assessment of those who are overweight, prospective donors with an abnormal fasting glucose concentration, a history of gestational diabetes, or a first-degree relative with diabetes should be evaluated with an oral glucose tolerance test. An abnormal glucose tolerance test result is a contraindication to donation. Patients often lose weight and otherwise change their lifestyle (exercise, diet), leading to an improvement in their results and eventual acceptance as donors. It is important that these lifestyle and risk modifications be sustained after donation occurs.

Renal Abnormalities in the Living Donor

As well as factors identified in the history (e.g., previous calculi, urinary tract infections, prostatic disease), a variety of previously unidentified renal abnormalities can be encountered in prospective donors during their assessment. These include microhematuria, renal scarring (e.g., polar distortion suggesting reflux nephropathy), renovascular abnormalities, and renal masses and cysts.

Isolated microhematuria in a prospective donor necessitates consideration of thin basement membrane nephropathy, Alport syndrome (carrier status in women may cause minor or moderate abnormalities), and IgA nephropathy, as well as urinary tract infection, malignancy, and nephrolithiasis. Persistent microhematuria is relatively common and is evident in approximately 3% of the general population.[44] Among the possible disorders, IgA nephropathy is generally a contraindication to live donation, whereas thin basement membrane nephropathy may not necessarily be so.[45] The implications of isolated mesangial IgA without other manifestations of glomerulonephritis requires further research, and donation should be decided in the context of family history, absolute renal function, presence of interstitial disease, and age. If persistent isolated asymptomatic microhematuria is detected during living donor evaluation, a workup should include cystoscopy and urinary cytology. A renal biopsy also should be considered because glomerular hematuria cannot otherwise be excluded. If there is a possibility of familial disease (e.g., Alport syndrome, IgA nephropathy), this also helps clarify the prospective donor's future risk for progressive renal disease.[44]

Those with a history of bilateral or recurrent stones and those with systemic conditions associated with recurrent stone disease should not donate. An asymptomatic potential donor with a current single stone is suitable if the donor does not have a high risk for recurrence, if the stone is smaller than 1.5 mm, and especially if the stone is potentially removable during transplantation.[45] The evaluation of an asymptomatic donor with a single prior episode of nephrolithiasis should include evaluation of serum calcium, creatinine, albumin, and parathyroid hormone levels; spot urine for cystine; urinalysis and urine culture; spiral CT scan; chemical analysis of the stone, if available; and 24-hour urine measurement of oxalate, uric acid, and creatinine.

Atherosclerotic renal vascular disease is a relative contraindication to living donation. If it is discovered, the donor should be normotensive, have normal renal function, and have only unilateral disease. Careful evaluation for CHD and peripheral vascular disease should be undertaken, given the significant association of renovascular disease with atherosclerosis elsewhere. Fibromuscular dysplasia is found in 2% to 4% of prospective donors. Donors with severe and diffuse disease should not be accepted for donation. The age of the prospective donor should be considered, with the outcome in donors older than 50 years more predictable and benign than in younger donors.[45]

Malignancy

A history of certain malignancies is a contraindication to live kidney donation. These include melanoma, testicular cancer, renal cell cancer, bronchial and breast cancer, choriocarcinoma, hematologic malignant neoplasm, and multiple myeloma.[39] A history of malignancy may be acceptable for donation if prior treatment does not decrease renal reserve, place the donor at increased risk for renal disease, or increase the operative risk for nephrectomy. A history of malignancy may be acceptable if the specific cancer is curable and transmission of the cancer can be reasonably excluded; consultation with an oncologist may be required. Examples of cancers with low risk for transmission include certain mild forms of prostate, bladder, and cervical cancer. Consent to receive a renal transplant must include a discussion with the donor and the recipient regarding the fact that risk for transmission of malignancy cannot be completely excluded.

Cardiovascular and Pulmonary Disease

In prospective donors, the cardiac assessment should be based on the history, risk factors, examination, and electrocardiographic findings. An exercise or pharmacologic stress test and echocardiography may be warranted in certain circumstances. Individuals with myocardial dysfunction or coronary ischemia are at increased perioperative risk and should generally not donate. Pulmonary contraindications to donation include chronic lung diseases that significantly increase the anesthetic risk. If indicated by history and examination, pulmonary function testing, echocardiography, or sleep studies should be performed. All donors should cease smoking for at least 8 to 12 weeks before surgery to minimize the risk for postoperative pneumonia.

COMPATIBILITY AND IMMUNOLOGIC CONSIDERATIONS

Blood Group Compatibility

Traditionally, transplantation across incompatible blood groups has been avoided because of the risk for hyperacute rejection mediated by preformed anti-A or anti-B antibodies to the carbohydrate blood group antigens, expressed by endothelial cells as well as by red blood cells. In recent years, ABO-incompatible transplantation has become more widespread, largely based on excellent outcomes described initially by Japanese centers.[46] "Desensitizing" the recipient can avert hyperacute rejection. This involves removal of blood group antibodies by plasma exchange or immunoadsorption to achieve target titers. Preemptive splenectomy or rituximab administration (anti-CD20 monoclonal antibody) also is often used; however, the need for these measures is not clear. Rejection is predicted by high initial antibody titers and high rebound titers early after transplantation.[47] A further period of plasma exchange or immunoadsorption after transplantation is commonly instituted, whereas other centers determine the need for these therapies preemptively based on post-transplantation antibody titers. With use of this protocol, patient and graft survival appears to be equivalent to that of blood group–compatible transplantation for the short to medium term (up to 9 years).[46] Longer term results are awaited. A comprehensive overview and summary of current approaches relating to antibody-incompatible transplants is available at the British Transplantation Society website (www.bts.org.uk).

Human Leukocyte Antigen Compatibility

Tissue typing of recipient and donor determines their HLA match. HLA antigens are coded on chromosome 6, with half (one haplotype) inherited from each parent. The major histocompatibility class I HLA-A and HLA-B and class II HLA-DR antigens are routinely determined, because rejection responses are thought to most commonly stem from mismatches at these alleles. There is an increasing awareness of the importance of immune responses to other HLA antigens, and many centers now look for the presence of antibodies to HLA-C, HLA-DQ, and HLA-DP. A six-antigen (HLA-A, HLA-B, and HLA-DR) match confers a graft survival advantage compared with zero antigen matches for both deceased and living donor transplantation of 10% at 10 years.[48] In addition to determination of the HLA compatibility, crossmatching and screening for anti-HLA antibodies are performed to assess the risk for rejection.

Assessing Human Leukocyte Antigen Sensitization

The principle of screening for antibodies against HLA antigens using panel reactivity is shown in Fig. 102.4. IgG antibodies against class I (HLA-A and HLA-B) antigens are highly associated with acute rejection. IgM antibodies against HLA antigens also may predict rejection if present in current but not past sera; however, as their presence is less clinically relevant, they are usually removed by treatment of sera with dithiothreitol to aid in the interpretation of the test (Table 102.1). Autoantibodies (such as may occur in lupus) also may give false-positive

TABLE 102.1 **Interpretation of the Crossmatch Test**

	CROSSMATCH (NORMAL PROCEDURE)		CROSSMATCH (IgM DEPLETED*)		
Antibody to MHC Class	**T Cells**	**B Cells**	**T Cells**	**B Cells**	**Risk for Antibody-Mediated Graft Damage**
IgG against class I	+	+	+	+	Yes
IgM against class I	+	+	–	–	Yes; IgM class I antibodies may be harmless if present in old sera only but not in the current serum
IgG against class II	–	+	–	+	Yes
IgM against class II	–	+	–	–	Unknown
IgM autoantibodies	+	+	–	–	No

Ig, Immunoglobulin; *MHC,* major histocompatibility complex.
*Dithiothreitol is used to deplete IgM antibodies (see text).

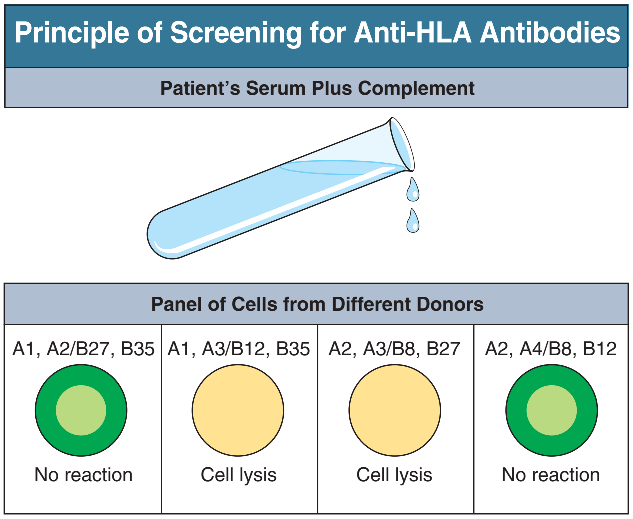
Principle of Screening for Anti-HLA Antibodies
Patient's Serum Plus Complement
Panel of Cells from Different Donors
A1, A2/B27, B35
A1, A3/B12, B35
A2, A3/B8, B27
A2, A4/B8, B12
No reaction
Cell lysis
Cell lysis
No reaction

Fig. 102.4 **Principle of screening for anti–human leukocyte antigen (HLA) antibodies.** The patient's serum is tested with a panel of cells of known HLA types. The most common HLA antigens are represented in such panels. In this example, the A3 antigen is the only antigen present in the two lysed cell populations and absent from the nonlysed samples. Therefore the patient's serum contains anti-HLA A3 antibodies.

results and can be determined by prior absorption with autologous lymphocytes.

Sensitization to HLA antigens generally occurs through blood transfusion, pregnancy, or prior transplantation. Presence in the recipient of antibodies to donor-specific HLA antigens can result in hyperacute rejection. Crossmatching of donor lymphocytes with recipient serum allows screening for this possibility. Terasaki and coworkers pioneered the complement-dependent cytotoxicity (CDC) crossmatch.[49] This assay determines the presence of antibodies thought to be of clinical significance by mixing donor T or B lymphocytes with recipient serum in the presence of complement. The sensitivity of the assay can be augmented by the addition of anti-human globulin. Presence of a positive T cell CDC crossmatch to the donor is highly predictive of hyperacute rejection,[49] whereas a B cell CDC crossmatch is more subject to false-positive results but should prompt a search for donor-specific antibodies.[50] A positive T cell crossmatch is an absolute contraindication to transplantation.

The flow crossmatch is more sensitive than the CDC in detecting antibody capable of binding to donor T or B lymphocytes. Binding of antibody from donor serum is detected by flow cytometry after probing with a fluorescein-labeled antiimmunoglobulin antibody. The predictive value of a positive flow crossmatch for rejection is less than that of a CDC crossmatch because of its increased sensitivity, and it does not assess the ability of the antibody to fix complement. In most centers, it is not routinely performed before deceased donor transplants, but it is commonly performed in a living donor transplant workup. A positive-flow crossmatch (with a negative CDC crossmatch) is not an absolute contraindication to proceeding; however, it may lead to alteration of the immunosuppressive regimen (e.g., use of a desensitization protocol) to decrease the risk or severity of antibody-mediated rejection.

Determination of the presence of anti-HLA antibodies in the recipient's serum is increasingly used as a means of predicting rejection. This virtual crossmatch compares the specificity of the antibodies identified with the prospective donor's HLA typing. Donor-specific anti-HLA antibodies are correlated with worse graft survival even in the setting of a negative crossmatch.[51] Antibodies can be detected through panel reactive antibody testing, by enzyme-linked immunosorbent assay, or with more sensitive antigen-coated bead techniques. Beads coated with a single HLA antigen are mixed with recipient serum and probed with a fluorescein-labeled antiimmunoglobulin antibody. Beads that bind antibody are therefore identified by fluorescence. The decision on whether to proceed with transplantation in the context of this information is complex. Recommendations for detection and characterization of clinically relevant antibodies in solid organ transplantation are summarized by the British Society of Histocompatibility and British Transplantation Society and are available at www.bts.org.uk. A more recent set of guidelines was also published after a Consensus Conference on Antibodies in Transplantation, held in 2012.[52]

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SELF-ASSESSMENT QUESTIONS

1. Which of the following recipient factors is an absolute contraindication to transplantation?
   - **A.** Active sepsis
   - **B.** HIV infection
   - **C.** Obesity
   - **D.** Age older than 70 years
   - **E.** Previous malignancy
2. In predicting the risk for cardiac death in potential kidney transplant recipients, stress echocardiography performs best in terms of which of the following parameters?
   - **A.** Sensitivity
   - **B.** Specificity
   - **C.** Positive predictive value
   - **D.** Negative predictive value
   - **E.** A and B equally
3. Which of the following brain-dead donors meets the definition for an expanded-criteria deceased donor (as previously used in the United States)?
   - **A.** A previously well 53-year-old person with a serum creatinine at donation of 1.7 mg/dl (150 µmol/l)
   - **B.** A 48-year-old person with diabetes, hypertension, vascular disease, and smoking history
   - **C.** A 48-year-old person with hypertension and death from a cerebrovascular accident
   - **D.** A 62-year-old person with no significant medical history
   - **E.** A 58-year-old person with hepatitis
4. Which of the following investigations would you *not* routinely perform on a 67-year-old man to assess his suitability to donate a kidney to his wife?
   - **A.** Urine microscopy
   - **B.** Colonoscopy
   - **C.** Hepatitis serology
   - **D.** Electrocardiogram
   - **E.** Renal imaging
5. Which of the following will *best* identify a high risk for hyperacute rejection?
   - **A.** Recipient tissue typing
   - **B.** Positive flow crossmatch
   - **C.** Positive T cell cytotoxicity–dependent crossmatch
   - **D.** Positive virtual crossmatch
   - **E.** Donor O blood group

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Kidney Transplantation Surgery

Adam D. Barlow, Michael L. Nicholson

SOURCES OF KIDNEYS FOR TRANSPLANTATION

The usual and most frequent source of kidneys for transplantation has been donation after brain death (DBD), formerly known as donation from a heart-beating cadaveric donor. The increasing worldwide discrepancy between the availability of and the need for renal allografts[1] has led to the increasing use of alternative sources of organs, including donation after cardiac death (DCD) donors (previously known as non–heart-beating donors) and living donors. The evaluation and selection of donors are discussed in Chapter 102. Here we discuss surgical aspects of retrieval and transplantation of kidneys.

DONATION BEFORE CARDIAC DEATH DONORS

The potential DBD donor is maintained by artificial ventilation in a critical care setting until death has been diagnosed by brainstem death criteria,[2] the consent of the next of kin for donation has been given, and the necessary legal and institutional approvals have been obtained.

In the operating room some dissection is undertaken initially to define any aberrant anatomy and increase the speed and safety of organ retrieval after perfusion (warm dissection). Cannulation of the aorta and inferior vena cava is performed while the heart is still beating. This allows perfusion of the organs with cold preservative solution immediately before cardiac arrest, minimizing warm ischemia. The priorities of the organ retrieval team are influenced by the range of organs being donated. Heart, lung, liver, and pancreas retrieval take priority over kidney retrieval, which may significantly lengthen the ischemic time. The kidneys are removed with a cuff of aorta (Carrel patch) attached to the renal artery, with the maximum achievable length of renal vein, and 10 to 15 cm of ureter. The length of the right renal vein should be maximized by including a portion of inferior vena cava in continuity. Care is taken to avoid damage to polar and other accessory arteries, especially the lower pole artery, which may supply the ureter. Stripping of adventitial tissue from the ureter must also be avoided, because this also may compromise its blood supply.

The kidneys are flushed with ice cold preservation fluid until the effluent is clear and then are stored for transport in crushed ice or on a perfusion machine (see the discussion of renal preservation).

DONATION AFTER CARDIAC DEATH DONORS

Before consensus was reached regarding the definition of brainstem death, DCD donors were the main source of transplant organs. These donors were intensive care unit based and had suffered head injuries or cerebrovascular accidents deemed irrecoverable, but organ retrieval could proceed only after cardiorespiratory death. This changed with the introduction of brainstem death legislation, but the use of DCD kidneys has recently increased again in response to the shortage of suitable organs for transplantation. An international consensus has defined categories of DCD donors[3] to facilitate legal and ethical discussion and to highlight possible differences in organ viability (see Chapter 102, Box 102.6). DCD kidneys sustain a period of warm ischemia, the period between cardiac arrest and the time that in situ cold perfusion is started. The duration of ischemia correlates with rates of primary nonfunction, delayed graft function, acute rejection, allograft, and patient survival. The main requirement of organ procurement from DCD donors is therefore to achieve rapid in situ perfusion of the kidneys to limit warm ischemia. This requires an emergency response team of surgeons and transplant coordinators, with considerable on-call and logistic commitments.

DCD donors may be either uncontrolled (Maastricht categories I and II) or controlled (Maastricht categories III through V). In controlled donors, cardiac arrest is expected, and it is therefore possible to reduce the warm ischemia time to only a few minutes because the surgical retrieval team will be on standby. Unexpected donor cardiac arrest may result in prolonged warm ischemia times. The duration of reversible warm ischemia time that the human kidney can sustain is unknown, but DCD kidneys with warm ischemia exceeding 60 minutes are considered by many to be of marginal suitability.

Donation After Cardiac Death Protocol

Centers involved with DCD donation should adhere to the Maastricht protocol,[4] which includes the following principles:

- Approval by the local medical ethics committee
- Diagnosis of death by doctors who are independent of the transplantation team
- 5-Minute rule (after declaration of cardiac death, the body is left untouched for a period of at least 5 minutes before intervention)
- Rapid in situ cooling with use of a catheter inserted into the aorta
- Organ retrieval by standard surgical techniques

Uncontrolled Donation After Cardiac Death Donors

After a period of unsuccessful resuscitation, confirmation of cardiac death, and observation of the 5-minute rule, cardiac massage and ventilation with 100% oxygen are recommenced in an attempt to deliver oxygenated blood to the kidneys. A mechanical resuscitation device may be used. In situ renal cooling is effected by placing a double-balloon, triple-lumen perfusion catheter into the aorta via a femoral artery cutdown (Fig. 103.1) with instillation of preservation solution. Alternatively, the donor can be moved to an operating room as soon as death has

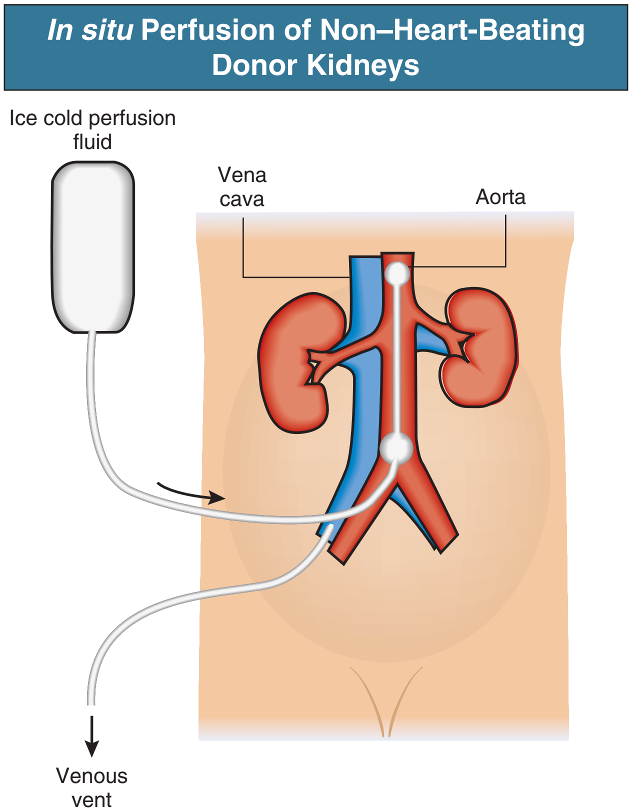


Fig. 103.1 Technique for in situ perfusion of donation after cardiac death kidneys. A double-lumen, double-balloon arterial catheter is introduced through the femoral artery and the lower balloon inflated at the aortic bifurcation and the upper balloon above the renal arteries. Ice-cold perfusion fluid is introduced and vented through the femoral vein until the effluent becomes clear.

occurred, and the aortic perfusion catheter placed directly at laparotomy rather than via a femoral artery cut-down.

Controlled Donation After Cardiac Death Donors

For controlled DCD donors, the transplantation team awaits cardiac arrest; after confirmation of death, the 5-minute rule is observed and then the perfusion catheter is inserted via the femoral artery. Alternatively, the patient can be taken to the operating room before cardiac death if the next of kin gives consent.

LIVING KIDNEY DONORS

In the United States in 2014, 30% of renal transplants were from living donors,[5] compared with 34% in the United Kingdom.[6] After a rapid increase in living donor transplantation at the beginning of this decade, rates have become more static. Superior recipient post-transplantation outcome compared with use of kidneys from deceased donors,[7] the potential for preemptive transplantation before dialysis, and the ability to plan the procedure (allowing optimization of recipient condition) are major advantages and justify continued efforts to expand use of living donors. The medical evaluation of the living donor is discussed in Chapter 102 (see Boxes 102.8 and 102.9).

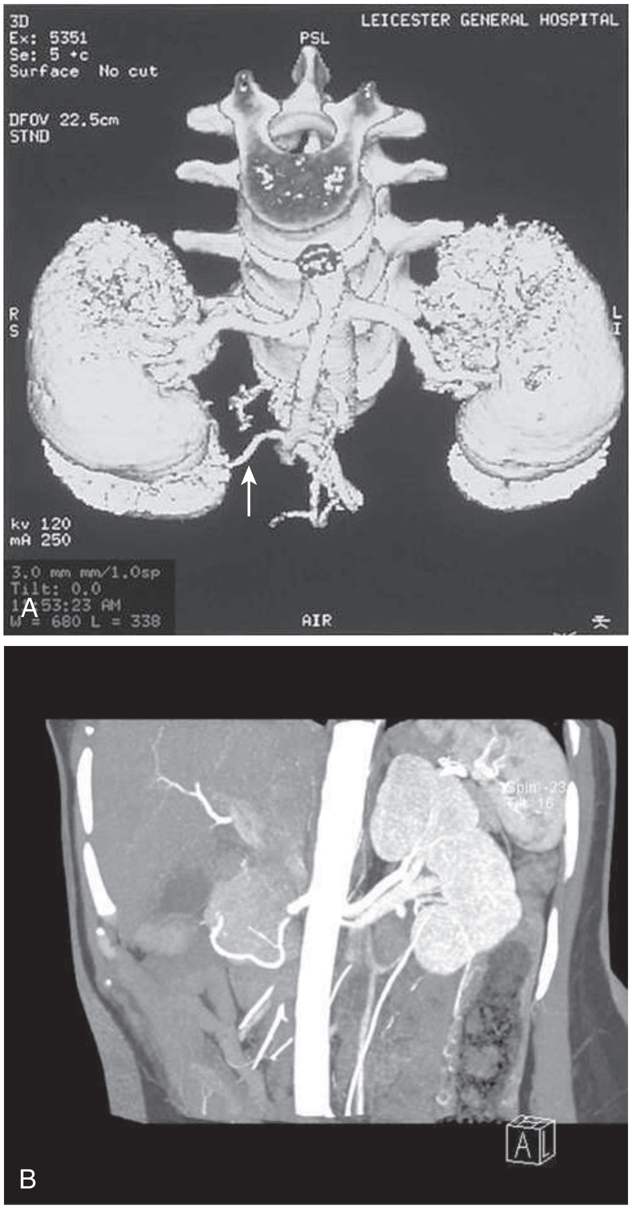


Fig. 103.2 Living donor preoperative computed tomographic angiogram. (A) Three-dimensional reconstruction of arterial supply. Note the lower pole artery to the right kidney *(arrow),* which may supply the ureter as well as the lower pole parenchyma. (B) Conventional image showing single artery and vein to the left kidney.

Preoperative Imaging

Preoperative imaging of living donors confirms the presence of two functioning kidneys, indicates pathology that would preclude donation, and provides anatomic information necessary for planning the procedure. Imaging assumes paramount importance before minimal access donor nephrectomy because of the reduced operative exposure and particular difficulties in the identification of complex vascular anatomy. The location, size, and number of renal arteries and veins needs to be accurately described preoperatively. Angiography combined with excretion urography is now obsolete. For preoperative description of the main renal artery and vein anatomy, magnetic resonance angiography and computed tomographic angiography are comparable,[8] but computed tomographic angiography is more sensitive and specific for complex vascular anatomy and provides excellent correlation between imaging and surgical findings[9] (Fig. 103.2).

Minimal Access (Laparoscopic) Donor Nephrectomy

Living donor nephrectomy has traditionally been performed through an open incision, necessitating a prolonged period of recovery. This

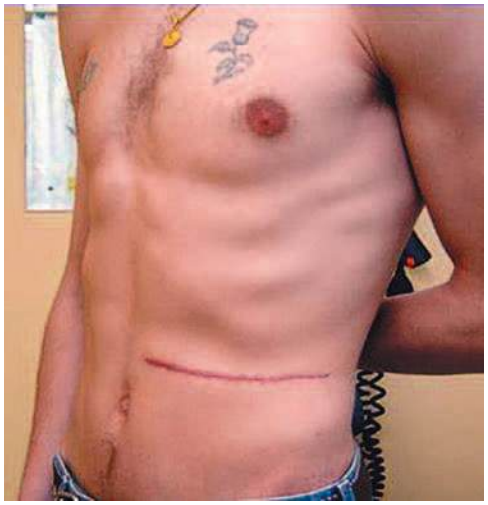


Fig. 103.3 Flank wound from open nephrectomy.

BOX 103.1 Donor Benefits of Minimally Invasive Donor Nephrectomy

- Shorter incisions
- Less pain
- Shorter hospital stay
- Shorter recovery
- Better cosmetic appearance

and the cosmetic implications of a large flank wound may discourage potential donors (Fig. 103.3). To reduce such disincentives, there has been a move toward minimally invasive donor nephrectomy, first performed as a transperitoneal laparoscopic procedure (laparoscopic donor nephrectomy [LapDN]).[10] LapDN is associated with decreased severity and duration of postoperative pain, shorter inpatient stay, quicker return to work and normal activities, and improved cosmetic result compared with open donor nephrectomy[11] (Box 103.1). Furthermore, the overall societal cost of LapDN is lower[12] and recipient quality-of-life scores are higher.[13] The procedure is, however, technically demanding, and there is potential for damage to the renal parenchyma, vessels, and ureter during dissection. It takes longer than open nephrectomy and exposes the allograft to a longer period of warm ischemia.[11]

Nevertheless, retrospective data suggest that minimal access donor nephrectomy not only offers postoperative advantages to the donor, but also increases the number of transplants performed by reducing donor disincentives; estimates range from a 25% to a 100%[14] increase in transplantation activity. The widespread introduction of LapDN at the beginning of this decade saw an initial dramatic increase in the number of live kidney donors. However, rates have been static in both the United States and the United Kingdom over the last 5 years, suggesting that we may have seen the maximum benefits of this effect. Three minimal access approaches have been described: transperitoneal, extraperitoneal, and hand-assisted living donor nephrectomy.

Transperitoneal Laparoscopic Donor Nephrectomy

Pneumoperitoneum is established, and four laparoscopic ports are usually required (Fig. 103.4). After laparoscopic dissection a Pfannenstiel incision is made through which the kidney is brought out within an endoscopy retrieval bag after control and division of the artery vein and ureter.

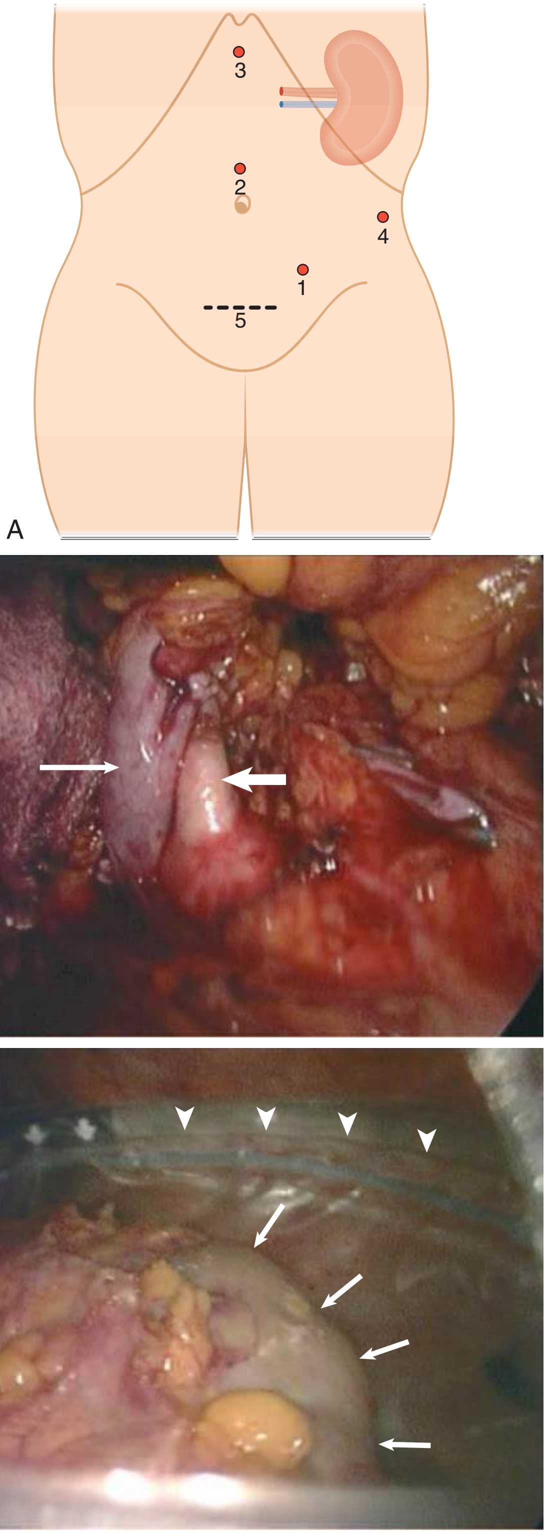


Fig. 103.4 Technique for laparoscopic donor nephrectomy. (A) Positions for four laparoscopic ports (*1* to *4*) and Pfannenstiel incision *(5)* through which the kidney is removed. (B) Intraoperative view showing left renal artery *(short arrow)* and vein *(long arrow)* prepared for control and division. (C) Intraoperative view showing the kidney (*arrows* mark lateral margin) placed in the endoscopic retrieval bag *(arrowheads mark the edge of the bag)*.

Hand-Assisted Laparoscopic Donor Nephrectomy

The hand-assisted technique allows tactile sense to facilitate dissection, retraction, and exposure. It is said to be easier to learn and can be safely and efficiently performed by surgeons with less laparoscopic experience. The hand-assist device allows the operator's nondominant hand to enter the abdomen through an airtight system.

Retroperitoneoscopic Operative Technique

The retroperitoneal approach avoids breaching the peritoneum, displays the renal anatomy in a very different manner, and may be easier for retrieving the full length of the vessels, especially on the right side. The disadvantage is that a more limited operating space is available than with the transperitoneal or hand-assisted laparoscopic techniques.

Contraindications to Minimal Access Donor Nephrectomy

There are no absolute contraindications other than those applying to the open operation. The relative contraindications are dictated by donor factors and the experience of the surgeon. The donor must be fit for anesthesia, including the physiologic stress of pneumoperitoneum. Obesity is a relative contraindication for both open and laparoscopic surgery, and the hand-assisted approach may be better suited in such patients. Previous abdominal surgery is a further relative contraindication because of the potential for adhesions. Multiplicity of renal vessels should not hinder LapDN.

Effect of Pneumoperitoneum

Transient intraoperative oliguria secondary to decreased renal blood flow is a frequent occurrence during laparoscopic procedures. Proposed mechanisms include decreased cardiac output, renal vein compression, ureteral obstruction, renal parenchymal compression, and systemic hormonal effects. Intracranial pressure increases during pneumoperitoneum, with release of vasoconstrictor agents that decrease renal blood flow. Use of a lower pressure reduces the adverse effects of pneumoperitoneum on renal perfusion. In donor nephrectomy, impaired renal blood flow may compromise early allograft function and compound the damaging effects of warm and cold ischemia and operative manipulation of the kidney. Laparoscopically derived donor kidneys have higher serum creatinine up to 1 month post-transplantation compared with open surgery, but thereafter graft function is equivalent.[15] The pioneers of LapDN used high volumes of crystalloid preoperatively and intraoperatively to maintain renal perfusion in the presence of pneumoperitoneum. We have seen two episodes of unilateral pulmonary edema in the dependent lung, and we now recommend volume loading the donor with 2 liters of crystalloid the night before surgery and only using replacement fluid during surgery. This protocol has led to no apparent detriment to graft function.

Graft Function and Acute Rejection

There is no consistent evidence that graft function differs among kidneys retrieved by open, laparoscopic, or hand-assisted donor nephrectomy. The exception is that rates of delayed graft function and acute rejection may be higher in pediatric recipients, especially the 0 to 5-year age group.

Pretransplantation ischemia could, in theory, render the donor kidney more immunogenic by inducing major histocompatibility complex (MHC) class II expression. However, despite the longer warm ischemia time, acute rejection rates and severity of rejection are not higher in laparoscopic than in openly retrieved living donor kidneys.

Technical Issues

Ureteral ischemia was more common in early experience of LapDN but can be avoided if care is taken to ensure that sufficient periureteral tissue is taken and that the dissection does not occur too close to the renal pelvis.

Multiple arteries need not be a barrier to successful use of grafts from laparoscopic donors. In open donor nephrectomy, the right kidney is retrieved in 20% to 30% of procedures, whereas LapDN uses the right kidney in less than 10%,[16] reflecting concern over the operative safety of the right-sided laparoscopic operation, principally the difficulties involved in obtaining an adequate length of renal vein. It has been argued that this practice has led to compromise of the principle that the better kidney should remain with the donor.

Postoperative Recovery

After uneventful open nephrectomy, the donor can expect to be discharged from the hospital in 5 or 6 days and is able to return to work after 3 to 6 weeks, although return to work has been shown to be 2 to 3 weeks later in open nephrectomy compared with LapDN.[11] After LapDN the donor usually leaves hospital in 2 to 4 days and can return to work in 3 to 6 weeks.

Choice of Donor Operative Technique

The choice of operative procedure depends on the local expertise of the surgeons. There is accumulating evidence that the laparoscopic operation removes some of the disincentives to donation, and this approach is likely to be adopted widely in the future.

RENAL PRESERVATION

Preservation of deceased donor organs is crucial to allow time for matching, sharing of organs, and preparation of the recipient. Damage from hypothermia and reperfusion must be minimized. There is little standardization of the type of preservation solution used. Marshall's hyperosmolar citrate solution and histidine-tryptophan-ketoglutarate are popular choices in Europe, but University of Wisconsin (UW) solution is more commonly used in the United States because extended preservation times are more often required.

Organs can be preserved by cold storage (kept in crushed ice after flushing with preservation solution) or by machine-driven pulsatile perfusion. The proposed benefits of machine perfusion come from allowing aerobic function through provision of oxygen and substrate and removal of metabolic end-products. Although machine perfusion has been used for many years, there is still no consensus about its superiority to cold storage nor about the best perfusion parameters. Recent randomized trials have yielded conflicting results; a U.K. trial of DCD kidneys showed no benefit,[17] whereas a European trial demonstrated reduced delayed graft function in deceased donor transplants after machine perfusion.[18]

A novel approach to kidney preservation, only recently introduced into clinical practice, is *ex vivo* normothermic perfusion. Early results are promising,[19] but the technique needs to be studied in larger clinical trials, one of which is ongoing in the United Kingdom.

Decisions on the use of a kidney from a marginal donor can be supported by data from machine or normothermic perfusion; high perfusion pressures are associated with primary nonfunction and delayed graft function.

RENAL TRANSPLANTATION PROCEDURE

The transplanted kidney is placed heterotopically in one or another iliac fossa. The inferior epigastric vessels are ligated, as is the round ligament of the uterus in female patients. Occasionally the inferior epigastric artery may be preserved and used for revascularization of small polar arteries. In male patients the spermatic cord is mobilized

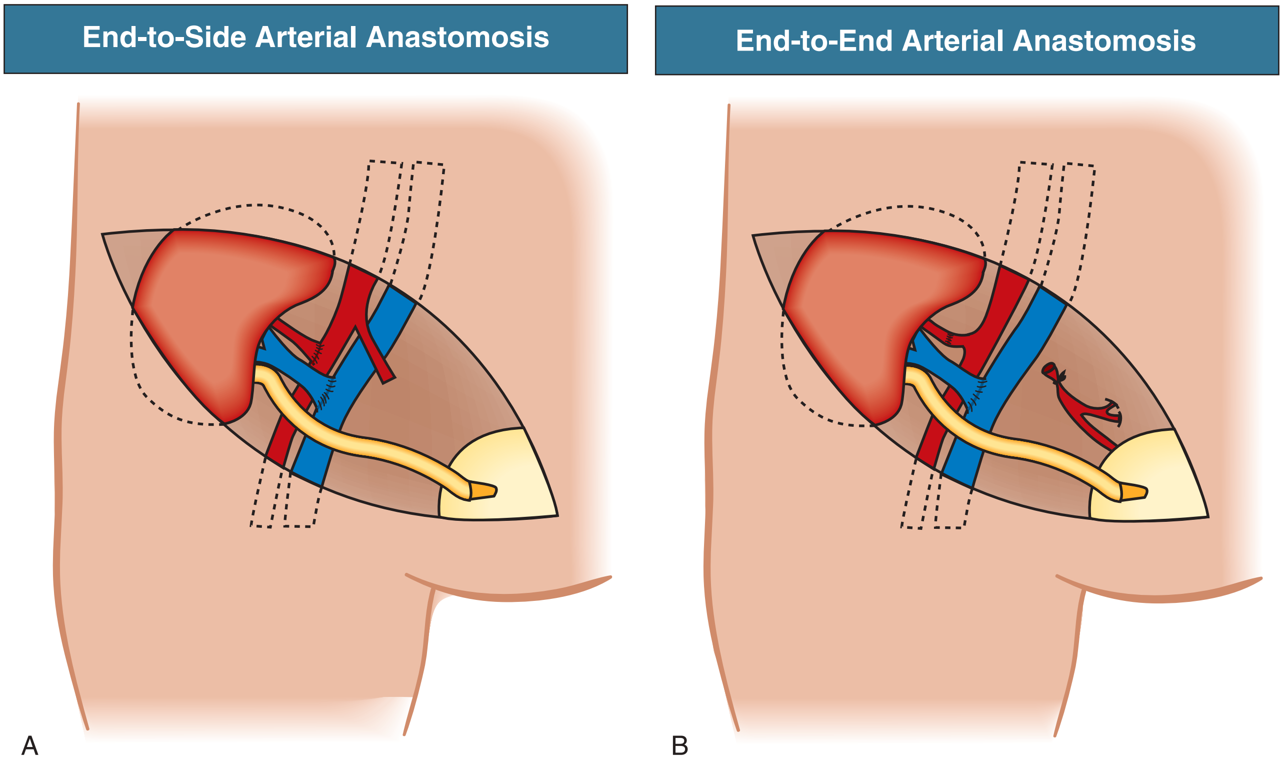

End-to-Side Arterial Anastomosis
End-to-End Arterial Anastomosis
A
B

Fig. 103.5 **Vascular anastomosis techniques for renal transplantation.** (A) End-to-side anastomosis to the external iliac artery. (B) End-to-end anastomosis to the divided internal iliac artery, suitable for living donor transplantation in which no aortic patch is available.

and preserved. The peritoneum should not be breached, but instead swept superiorly to reveal the extraperitoneal bed into which the transplanted kidney will be placed. The iliac blood vessels are then mobilized, with care taken to meticulously ligate all the associated lymphatic channels to reduce the risk for post-transplantation lymphatic leak.

Vascular Anastomosis

The renal vein is anastomosed end to side to the external iliac vein. The arterial anastomosis can be performed either end to side to the external iliac artery or end to end to the divided internal iliac artery (Fig. 103.5). The end-to-side anastomosis is technically easier and is the usual method used in cadaveric transplantation, where it is possible to include a Carrel aortic patch with the renal artery.

With living donor kidneys it is not possible to include a Carrel patch, and occasionally a cadaveric kidney may be provided without a useable patch. In these circumstances the options are to anastomose the renal artery end to end to the divided internal iliac artery or end to side to the external iliac artery. Use of an aortic punch to create a circular arteriotomy may facilitate the latter technique. For living donor kidneys most surgeons use the external iliac artery. It is our experience that positioning the kidney is often easier if the internal iliac artery has been used for the anastomosis, but this does risk buttock claudication and potentially increases the risk for erectile dysfunction in male recipients.

After completion of the vascular anastomoses, the kidney must sit in such a position that the renal vessels are not kinked. The transplanted kidney can be placed laterally in the iliac fossa or may be placed in a subrectus pouch fashioned specifically for the purpose.[20] In the latter case the renal vessels run laterally from the kidney, and this should be noted when a post-transplantation biopsy is performed. An operative diagram of the position of the kidney and vessels is therefore an important component of the clinical notes.

If there are multiple renal vessels, the number of anastomoses should be minimized. This usually can be achieved by careful bench surgery before implantation. If there are two or more renal arteries, their aortic patches are joined in such a way that a single arterial anastomosis is required. If necessary, recipient iliac artery or saphenous vein is used to facilitate reconstruction. Occasionally, small polar arteries will be recognized only after a kidney has been retrieved, and it is particularly important to reanastomose lower polar arteries accurately because these may provide all the ureteral blood supply. In the case of double renal veins, the most common course of action is simply to ligate the smaller vein; the larger one is usually sufficient to drain the whole kidney. If there are two equally sized veins, both may need to be anastomosed separately to the external iliac vein.

Urinary Drainage

The traditional method of ureteral anastomosis is the Politano-Leadbetter technique, involving a transvesical ureteroneocystostomy with creation of a submucosal antireflux tunnel. The end of the transplanted ureter is drawn through a submucosal tunnel from outside to inside and sutured to the bladder mucosa. The majority of surgeons now prefer the technically simpler extravesical ureteroneocystostomy onlay in which the spatulated end of the ureter is anastomosed to the cystostomy and the divided muscle layer is then resutured over the ureter to create a short antireflux muscle tunnel. The onlay method has the advantage of being possible with only a short length of ureter. The shorter the ureter, the less likely it is that there will be an inadequate blood supply to the distal end, thereby reducing the risks for ischemic ureteral leaks or stenosis. A temporary double-J ureteral stent is usually placed. Stents reduce the impact of small technical errors while the ureter is leaking and reduce major urologic complications to an incidence of 1.5%.[21] However, they are a potential source of urinary tract infection, can become

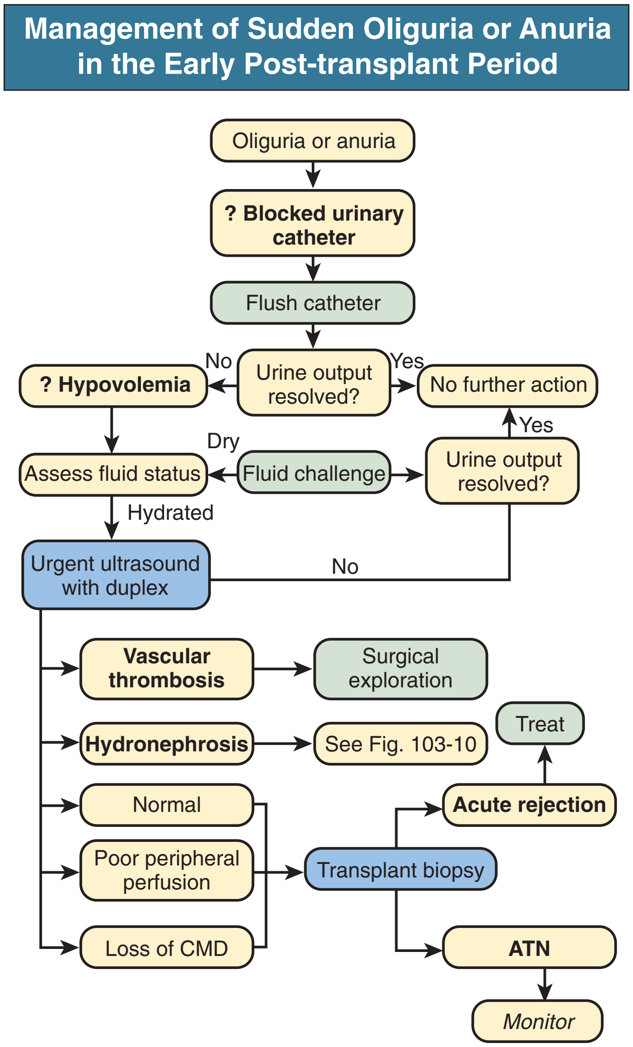


Fig. 103.6 Management of sudden oliguria or anuria in the early post-transplant period. *ATN,* Acute tubular necrosis; *CMD,* corticomedullary differentiation.

encrusted or blocked by debris, and can migrate or fragment. Nevertheless, antibiotic prophylaxis is not justified because it increases the risk for infection with multiresistant organisms. A further danger is the forgotten stent that has not been removed, which should always be considered in patients with unexplained and persistent lower urinary tract symptoms after transplantation. Stents are usually removed 4 to 6 weeks post-transplantation, and this can be performed without general anesthesia with use of a flexible cystoscope.

Alternative Techniques of Urinary Reconstruction

Renal transplantation is quite commonly performed in patients who have abnormal bladders. In many patients it is possible to anastomose the transplanted ureter to the bladder in the hope that the bladder can be rehabilitated, if necessary, with use of post-transplantation intermittent self-catheterization. Nonetheless, some patients require urinary diversion with an ileal conduit. The conduit should be fashioned at least 6 weeks before transplantation, but it may have been present for many years. If so, a contrast study (a conduitogram) should be performed before transplantation to exclude the development of conduit stenosis, although this is rare. The transplanted kidney is best placed in the ipsilateral iliac fossa to avoid tension in the ureter, and it may be preferable to deliberately place the transplanted kidney upside down so that the ureter runs cranially and has a more direct route to the conduit. After revascularization, the peritoneum is opened and the ureter is anastomosed to the conduit over a double-J stent. Excellent long-term results have been achieved with this technique.[22]

Drainage and Wound Closure

Both the transplant bed and the subcutaneous tissues may be drained to prevent the accumulation of serosanguineous fluid or lymph around the transplanted kidney, although many surgeons no longer routinely place drains. The skin is best closed with a subcuticular absorbable suture and then dressed with a clear adhesive dressing so ultrasound scanning can be performed early without disturbing the wound. For this reason, metal clips are rarely used for the skin.

Postoperative Course

The recipient is nursed in a general ward with standard precautions and no need for reverse barrier nursing. There is no benefit to continuing prophylactic antibiotics beyond a single dose given at induction of anesthesia. Prophylaxis against thromboembolic disease is in the form of thromboembolic deterrent stockings and low molecular weight heparin (LMWH) is continued until discharge. Oral fluids and diet are commenced as tolerated immediately after surgery. Maintenance immunosuppressive agents are given orally, except in the presence of a prolonged postoperative ileus with high volumes of nasogastric drainage, when they should be administered intravenously. If recovery is straightforward, the bladder catheter and wound drains are usually removed by day 5, and the recipient is fit for discharge after 7 to 10 days to be kept under close outpatient monitoring.

SURGICAL COMPLICATIONS OF RENAL TRANSPLANTATION

There is a small but significant incidence of technical complications, which can be minimized by avoiding damage to the kidneys at the time of the retrieval. Nonetheless, the presence of multiple renal vessels and donor atherosclerotic disease does increase the likelihood of technical problems in the recipient, as do recipient obesity, atherosclerosis, and previous transplantation. Algorithms to aid in the management of complications in the early post-transplant period can be found in Figs. 103.6 and 103.7.

Wound Infection

The use of preoperative prophylactic antibiotics, commonly amoxicillin–clavulanic acid, has reduced the incidence of wound infection to less than 1%. If a wound infection does occur, treatment is with antibiotics, guided by microbiologic wound swabs, and drainage of collections as necessary.

Wound Dehiscence

The risk for wound dehiscence is increased in obese and diabetic patients and those receiving sirolimus. Identification and treatment of any infection are mandatory. Resuturing of the wound is rarely justified. Large areas of dehiscence often benefit from vacuum-assisted closure, but the majority require only frequent dressing.

Vascular Complications

Transplant vascular thrombosis is a feared complication that may cause early and irreversible graft failure. Although there are also significant hemorrhagic risks, routine perioperative prophylaxis should be given with subcutaneous LMWH, and some units prescribe aspirin for the first few postoperative months.

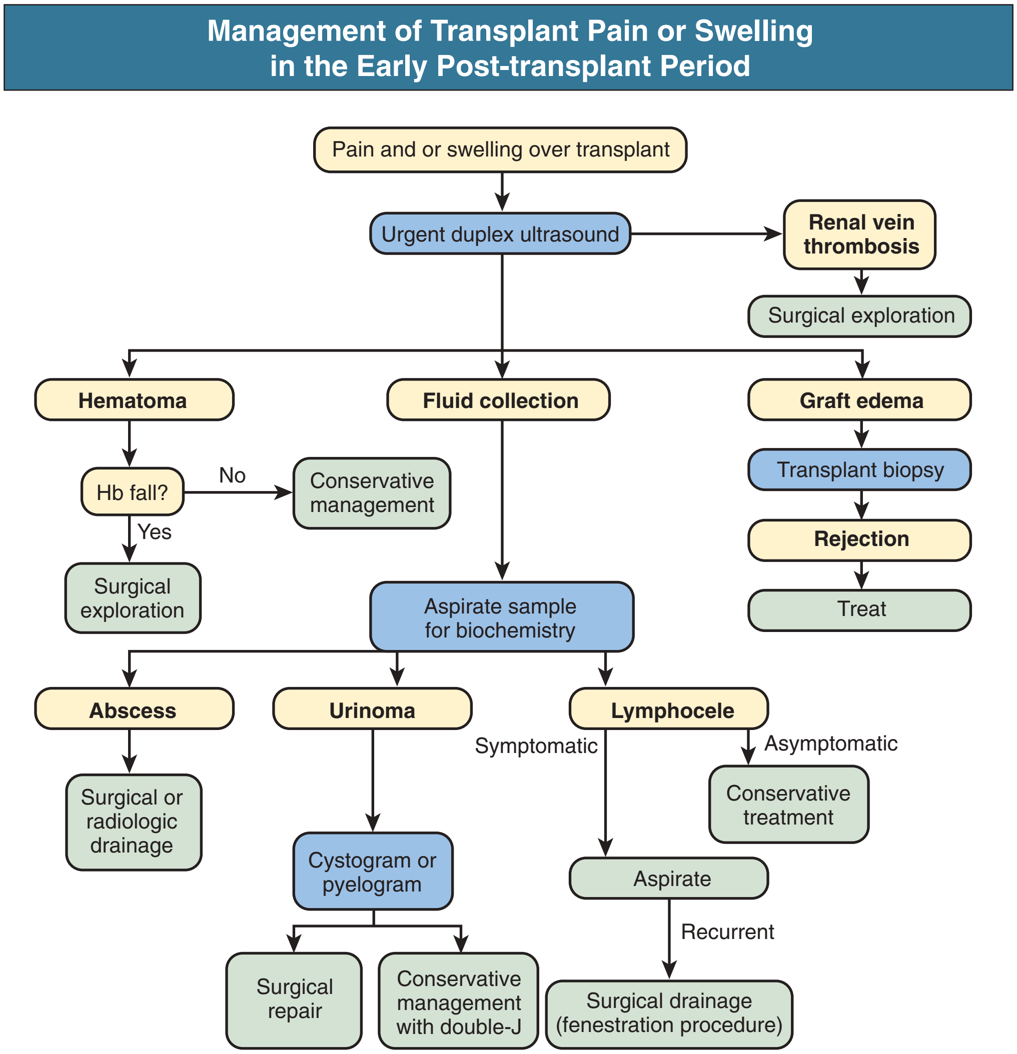

Management of Transplant Pain or Swelling in the Early Post-transplant Period
Pain and or swelling over transplant
Urgent duplex ultrasound
Renal vein thrombosis
Surgical exploration
Hematoma
Fluid collection
Graft edema
Hb fall?
No
Yes
Conservative management
Transplant biopsy
Rejection
Treat
Surgical exploration
Aspirate sample for biochemistry
Abscess
Urinoma
Lymphocele
Symptomatic
Asymptomatic
Surgical or radiologic drainage
Conservative treatment
Cystogram or pyelogram
Aspirate
Recurrent
Surgical repair
Conservative management with double-J
Surgical drainage (fenestration procedure)

Fig. 103.7 Management of transplant pain or swelling in the early post-transplant period. *Hb,* Hemoglobin.

Bleeding From Vessels in the Renal Hilum

Careful postoperative observation and regular hemoglobin and hematocrit measurements are crucial for the early detection of bleeding. Output from the transplant drains may give an early indication of heavy blood loss. Unsecured small vessels in the renal hilum may not be obvious during surgery, but they may start bleeding postoperatively. This form of blood loss can be slow, persistent, and serious. If the patient's condition allows, urgent imaging may be performed to secure a diagnosis, but the best course of action is usually emergency exploration of the transplant under general anesthesia.

Anastomotic Hemorrhage

Anastomotic hemorrhage is a rare occurrence, usually caused by a technical surgical error, and is more common with multiple arteries and the use of antiplatelet agents.[23,24] Early after transplantation, the patient may report pain over the graft. This symptom always should be taken seriously. There also may be pain in the back or the rectum caused by a tension hematoma in the retroperitoneum or pelvis. Significant hemorrhage will be attended by circulatory collapse, with tachycardia and hypotension. There will be a decrease in the hemoglobin and hematocrit, sometimes to alarmingly low levels. The patient must be returned to the operating room immediately and the transplant reexplored.

Hemorrhage also can occur some weeks after transplantation because of the development of a mycotic aneurysm of the renal artery. In the rare case of a ruptured mycotic aneurysm, an immediate graft nephrectomy is required, but the mortality is high.

Renal Artery Thrombosis

Renal artery thrombosis is a rare event, occurring in less than 1% of transplants. The usual outcome is loss of the kidney. Acute arterial thrombosis may occur intraoperatively or during the first days or weeks after transplantation. Potential causes include hyperacute rejection or a procoagulant state, but most cases are caused by a technical error during the anastomosis of small or atheromatous vessels.[24] Successful vascular anastomosis requires that the vessels are not under tension and that there is a smooth transition between the two endothelial surfaces; sutures must be placed through all layers of the vessel walls so an intimal flap is avoided. Vascular adventitia is thrombogenic and must be excluded from the lumen of the anastomosis. The risk for renal artery thrombosis is increased in the presence of atherosclerosis, persistent hypotension, volume depletion (e.g., diarrhea, excessive preoperative dialysis), and prothrombotic states, including diabetes.

Renal arterial thrombosis manifests with sudden anuria, the differential diagnoses being a blocked urinary catheter, dehydration, acute tubular necrosis, or a urologic complication. A high index of suspicion is required to make this diagnosis, particularly in the immediate postoperative period. The only worthwhile investigation is an urgent duplex ultrasound scan, but if the diagnosis is seriously entertained, the only hope of saving the transplant is to reexplore it immediately in the hope that a correctable cause can be found. The reality is that unless the acute arterial thrombosis occurs during surgery, there is little chance of saving the transplanted kidney. Acutely thrombosed grafts must nevertheless be explored and removed to avoid the development of sepsis in a necrotic graft, a potentially fatal complication.

Renal Vein Thrombosis

Renal vein thrombosis is more common than arterial thrombosis and occurs in 1% to 6% of renal transplants.[24,25] Although it may result from a technical error at the time of surgery, its cause is usually less certain. The renal vein can certainly be twisted or kinked if it is not correctly placed after completion of the vascular and ureteral anastomoses. The peak incidence of renal vein thrombosis is 3 to 9 days after transplantation[26]; transplant patients with good initial graft function will have a sudden loss of urine output, which is often markedly blood stained, associated with severe pain arising from swelling and (very rarely) rupture of the allograft. The ipsilateral leg may swell if there is involvement of the iliac venous system. Renal vein thrombosis also may be occult and is one differential diagnosis of delayed graft function. Duplex ultrasound scanning is the best investigation. In an established renal vein thrombosis this may show an obviously swollen allograft with surrounding hematoma and an absence of renal perfusion. Lesser degrees of thrombosis, or indeed incipient thrombosis, may be highlighted by an absence of arterial flow in diastole. An even later development is a reversal of flow in diastole.

As with arterial thrombosis, if this diagnosis is entertained, the best course of action is to reexplore the transplant as an emergency. The renal vein anastomosis can be opened to allow clot to be extracted, and the venotomy is then closed and the kidney observed for improvement. A more radical alternative is to immediately explant the kidney by taking down the arterial, venous, and ureteral anastomoses. The kidney can then be reflushed with cold perfusion fluid on the back table and held in preservation fluid at 4° C. This allows much more time to assess the cause of the venous thrombosis, and if the kidney remains viable, the transplant operation can be repeated. If the transplant is already infarcted or cannot be adequately flushed with preservation fluid, the organ will need to be discarded anyway and nothing is lost by immediate explantation. Successful emergency surgical exploration with subsequent long-term function is rare. Interventional radiographic techniques offer an alternative to surgery. The renal vein can be selectively catheterized via the ipsilateral femoral vein, and graft thrombolysis then may be attempted. This technique is particularly useful when renal vein thrombosis occurs late after transplant and the risk for systemic anticoagulation is low. The use of various thrombolytic agents has been reported, including heparin, urokinase, streptokinase, and tissue plasminogen activator, with no consensus as to which is the most appropriate.

Transplant Renal Artery Stenosis

Transplant renal artery stenosis is a later complication occurring 3 to 48 months after transplantation. Not all stenoses are of functional or clinical significance, as shown by studies in which all functioning transplants have undergone angiography.[27] Causal factors include donor and recipient atherosclerosis, factors associated with surgical technique, and severe acute rejection.[28] The presentation and management of transplant renal artery stenosis are discussed in Chapter 41.

Lymphocele

Small, clinically insignificant lymphatic collections can be demonstrated by ultrasound scan in up to 50% of renal transplants.[29] Larger lymphoceles that cause complications or require treatment occur in 2% to 10% of patients.[30] The source of peritransplant lymph leaks is the lymphatic channels around the iliac arterial system rather than the lymphatics of the transplanted kidney itself.[31] Therefore, during the dissection of the iliac arterial system, all the surrounding lymphatic channels must be meticulously secured with nonabsorbable ligatures or metals clips. Wound suction drains should not be removed postoperatively until less than 30 ml of fluid is produced on 2 consecutive days. It is safe to leave drains in place for several weeks post-transplantation to allow a low-volume lymphatic leak to seal by gradual fibrosis. Despite the theoretical risk for infection, this does not seem to be a problem in practice. If necessary, the patient can be discharged from the hospital with the drain in situ.

Compression of the transplanted ureter leading to renal dysfunction is produced only by very large lymphoceles (volume >300 ml). The peak incidence is at 6 weeks, but a lymphatic collection may manifest 2 weeks to 6 months after transplantation.[29] Most lymphatic collections are found anterior to the iliac vessels and lying between the transplant and the bladder (Fig. 103.8). Presenting features may include wound or ipsilateral thigh swelling in association with suprapubic discomfort and urinary frequency caused by bladder compression. Other presentations include pain over the transplanted kidney, sometimes associated with fever, ureteral obstruction with graft dysfunction, and ipsilateral thrombophlebitis. However, the vast majority are asymptomatic and manifest as an incidental finding during an ultrasound scan being performed for another reason. It is important to aspirate all peritransplant fluid collections under ultrasound control to aid diagnosis. Macroscopic

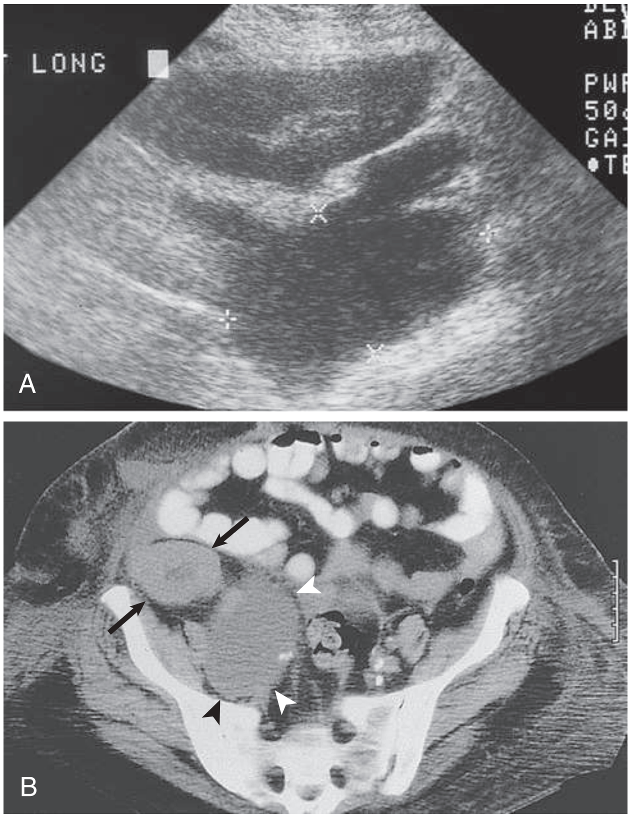


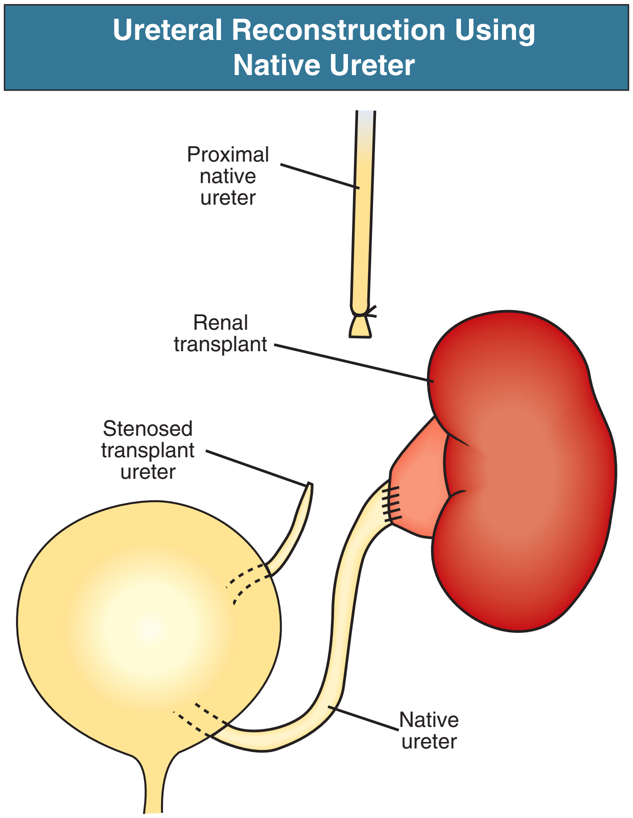
Fig. 103.8 **Post-transplantation lymphocele.** (A) Ultrasound appearance. A large echolucent lymphocele can be seen inferior to the transplanted (marked by *crosses*). (B) Computed tomography appearance. A 5- × 5-cm lymphocele *(arrowheads)* is present under the transplanted kidney *(arrows)*.

findings are usually sufficient to differentiate infected from noninfected lymph, and biochemical analysis of the fluid allows a urine leak to be excluded. Computed tomography or magnetic resonance imaging is an essential investigation if surgery is being contemplated, particularly if a laparoscopic procedure is planned. This allows accurate definition of the relationship between the lymphocele and the transplanted ureter. If the ureter is bow-strung across the superior surface of the lymphocele, it could be damaged during a laparoscopic fenestration procedure.

Many small lymphoceles are asymptomatic and will resolve spontaneously given enough time. If action is deemed necessary, first-line treatment is aspiration under ultrasound control. If there is a recurrence, further aspirations can be performed or an external drain can be placed with ultrasound guidance. If these simple measures fail, open or laparoscopic surgical drainage may be required. A 5-cm-diameter disk of the lymphocele wall is removed to create a large opening into the peritoneal cavity, allowing reabsorption of the lymph through the abdominal lymphatic drainage system. These peritoneal fenestrations have a tendency to heal before the lymphocele is completely reabsorbed, leading to early recurrence; a metal or omental plug may prevent this.

Urologic Complications

Urinary tract complications are relatively common after renal transplantation, with an incidence of 5% to 14%.[32] Although they can be difficult to manage, they only rarely cause graft loss or mortality. The relatively high incidence of urologic problems is a consequence of the tenuous blood supply of the transplanted ureter. After kidney retrieval, the only ureteral blood supply that is preserved is derived from the renal artery near the hilum of the kidney, and this can be easily damaged during retrieval.



Ureteral Reconstruction Using Native Ureter

Fig. 103.9 Ureteral reconstruction using native ureter.

Urinary Leaks

Urinary leaks most commonly occur because of ischemic necrosis in any part of the transplanted urinary collecting system. The distal ureter has the poorest blood supply and is therefore the most common site. Less commonly, leaks occur from the renal pelvis or the midportion of the ureter, which may be a result of unrecognized direct damage to the ureter during organ retrieval. Urinary leaks tend to occur in the first few days after transplantation but can manifest much later. The usual presentation is with straw-colored fluid leaking directly from the transplant wound or accumulating in the drains in association with oliguria. Alternatively, extravasating urine may accumulate as a peritransplant fluid collection. This manifests as a painful swelling of the wound, and the patient may have a fever. In either case, the extravasated fluid must be differentiated from lymph by biochemical analysis of the fluid and a simultaneous serum sample. Urine will have markedly elevated urea and creatinine levels compared with the patient's serum, whereas lymph will have a similar biochemical profile.

The presence of a urinary fistula should be confirmed by antegrade or retrograde pyelography. Both of these techniques present challenges. Antegrade puncture of a nondilated pelvicaliceal system is technically difficult but usually possible. Retrograde cannulation of the transplanted ureteral orifice can be attempted with a flexible cystoscope. This is also a difficult maneuver because the transplanted ureter is implanted into the dome of the bladder rather than at its base. If the urine leak is contained as a urinoma, ultrasound will demonstrate a fluid collection between the transplanted kidney and the bladder, which can be sampled by needling or drained by the placement of a suitable percutaneous catheter.

The management of urinary leaks has changed significantly in recent years. The former practice of early reexploration and surgical reconstruction[33] is no longer always necessary. Interventional radiographic techniques offer an alternative, at least for initial treatment. The aim is to place a double-J (pigtail) ureteral stent across the region of damage via an antegrade nephrostomy; this may allow time for the urinary fistula to heal.[34] This technique, however, is unlikely to be successful if there is significant ischemic necrosis of the ureter, in which case, surgery still has a role. Reexploration of kidney transplants is straightforward in the early postoperative period but may be a considerable challenge later because of the development of an intense peritransplant fibrotic reaction. The choice of operative procedure for a necrotic distal ureter depends on the length of remaining viable ureter. If there is sufficient length after excision of the necrotic distal portion, the transplanted ureter may simply be reimplanted into the bladder. If this is not possible, the urinary tract should be reconstructed with use of the patient's native ureter. Depending on length of viable transplanted ureter, there is a choice between anastomosing the native ureter to the transplanted ureter proximal to the ischemic segment (ureteroureterostomy) or to the transplanted renal pelvis (ureteropyelostomy; Fig. 103.9). Whichever technique is chosen, the anastomosis should be protected with a double-J stent. Although these techniques require the native ureter to be ligated proximally, there is usually no need to perform an ipsilateral nephrectomy.[35] Postoperatively, the antegrade nephrostomy can be left in situ so a contrast study can be performed after 7 to 10 days to confirm healing of the new anastomosis. If the transplant recipient has undergone an ipsilateral nephrectomy in the past or the native ureter is too diseased to be used for reconstruction, a Boari bladder flap can be used to reconstruct the urinary tract.

Ureteral Obstruction

Obstruction of the transplanted ureter may occur at any time after transplantation. It should always be considered in the differential diagnosis of acute transplant dysfunction and excluded by ultrasound examination. The management of transplant ureteral obstruction is

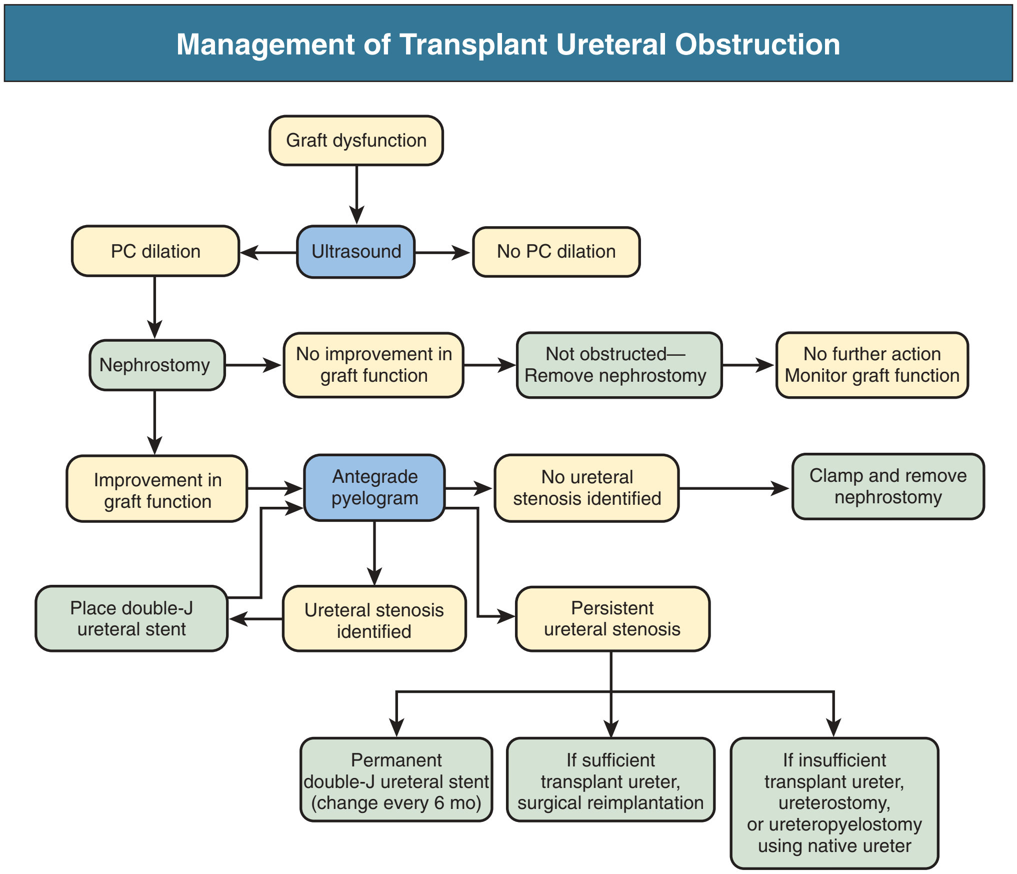

Management of Transplant Ureteral Obstruction
Graft dysfunction
Ultrasound
PC dilation
No PC dilation
Nephrostomy
No improvement in graft function
Not obstructed—Remove nephrostomy
No further action Monitor graft function
Improvement in graft function
Antegrade pyelogram
No ureteral stenosis identified
Clamp and remove nephrostomy
Place double-J ureteral stent
Ureteral stenosis identified
Persistent ureteral stenosis
Permanent double-J ureteral stent (change every 6 mo)
If sufficient transplant ureter, surgical reimplantation
If insufficient transplant ureter, ureterostomy, or ureteropyelostomy using native ureter

Fig. 103.10 Management of transplant ureteral obstruction. *PC,* Pelvicaliceal.

summarized in Fig. 103.10. Early obstruction is uncommon and suggestive of a technical error, such as creating a submucosal bladder tunnel that is too tight, kinking of a redundant length of ureter, and incorrect suture placement during anastomosis. Early obstruction may be caused by a blood clot in the ureter, bladder, or catheter. Bleeding may occur from the ureterovesical anastomosis or cystostomy or after a transplant biopsy. It is common practice to drain the urinary bladder using a three-way irrigating catheter because small-diameter two-way Foley catheters are easily blocked by blood clot.

Late ureteral obstruction may occur at the vesicoureteral or pelviureteral junctions. Ischemia that is not severe enough to cause necrosis is presumed to be the cause of most vesicoureteral obstructions.[36] Renal transplants invariably excite a pronounced perigraft fibrotic response, and this is more likely to be the cause of an obstruction at the level of the pelviureteral junction. It is also possible that acute rejection episodes contribute to subsequent fibrosis.[34] BK polyoma virus also can cause late ureteric obstruction because of hypertrophy of ureteric epithelial cells in combination with infiltration of inflammatory cells.

An ultrasound scan will demonstrate a dilated pelvicaliceal system. However, long-standing kidney transplants may have quite marked pelvicaliceal dilation without being obstructed. This most commonly causes uncertainty in assessment of whether obstruction may be contributing to chronic allograft dysfunction in a patient with biopsy-proven chronic allograft nephropathy. Further investigation is needed to confirm or refute the presence of obstruction and define its anatomy. Retrograde pyelography has a low success rate because of the difficulty of catheterizing the transplanted ureteral orifice at cystoscopy. Therefore percutaneous nephrostomy followed by antegrade pyelography is the investigation of choice in suspected transplant ureteral obstruction. The nephrostomy is performed under antibiotic cover using ultrasound control, and the nephrostomy tube should be left in place for a few days. If serum creatinine decreases during this period, obstruction is confirmed. If there is no improvement in renal function, significant obstruction can be confidently excluded. This simple observation avoids the need for an antegrade pressure study (Whittaker test), which may be difficult to interpret in transplanted kidneys. After external decompression of the transplanted kidney for a few days, an antegrade pyelogram is obtained to accurately define the anatomy of the obstructing lesion.

Nonoperative approaches for the treatment of transplant ureteral stricture are often preferred.[37] The simplest approach is to place a double-J stent across the stricture via a percutaneous nephrostomy. This may require initial balloon dilation.[38] The stent can be removed after 6 weeks, but the restenosis rate is high. An alternative is long-term stenting, changing the stent every 6 months. The disadvantage of this method is a high incidence of urinary tract infection, with potential severe consequences for immunosuppressed patients, and long-term antibiotic prophylaxis is a sensible precaution. Open surgical management still has a place in the management of ureteral obstruction. The operation performed depends on the site of obstruction and remaining length of healthy transplanted ureter proximal to the obstruction (see discussion of urinary leaks). Not all cases of obstruction require intervention. When there is a mild degree of obstruction not associated with urinary tract infection and in a long-standing kidney that is affected by chronic allograft nephropathy, it may be better to simply monitor transplant function, reserving intervention for a later date should it become necessary.

Complications in the Transplant Bed

A number of nerves may be encountered in the retroperitoneal dissection required for kidney transplantation. These include the lateral femoral cutaneous nerve and the femoral, obturator, and sacral nerves. Each of these may be damaged by a traction injury, particularly when modern fixed wound retraction systems are used, because these can exert a great deal of pressure on the surrounding tissues. Patients with such neurapraxias should recover completely, but this may take some months, and the condition can be very disabling.

In male transplant recipients, the spermatic cord must be mobilized during the dissection to gain access to the retroperitoneal space. Damage to the testicular artery in the cord can result in testicular atrophy.

TRANSPLANT NEPHRECTOMY

The optimal management strategy for patients with a failed renal transplant remains unclear, with a lack of good-quality evidence. Transplant nephrectomy is mandatory for early graft failure caused by vascular thrombosis, capsular rupture, and irreversible rejection. However, the management of a renal transplant that has chronically failed is more challenging. The options are transplant nephrectomy or leaving the graft in situ, with or without continuation of immunosuppression. Mortality from both infection and cardiovascular disease has been shown to be higher in patients with failed grafts continuing immunosuppression.[39] However, weaning and discontinuation of immunosuppression also have been shown to increase the risk for transplant nephrectomy and allosensitization.[40]

If the graft remains in situ without immunosuppression, signs and symptoms such as pain, fever, hematuria, and thrombocytopenia may prompt transplant nephrectomy, although the patient also can be treated initially with corticosteroids.

Historically, transplant nephrectomy was advocated to remove antigenic stimulation for anti–human leukocyte antigen (anti-HLA) antibody production, which might adversely affect the possibility of retransplantation. However, there is some evidence that transplant nephrectomy, particularly late after transplantation, may actually increase allosensitization.[41] The suggestion is that the graft may act as an “immunologic sponge” to absorb antibody or may regulate the production of antidonor antibody by the recipient’s immune system.

Early graft nephrectomy is straightforward, but after the first few weeks kidney transplants usually develop quite intense perigraft fibrosis, and this can make late allograft nephrectomy a difficult technical challenge. A subcapsular dissection is preferred, and after removal of the kidney, the hilum is sutured, leaving a cuff of donor vessels in place. Careful hemostasis is required, and the whole raw capsular bed should be cauterized. The wound is usually closed without drains.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is/are *false* regarding organ donation and retrieval?
   - **A.** For donation after brain death the aorta is cannulated after cardiac arrest.
   - **B.** Donation after cardiac death kidneys sustain a period of warm ischemia during retrieval.
   - **C.** Approximately 35% of renal transplants in the United Kingdom are currently from living donors.
   - **D.** Laparoscopic donor nephrectomy is contraindicated with multiple renal arteries.
   - **E.** The usual hospital stay after laparoscopic donor nephrectomy is 2 to 4 days.
2. Which of the following is/are *true* regarding the renal transplant surgical procedure?
   - **A.** The kidney is placed in an extraperitoneal position in one or the other iliac fossa.
   - **B.** For cadaveric renal transplants the renal artery is usually anastomosed to the internal iliac artery.
   - **C.** Lower pole renal arteries can be sacrificed without increasing the risk for ureteral complications.
   - **D.** The transplant ureter is anastomosed directly to the bladder.
   - **E.** Transplant ureteral stents should remain in place for 3 months.
3. Which of the following is/are *not* risk factors for transplant renal artery thrombosis?
   - **A.** Atherosclerosis
   - **B.** Dehydration
   - **C.** von Willebrand disease
   - **D.** Diabetes
   - **E.** Protein C deficiency
4. Which of the following is/are *true* regarding urologic complications after renal transplantation?
   - **A.** Urologic complications are less common than vascular complications.
   - **B.** Urologic complications invariably manifest early.
   - **C.** Urine leaks are diagnosed by markedly raised urea and creatinine levels in the fluid compared with serum.
   - **D.** Reexploration and surgical reconstruction are always required for urine leaks.
   - **E.** Transplant ureteral stenosis is associated with BK polyoma virus infection.
5. Which of the following is/are *true* regarding transplant nephrectomy?
   - **A.** Transplant nephrectomy is mandatory for early graft failure caused by thrombosis.
   - **B.** Transplant nephrectomy reduces allosensitization.
   - **C.** Mortality is higher in patients with failed grafts weaned from immunosuppression.
   - **D.** Graft nephrectomy, particularly late after transplantation, is straightforward.
   - **E.** All failed renal transplants should be removed.

104

Prophylaxis and Treatment of Kidney Transplant Rejection

James E. Cooper, Erik Stites, Alexander C. Wiseman

The clinical presentation of the immune response to transplanted tissue (referred to as *rejection*) became apparent in 1960 when, after successful proof-of-principle kidney transplants were performed in identical twins, kidney transplantation was attempted between immunologically dissimilar individuals.[1] Eleven patients underwent lymphoid irradiation to prevent rejection after kidney transplant from nonidentical donors. Although 10 of 11 died of overwhelming infection, illustrating the potential consequences of immunosuppression, the lone surviving patient from this series subsequently experienced two episodes of acute rejection, both of which were treated with corticosteroids, and recovered good graft function. Thus began the development of immunosuppressive agents that could prevent and treat rejection while not inducing severe life-threatening side effects. As a result of the development of newer immunosuppression medications, the incidence of acute rejection in the first year after transplant has significantly decreased over time and is now approximately 10% to 15%[2] (Fig. 104.1). However, the management of chronic rejection has remained a challenge, with continued attempts to better define the nature of injury and methods to prevent or reverse this process. As attention shifts to limiting the toxicity of immunosuppression medications (e.g., withdrawal of corticosteroids or calcineurin inhibitors [CNIs]) and attempts to increase access to transplant (e.g., performing transplants across human leukocyte antigen [HLA] and blood type barriers), management of acute rejection continues to be an important clinical issue.

DEFINITION

Rejection (both acute and chronic) is defined by histologic findings after kidney transplant biopsy. A biopsy considered adequate for analysis contains at least 10 glomeruli and 2 small arteries, stained for hematoxylin and eosin (HE), periodic acid–Schiff (PAS) or methenamine silver, and Masson trichrome, and a biopsy with 7 to 9 glomeruli and 1 artery is considered of marginal adequacy. When performed for clinical indications (renal dysfunction), two separate cores should be obtained because the findings of rejection are often patchy in distribution (Fig. 104.2).[3]

The Banff Working Classification of Renal Allograft Pathology forms the basis of the histologic definition of rejection and is updated biannually (Box 104.1). First developed in 1993 with a primary focus on T cell–mediated acute inflammatory infiltrates to classify the degree of rejection, updates in the classification differentiated humoral (antibody-mediated) and T cell responses and further distinguished a chronic humoral form of injury previously classified as chronic allograft nephropathy (see Chapter 107).[4] This was based on the indirect identification of antibody-mediated injury by evidence of complement (C4d) deposition. C4d is a fragment of C4b that is generated after immunoglobulin G (IgG) and IgM binding to host antigens with activation of the classical complement pathway. C4b/C4d forms a covalent bond with proteins on tissue such as capillary endothelial cells via a sulfhydryl group and remains bound to tissue after immunoglobulin and other complement products have been released.[5] Staining for C4d, either by immunohistochemistry or immunofluorescence, indicates that an antibody-mediated process may be involved.

Although the detection of C4d remains a specific marker for antibody-mediated graft pathology, significant limitations in sensitivity have led to the recognition of C4d-negative antibody–mediated rejection.[6] Studies of endothelial-associated transcript (ENDAT) expression[7,8] and C4d-negative histologic findings from protocol biopsy studies in patients with microvascular inflammation[9] helped identify the clinical importance of C4d-negative antibody–mediated rejection, which led to these updated Banff criteria.

Antibody-Mediated Rejection

Acute antibody-mediated (humoral) rejection occurs in 5% to 7% of all transplants and is present in 20% to 30% of episodes of acute rejection[10] in patients at lower immunologic risk, occurring typically within the first few weeks of transplantation or in association with a change in immunosuppression. Although patients who have preexisting donor-specific HLA alloantibodies (donor-specific antibodies) are at higher risk for acute humoral rejection, the identification of de novo donor-specific antibodies at the time of graft dysfunction is common. The diagnosis of acute humoral rejection requires (1) evidence of circulating donor-specific antibodies, (2) evidence of current/recent antibody interaction with vascular endothelium, and (3) evidence of tissue injury (Fig. 104.3).[6] Patterns of injury associated with acute humoral rejection range from acute tubular cell injury suggestive of acute tubular necrosis to thrombotic microangiopathy, but neutrophils and/or macrophages are typically present in peritubular capillaries. The requirement for evidence of antibody/endothelial interaction has been expanded beyond C4d staining and now includes at least moderate microvascular inflammation or evidence of increased ENDAT expression if using a validated assay.

Chronic active antibody-mediated rejection has been identified as a leading cause of late allograft loss[7,11] and is likely the result of an indolent alloimmune response that can result in transplant glomerulopathy and microcirculatory inflammation. Although transplant glomerulopathy is often associated with circulating donor-specific antibodies and C4d deposition, these diagnostic markers are not detected in 30% to 50% of cases.[12] One possibility is that these lesions are not solely due to a humoral response. Alternatively, the failure to detect these

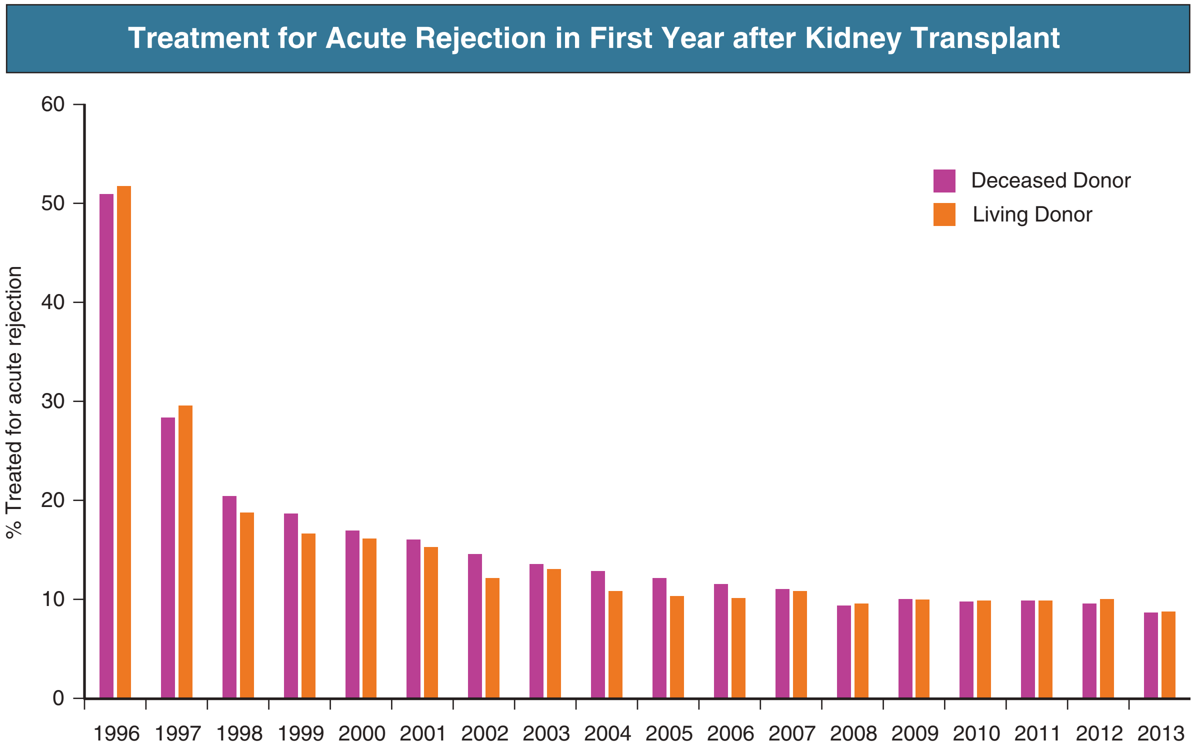

Fig. 104.1 **Treatment for acute rejection within 1 year of transplant in the United States, 1996 to 2013.** (From 2015 U.S. Renal Data System [USRDS] data report.)

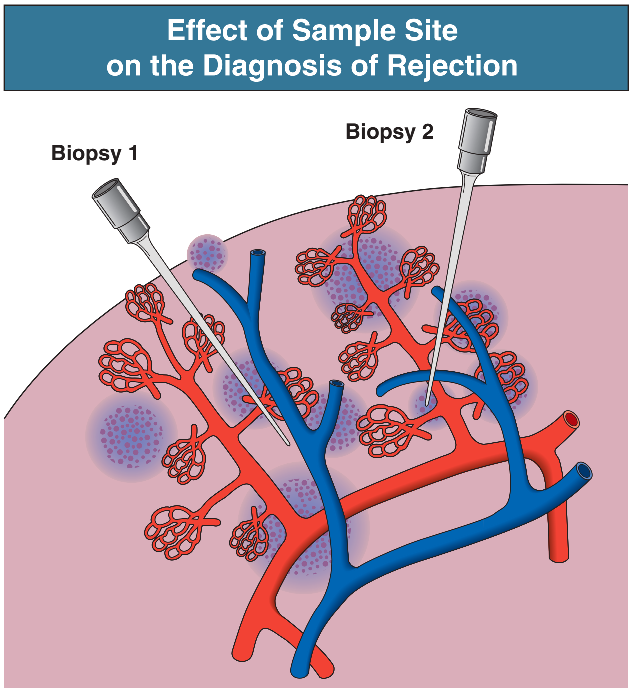

Fig. 104.2 **Biopsy technique.** Acute rejection begins as patchy, focal infiltrates and becomes homogeneous only in advanced stages. The intensity of mononuclear infiltrate seen on biopsy sample would differ between core 1 and core 2. Routinely taking two core biopsy samples can help decrease the sampling errors, which can affect the histologic interpretation of rejection.

markers could be due to non–complement-fixing antibodies and/or the waxing/waning nature of the humoral response.

The current Banff diagnostic criteria for chronic humoral rejection require (1) evidence of donor-specific antibodies, (2) evidence of current/recent antibody interaction with vascular endothelium, and (3) evidence of chronic tissue injury such as transplant glomerulopathy, multilamination of the peritubular capillary basement membrane, and/or arterial intimal fibrosis (Fig. 104.4).

T Cell–Mediated Rejection

The original pathologic description of rejection is now referred to as *T cell–mediated rejection*. The classification of acute T cell–mediated rejection (acute cellular rejection [ACR]) is based on the degree and location of mononuclear cell inflammation. Because interstitial inflammation and tubulitis are frequently present immediately beneath the renal capsule (subcapsular inflammation) in stable allografts, this finding is not considered when interpreting an allograft biopsy result for the presence of rejection. When severe, interstitial inflammation may extend into tubules via injury to the tubular basement membrane (tubulitis). The predominant phenotype of these infiltrates is a mixture of $CD4^+$ and $CD8^+$ T cells; however, B cells, eosinophils, and macrophages also may be present. Less commonly, endarteritis (endothelialitis) may be present in which T cells and macrophages extend under the arterial endothelium, a phenomenon that may or may not be accompanied by interstitial inflammation or tubulitis. The finding of interstitial infiltrates and tubulitis in a kidney transplant biopsy is not specific to ACR and other causes such as viral nephropathy (BK virus, less commonly cytomegalovirus), pyelonephritis, or post-transplant lymphoproliferative disease should be considered. In contrast, the histologic finding of endothelialitis is pathognomonic of ACR.

Acute T cell–mediated rejection is histologically classified in the Banff criteria by endothelialitis, the degree of interstitial inflammation, and the quantity of cells infiltrating into tubules. Type I ACR is

BOX 104.1 Banff Classification of Rejection

Antibody Mediated

Acute/Active

- I. Acute tissue injury with one or more of the following:
  - a. Microvascular inflammation ($g>0$, $ptc>0$)
  - b. Intimal arteritis ($v>0$)
  - c. Acute thrombotic microangiopathy
  - d. Acute tubular injury
- II. Evidence of current/recent antibody interaction with vascular endothelium with one or more of the following:
  - a. Linear peritubular capillary C4d staining
  - b. Moderate microvascular inflammation ($g+ptc\geq2$)
  - c. Increased expression of endothelial injury-associated gene transcripts in biopsy tissue
- III. Serological evidence of donor specific antibodies

Chronic Active

- I. Acute tissue injury with one or more of the following:
  - a. Transplant glomerulopathy ($cg>0$)
  - b. Severe peritubular capillary basement membrane multilayering
  - c. Arterial intimal fibrosis
- II. Evidence of current/recent antibody interaction with vascular endothelium with one or more of the following:
  - a. Linear peritubular capillary C4d staining
  - b. Moderate microvascular inflammation ($g+ptc\geq2$)
  - c. Increased expression of endothelial injury-associated gene transcripts in biopsy tissue
- III. Serological evidence of donor specific antibodies

T Cell Mediated

Acute

Mononuclear cell interstitial inflammation and tubulitis and/or arteritis

- IA: More than 25% interstitial infiltration, 4 to 10 mononuclear cells/tubular cross section
- IB: More than 25% interstitial infiltration, greater than 10 mononuclear cells/tubular cross section
- IIA: Intimal arteritis, mild to moderate (0% to 25% of luminal area)
- IIB: Intimal arteritis, severe (>25% of luminal area)
- III: Transmural arteritis and/or fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocyte inflammation

Chronic

Arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neointima

Borderline

Presence of 10% to 25% interstitial infiltration, fewer than 4 mononuclear cells/tubular cross section

Modified from reference 6.

cg, Chronic glomerulopathy; *g*, glomerulitis; *ptc*, peritubular capillaritis; *v*, vasculitis.

characterized by the absence of endothelialitis, with interstitial inflammation of at least 25% of the parenchyma, and tubulitis (Fig. 104.5). Type II ACR is characterized by vascular involvement/endothelialitis (Fig. 104.6). Type III ACR is characterized by vascular inflammation that extends to the media (transmural) and may be accompanied by fibrinoid change and necrosis of the smooth muscle cells (Fig. 104.7). Types II and III ACR may or may not be associated with elements of type I ACR; thus the pathologic description of rejection should not be viewed as a pathogenic continuum. However, types II and III ACR often require different therapeutic interventions and carry different prognostic implications than type I ACR (see later sections).

Chronic active T cell–mediated rejection is a histologic diagnosis that refers to arterial intimal fibrosis specifically with evidence of mononuclear cell infiltration and formation of neointima (Fig. 104.8). This is distinguished from chronic humoral rejection by the location of vascular injury and lack of evidence of pathogenic antibody; it is distinguished from other nonimmunologic processes that may lead to vascular and interstitial fibrosis by the presence of persistent infiltrating cells within vessels. This is covered in greater detail in Chapter 107.

Borderline Rejection

The finding of inflammation in 10% to 25% of the interstitium with tubulitis of less than four mononuclear cells per tubular cross-section is classified as borderline rejection, which remains a pathologic definition without clear clinical significance. When identified in the setting of graft dysfunction or with other findings such as glomerulitis, the risk for progression to clinical rejection on subsequent biopsies is increased and thus treatment may be considered.[13]

CLINICAL MANIFESTATIONS

The clinical presentation of acute rejection is common to both T cell–mediated and antibody-mediated rejection. Patients typically present with a rapid rise in serum creatinine and in severe cases may have decreasing urine output, weight gain, fever, or graft tenderness. The clinical findings are commonly nonspecific and other etiologies of graft dysfunction should be considered at the time of presentation (Box 104.2) in the context of an individual's risk for the development of acute rejection (Box 104.3). As a result of the increase in the number of patients who undergo transplant despite a risk factor for humoral rejection (e.g., presensitization; known donor-specific antibody in desensitization protocols; and ABO-incompatible transplants), approximately 25% of acute rejection episodes now have a humoral component. In acute humoral rejection there may be features of thrombotic microangiopathy with anemia, evidence of hemolysis, and thrombocytopenia. If there is immediate cyanosis of the graft on revascularization (hyperacute rejection) or an abrupt decline in urine output and graft tenderness 3 to 14 days after transplant (delayed hyperacute or accelerated rejection), donor-specific antibody is implicated. Typically there is type III ACR and interstitial hemorrhage on biopsy.

PROPHYLAXIS AND PREVENTION

Prophylaxis

The primary goal of transplant management is prevention of immunologic graft loss in the early period after transplant. Over time, the risk for acute rejection diminishes and the approach to immunosuppressive therapy shifts toward considerations of adverse effects of the therapy and risks for other events such as cardiovascular (CV) disease and malignancy. Therefore clinical practice follows a strategy of intensive immunosuppression and monitoring in the first months after transplant with a reduction in the intensity of treatment thereafter.

Prevention of Acute T Cell–Mediated Rejection: Induction Therapy

A brief course of potent immunosuppression at the time of transplant (referred to as *induction therapy*) is now commonly used to prevent acute rejection in transplant recipients, regardless of immunologic risk. According to the Scientific Registry of Transplant Recipients, approximately 85%

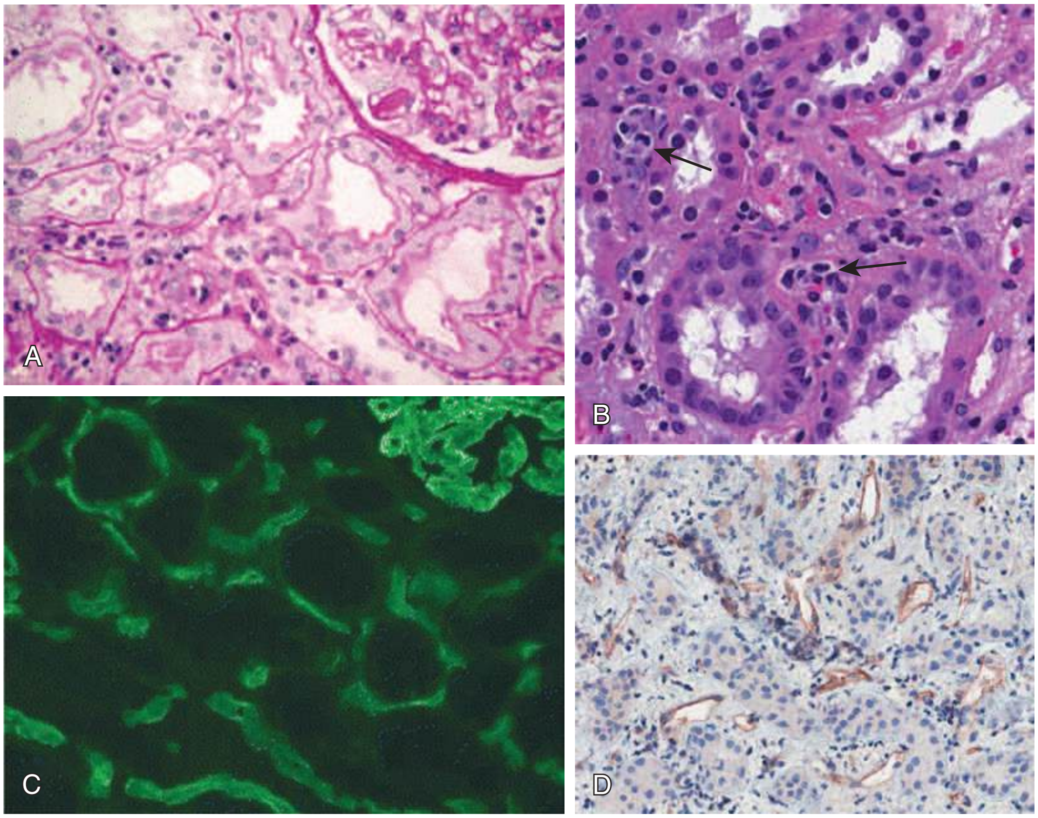

Fig. 104.3 Acute antibody-mediated rejection. (A) Peritubular and glomerular capillaries contain numerous polymorphonuclear leukocytes and mononuclear cells. (B) Numerous polymorphonuclear leukocytes are observed in a peritubular capillary *(arrows)*. Interstitial edema is noted. (Periodic acid–Schiff [PAS] stain, ×200.) (C) Immunofluorescence staining of peritubular capillaries with C4d. (Fresh frozen tissue sample, ×250.) (D) Immunohistochemistry demonstrating peritubular capillary staining of C4d. (Paraffin-embedded tissue, ×480.) (From reference 69.)

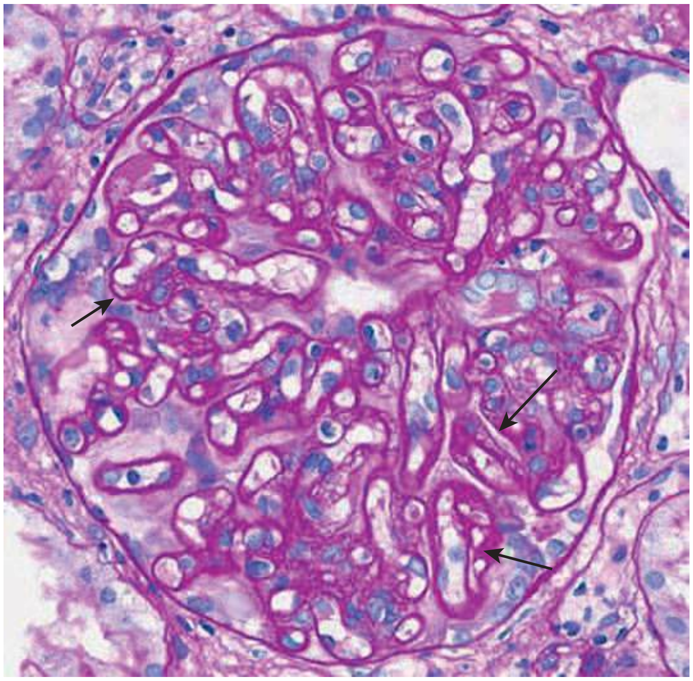

Fig. 104.4 Transplant glomerulopathy. Light microscopy showing typical membranoproliferative changes, including glomerular basement membrane duplication and thickening *(arrows)*.

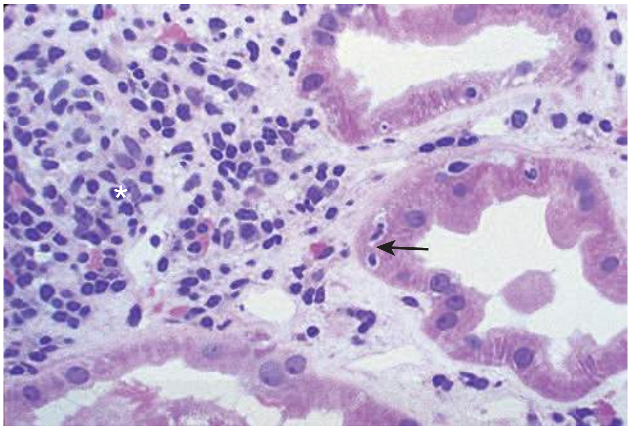

Fig. 104.5 Banff class I cellular rejection. Chronic allograft arteriopathy with the formation of a fibrous neointima *(between arrowheads)* and embedded mononuclear cell infiltration *(arrow)*. (Hematoxylin-eosin [HE] stain, ×200.) (Photomicrographs courtesy Dr. Maxwell Smith, University of Colorado, Denver, Colo.)

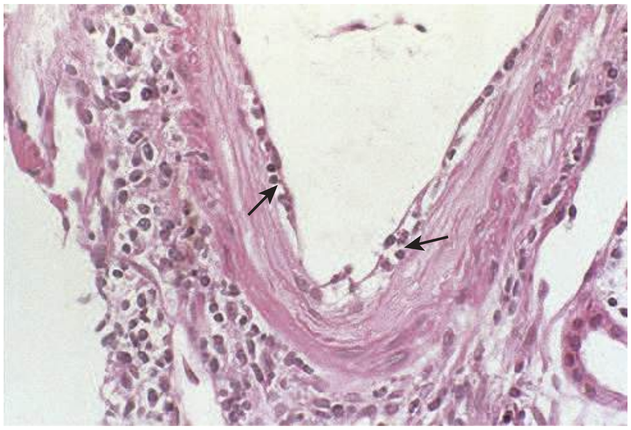

Fig. 104.6 **Banff class II cellular rejection.** Type II rejection, called *acute vascular rejection*, manifests with endothelialitis with mononuclear cell infiltration *(arrows)* beneath the arterial endothelium. (PAS stain, ×200.) (Courtesy Dr. Agnes Fogo, Vanderbilt University, Nashville, Tenn.)

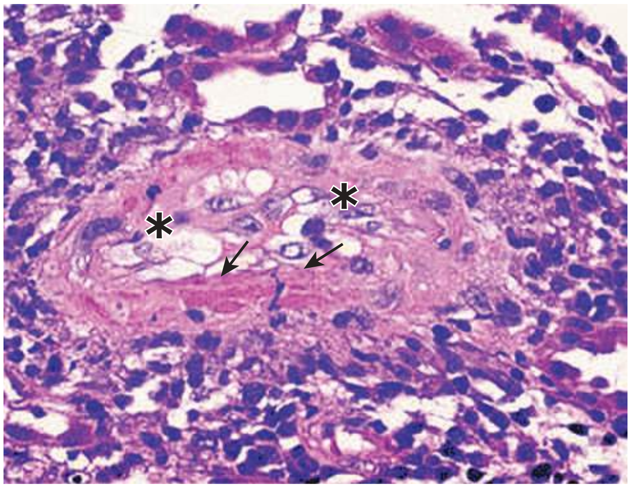

Fig. 104.7 **Banff class III cellular rejection.** Severe small-vessel vasculitis with transmural mononuclear cell infiltration, fibrinoid necrosis *(arrows),* and very swollen endothelial cells *(asterisks).* (PAS stain, ×400.) (From reference 70.)

of U.S. kidney transplant recipients received induction therapy in 2014. For higher risk patients such as those with prior sensitization (the presence of HLA antibodies quantified by percent reactivity against a panel of common HLA types, referred to as *percent panel reactive antibodies* or [PRA]), previous transplant, or African American ethnicity, induction therapy is usually combined with standard doses of immunosuppression to prevent rejection. For those with lower risk (living donor kidney recipients, first kidney transplants), induction therapy is often employed to minimize exposure to maintenance immunosuppression. The use of race as a risk factor for rejection has been questioned with a study demonstrating similar acute rejection rates in African Europeans compared with European Whites in France.[14] However, most studies still report a higher risk for rejection for African Americans than American Whites; thus induction therapy is commonly used in this population.[15]

Induction agents can be classified as T cell depleting or nondepleting. Nondepleting agents include the monoclonal humanized interleukin-2 (IL-2) receptor antibodies (IL-2ra) daclizumab (withdrawn from the market by the manufacturer because of lack of market demand) and basiliximab. The IL-2 receptor was identified as a potential immunosuppressive target because it is present on T cells and inhibition of IL-2/

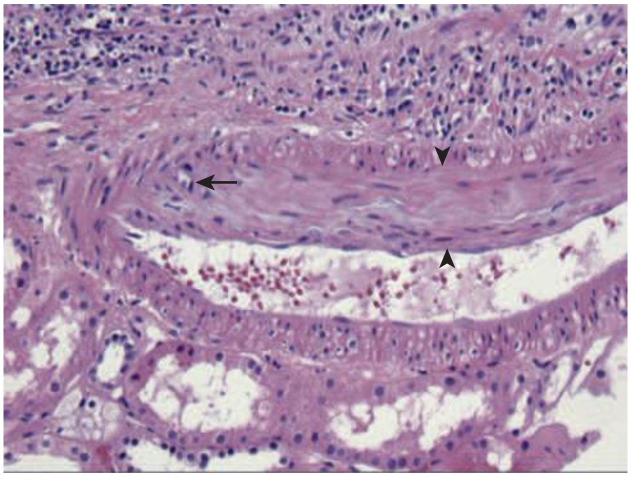

Fig. 104.8 **Chronic T cell–mediated rejection.** Chronic allograft arteriopathy with the formation of a fibrous neointima *(between arrowheads)* and embedded mononuclear cell infiltration *(arrow)*. (HE stain, ×200.) (Photomicrographs courtesy Dr. Maxwell Smith, University of Colorado, Denver, Colorado.)

BOX 104.2 Differential Diagnosis of Renal Allograft Dysfunction

Week 1 Post-Transplantation

- Acute tubular necrosis
- Hyperacute or accelerated rejection
- Urologic
  - Obstruction
  - Urine leak
- Vascular thrombosis
  - Renal artery
  - Renal vein
- Volume contraction

Less Than 12 Weeks After Transplantation

- Acute rejection
- Calcineurin inhibitor toxicity
- Volume contraction
- Urologic
  - Obstruction
- Infection
  - Bacterial pyelonephritis
  - Viral infections
- Interstitial nephritis
- Recurrent disease

Longer Than 12 Weeks After Transplantation

- Acute rejection
- Volume contraction
- Calcineurin inhibitor toxicity
- Urologic
  - Obstruction
- Infection
  - Bacterial pyelonephritis
  - Viral infections
- Chronic allograft nephropathy
- Recurrent disease
- Renal artery stenosis
- Post-transplantation lymphoproliferative disorder

BOX 104.3 Risk Factors for Acute Rejection

High Risk

- Sensitization (high panel reactive antibody percentage)
  - Previous transplantation
  - Pregnancy
  - Transfusion
- Delayed graft function
  - Deceased donor source
  - Increased donor age
  - Prolonged ischemic time
  - Donor brain death
  - Donor acute renal dysfunction
- HLA mismatching
- Positive pretransplantation B cell crossmatch
- ABO incompatibility
- Corticosteroid minimization
- Infection
  - Bacterial pyelonephritis
  - Cytomegalovirus
- Adolescent recipient
- African American recipient
- Previous rejection episode

Low Risk

- Zero HLA mismatch
- Elderly recipient of young donor kidney
- Preemptive transplantation
- Living donor source
- First transplant

HLA, Human leukocyte antigen.

IL-2r signaling inhibits T cell proliferation (see Chapter 101). Use of IL-2ra has resulted in a reduction in acute rejection rates with minimal side effects when combined with cyclosporine-based immunosuppression in the absence of mycophenolate.[16] Importantly, these agents have not been studied in a prospective randomized fashion in combination with a tacrolimus/mycophenolate-based maintenance regimen; thus questions remain regarding the relative benefits of the addition of IL-2ra with more potent, commonly used maintenance agents.[17]

Depleting agents include antithymocyte globulin and anti-CD52 monoclonal antibody (alemtuzumab). Unlike the IL-2ra agents, none of these agents have been compared with placebo for the prevention of rejection and thus their use as induction agents is considered off label in the United States. Antithymocyte globulin is a polyclonal preparation of antibodies directed at T cells prepared by immunizing animals with human lymphoid cells derived from the thymus. Currently, the most common antilymphocyte preparation in use is rabbit antithymocyte globulin (rATG,). Alemtuzumab binds to CD52, an antigen of unclear physiologic significance that is present on both B and T cells, and results in depletion of both lymphoid cell lines. Its ability to induce prolonged, significant lymphopenia for up to 6 to 12 months after dosing led to its use in refractory chronic lymphocytic leukemia. Unlike other depleting agents, it is a humanized antibody, and therefore has fewer infusion-related side effects than rATG. Initial trials suggest equivalence to other depleting agents in the prevention of rejection, but the long-term impact of prolonged lymphopenia on the risk for infection or post-transplant lymphoproliferative disorder has yet to be determined, and comparative trials of induction agents are lacking (see later discussion). Alemtuzumab has been rebranded for use in multiple sclerosis in the United States and thus will soon be cost-prohibitive as transplant induction therapy; however, it is still in use in some European centers.

Although depleting agents are effective in the inhibition of the T cell response, there is concern about long-term safety. Registry analyses suggest there is an increased risk for future development of lymphoma with depleting agents compared with nondepleting agents or no induction therapy,[18,19] an association that appears to be dose-dependent. Therefore the potential for recovery or improvement of graft function as a result of repeated or prolonged courses of depleting antibody therapy must be balanced against the potential long-term risk for malignancy.

Three multicenter randomized trials have compared the efficacy of induction agents in the prevention of acute rejection. A multicenter trial in patients at high risk for acute rejection (defined as recipients with an elevated risk for delayed graft function, elevated PRAs, repeat transplants, or HLA mismatches) compared the IL-2ra basiliximab to rATG with maintenance immunosuppression of cyclosporine, mycophenolate mofetil (MMF), and prednisone.[20] At 12 months, the rate of acute rejection in the basiliximab cohort was 26% versus 16% in the rATG arm. A second trial in patients at high risk for acute rejection (defined by elevated PRAs, repeat transplants, or loss of a previous kidney transplant to acute rejection) compared the IL-2ra daclizumab to rATG, with a remarkable increase in the risk for rejection for patients randomized to daclizumab (27%) compared with rATG (15%) at 1 year.[21] Thus for patients at increased risk for rejection, rATG provided greater prevention of acute rejection, supporting its use in higher risk populations. In contrast, the recently reported European multicenter randomized controlled HARMONY trial showed no difference in rejection rates among patients at low immunologic risk receiving either rATG followed by rapid steroid withdrawal or basiliximab with or without rapid steroid withdrawal.[22] Finally, a clinical trial compared anti-CD52 to either rATG in high-risk patients (repeat transplant, elevated PRAs, or Black race) or to an IL2-ra in low-risk patients, followed by early corticosteroid withdrawal and maintenance tacrolimus and mycophenolate immunosuppression.[23] Acute rejection rates over the first 12 months in the high-risk arms were 10% for anti-CD52 and 13% for rATG and in the low-risk arms were 20% for IL2-ra and 3% for anti-CD52, suggesting a benefit of anti-CD52 over IL2-ra in the population of low immunologic risk. Between 12 and 36 months, however, acute rejection rates in anti-CD52–treated patients were higher in both low- and high-risk arms, suggesting a delayed (>12 months) immunologic risk for immune reconstitution with anti-CD52 therapy. This may be problematic for transplant care providers who generally adhere to less rigorous late (>12 months) clinical monitoring protocols for otherwise stable transplant recipients. Therefore we recommend adhering to a more frequent late (>1 year) clinical monitoring protocol for patients receiving induction with alemtuzumab. In summary, it remains unclear whether induction therapy is required in low-risk patients pending further prospective head-to-head trials, whereas patients at higher immunologic risk appear to benefit from lymphocyte-depleting treatment. At our center, patients at high immunologic risk receive induction with rATG at 1.5 mg/kg for 3 doses and patients at low immunologic risk receive intravenous methylprednisolone without specific induction therapy. Common dosing regimens of induction agents are listed in Table 104.1.

Prevention of Acute Antibody-Mediated Rejection: Desensitization

The patient who has donor-specific antibodies or is blood type–incompatible to the donor before transplant has a near-universal risk for developing acute antibody-mediated rejection after transplant without pretransplant therapeutic intervention. Desensitization protocols may permit transplantation of these donor-recipient combinations.

TABLE 104.1 Agents Used for Induction and Treatment of T Cell–Mediated Rejection

Agent	Target	Dose (Induction)	Dose (Rejection)
Methylprednisolone	B cells, T cells, macrophages	250-500 mg IV with induction therapy, followed by taper over 1-5 days	3-5 mg/kg (250-500 mg) IV × 3-5 days
Basiliximab	IL-2 receptors on cells	20 mg IV × 2 on days 0 and 4	N/A
rATG	T cell surface antigens	1-1.5 mg/kg IV × 4-14 days	1-1.5 mg/kg IV × 7-14 days
Alemtuzumab	CD52 on T and B cells	30-60 mg × 1 or 2 on days 0 and 2	Same as induction

rATG, Rabbit antithymocyte globulin.

TABLE 104.2 Agents Used for Desensitization and Treatment of Antibody-Mediated Rejection

Treatment	Mechanism	Protocol (Desensitization)	Dose (Antibody-Mediated Rejection)
Plasma exchange*	Antibody removal	Two to four sessions or until XM acceptable, combined with IVIG	Two to five treatments, daily or every other day, combined with IVIG
IVIG*	Multiple, antibody inhibition?	100-200 mg/kg after plasma exchange until acceptable XM *or* 1-2 g/kg mo until transplant	100-200 mg/kg after plasma exchange
Rituximab*	Anti-CD20 B cell inhibition	375 mg/m^2 (day 15) combined with IVIG 1-2 g/kg (days 1 and 30)	375 mg/m^2 with plasma exchange and IVIG
Bortezomib	Plasma cell inhibition	Not established	1.3 mg/m^2 × four doses over 1-2 wk, usually combined with plasma exchange and IVIG
Eculizumab	Terminal complement C5 inhibition	Not established	For prevention in + XM transplant: 600-1200 mg/wk × 4 then biweekly until successful antibody reduction
Splenectomy	B cell removal	No longer used	N/A, for severe refractory cases only

*Commonly used.
IVIG, Intravenous immunoglobulin; *XM,* crossmatch.

Desensitization protocols typically involve removal of preformed antibody with plasma exchange and/or suppression of antibody production and action with intravenous immunoglobulin (IVIG) or B cell inhibition with rituximab. Several different desensitization strategies have been adopted by transplant centers over the previous decade and are generally influenced by factors such as type of transplant (living vs. deceased donor) and the degree of HLA-antibody reactivity one is attempting to overcome. In the case of living donation the crossmatch barriers are known in advance, allowing for plasma exchange followed by low-dose (100 to 200 mg/kg) IVIG to be employed and transplant to be pursued when the desired crossmatch results are obtained. Protocols consisting of monthly high-dose IVIG (1 to 2 g/kg) infusions with or without rituximab[24] have been used in situations in which pretransplant plasma exchange is not feasible, such as in sensitized patients without living donor options awaiting deceased donor kidneys; however, the effectiveness of this strategy has been questioned.[25]

Desensitization strategies have allowed transplantation in sensitized patients who otherwise may not be afforded the opportunity. However, these procedures are generally met with high rates of acute rejection, ranging from 20% to 70% (depending on a variety of factors, including specific protocol, induction immunosuppression, and immunologic risk), are often humoral and frequently progress to chronic antibody-mediated injury.[26,27] Despite these pitfalls, short-term graft survival after desensitization has been acceptable[26] and data suggest a survival benefit sustained for up to 8 years for desensitized patients undergoing transplant, compared with matched controls undergoing dialysis while on the waiting list.[28] Thus HLA desensitization for sensitized transplant candidates may be a reasonable option, especially for those with a living donor(s), and referral to a transplant center with experience in this field is warranted. Published desensitization agents and protocols are listed in Table 104.2.

Maintenance Therapy for Prevention of Acute Rejection

Current maintenance immunosuppression most commonly includes a CNI, an antiproliferative agent, and corticosteroids. This combination of agents forms the standard against which novel strategies are compared, such as corticosteroid withdrawal/avoidance and CNI withdrawal/avoidance. Cyclosporine has been replaced by tacrolimus as the preferred CNI in the United States, and together with the antiproliferative agent MMF, forms the most common immunosuppressive regimen in current practice in the United States and most Western countries (Table 104.3). More affordable regimens that include CsA and azathioprine (AZA) are commonly used in areas where access to health care resources is more limited; however, comparative clinical trials typically show more rejection in patients receiving this regimen.[29]

Calcineurin Inhibitors in the Prevention of Acute Rejection

Since the early 1980s when the introduction of CsA resulted in a reduction in the incidence of acute rejection and improvements in projected graft survival,[30] calcineurin inhibition has been a cornerstone of maintenance immunosuppression. Tacrolimus, first introduced in 1990s and compared head-to-head with CsA in multiple trials, appears to provide greater protection from acute rejection but with a different side effect profile. A recent meta-analysis of trials that compared tacrolimus and CsA-based immunosuppression demonstrated a reduction in risk for acute rejection by 31% but an increase in risk for development of diabetes by 86%. Tacrolimus was also associated with a better death-censored graft survival (hazard ratio, 0.56), particularly at target trough

TABLE 104.3 **Immunosuppression Regimens in the United States, 2011**

Regimen	Percent
Induction Regimens at Time of Transplant	
IL-2Ra	21
T cell depleting	59
Maintenance Regimens at Time of Hospital Discharge	
TAC/MMF-MPS/Pred	59
CSA/MMF-MPA/Pred	2
Corticosteroid free (any)	29
TAC/MMF-MPA	26
CSA/MMF-MPS	0.5

Modified from OPTN/SRTR Annual Report, 2012.

doses less than 10 ng/ml, a finding that was not shown in individual studies.[31]

Antiproliferative Agents in the Prevention of Acute Rejection

AZA was the first antiproliferative agent used in kidney transplantation and was used initially in conjunction with corticosteroids and later with CsA. Although its development was critical in the advancement of allotransplantation, acute rejection was quite common, with acute rejection rates of 35% to 40% in a number of clinical trials using CsA/AZA/prednisone. Newer antiproliferative agents emerged in the 1990s with MMF and later with the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus that significantly reduced the incidence of acute rejection.

MMF, a purine antagonist that interferes with DNA synthesis in rapidly dividing cells such as activated lymphocytes, gained popularity after a number of multicenter prospective clinical trials demonstrated an approximately 50% reduction in the incidence of acute rejection compared with that for AZA.[32,33] A recent meta-analysis of 23 studies showed MMF to be associated with significantly fewer cases of acute rejection and graft loss compared with AZA.[29] Most studies in this analysis report outcomes of MMF and AZA in combination with CsA and thus may not translate to regimens using tacrolimus. One drawback of MMF has been its gastrointestinal (GI) tolerability, which often results in reduction of therapy with attendant risks for acute rejection[34] and graft loss.[35] An MMF analogue, enteric-coated mycophenolate sodium (MPA), has been developed and appears to be "noninferior" in efficacy to MMF,[36] with fewer GI side effects reported in one open-label study.[37]

Similar to MMF, the mTOR inhibitors sirolimus and everolimus were initially tested in clinical trials as a substitute for AZA and demonstrated reductions in acute rejection rates similar to those with MMF.[38] mTOR inhibitors inhibit the progression from G1 to S phase of the cell cycle and appear to have additional antiproliferative effects on nonimmune cells that may contribute to an increase in side effects (impaired wound healing, lymphocele formation, proteinuria, and slower recovery from delayed graft function) but also may reduce the incidence of viral infection and malignancy.[39,40]

Acute Rejection Rates in Calcineurin-Sparing and Corticosteroid-Sparing Immunosuppression Regimens

There has been increasing interest in how best to minimize side effects of immunosuppression. Avoidance of CNIs offers the hope of prolonged graft survival given the inherent nephrotoxicity of these medications, and avoidance of corticosteroids offers the hope of reducing a number of cosmetic, metabolic, and CV side effects attributable to prednisone.

Early corticosteroid cessation (within 7 days after transplant) has become increasingly popular in the United States. In 2014, over 32% of all patients were discharged after transplant without maintenance prednisone therapy. Generally, patients at lower immunologic risk (low PRAs, first transplants) are selected,[41,42] and immunosuppression includes induction therapy, a CNI, and an antiproliferative agent. Acute rejection rates in single-center studies range from 10% to 15%. In the largest prospective, double-blind multicenter study to date of corticosteroid cessation versus standard corticosteroid maintenance,[43] a standard steroid taper or a rapid elimination of steroids at 7 days post-transplant was compared on the background of induction therapy plus a tacrolimus/MMF-based immunosuppression. Patient survival, graft survival, and creatinine clearance were comparable at 5 years. CV risk factors and weight gain were not significantly different between groups, but corticosteroid withdrawal was associated with less bone disease, less insulin-requiring new-onset diabetes, and lower triglyceride levels. One cause for concern with corticosteroid withdrawal was that rejection rates were higher (18% vs. 11%, $P = .04$), and a post hoc analysis suggested a higher rate of chronic allograft nephropathy in the corticosteroid withdrawal arm. In contrast, the aforementioned HARMONY study reported similar rejection rates and significant reductions in post-transplant diabetes in two rapid (8 day) steroid withdrawal arms (one using basiliximab and the other using rATG induction) compared with the control arm of basiliximab induction and maintenance steroids, with all patients receiving tacrolimus and MMF.[22]

Clinicians must weigh the possibility of higher rejection risk versus the potential benefits noted previously when counseling patients regarding corticosteroid withdrawal. Both the Astellas Corticosteroid Withdrawal and the HARMONY trials were performed in patients at low immunologic risk without the presence of or at low risk for delayed graft function; thus consideration for corticosteroid withdrawal is best supported for the patient with a lower expected risk for rejection (low immunologic risk, expected immediate graft function) or high expected risk for corticosteroid-related complications such as bone disease and diabetes.

CNI avoidance has been studied with both dual therapy (MMF/prednisone) and triple therapy with two antiproliferative agents (sirolimus/MMF/prednisone) in combination with induction therapy. In general, MMF/prednisone maintenance immunosuppression does not appear to be effective in the prevention of rejection (70% incidence in one pilot study[44]), and although single-center studies report acute rejection rates of 6% to 13% with sirolimus/MMF/prednisone therapy,[45,46] a large multicenter trial using this combination and target trough concentrations of sirolimus 4 to 8 ng/ml also revealed an excessively high acute rejection rate (38%).[47] CNI avoidance was more successful in the BENEFIT trial, which compared the costimulation blocker belatacept at 2 doses to CsA with IL2ra induction and MPA/prednisone maintenance.[48] Despite higher 1-year acute rejection rates in the belatacept arms (22% and 17% for higher and lower intensity, respectively, vs. 7% for CsA) graft survival was comparable and measured glomerular filtration rate (GFR) significantly higher for those receiving belatacept (65 and 63 ml/min for high- and low-intensity belatacept vs. 50 ml/min for CsA). At 7 years of follow-up, the belatacept arms experienced a 43% reduced risk for a composite end-point of death or graft loss compared with CsA.[49] Importantly, because of higher rates of post-transplant lymphoproliferative disorder associated with belatacept use in Epstein-Barr virus (EBV)-seronegative patients, this option is available only to those with confirmed EBV seropositivity. The BENEFIT studies included patients at low to moderate immunologic risk (PRAs <50% first transplant, <30% repeat transplant), and we suggest that

TABLE 104.4 **Maintenance Immunosuppression and Reported Rejection Rates in Randomized Multicenter Trials**

Regimen	Induction	CNI Dose or Trough Level Goal	Antiproliferative Dosing	Acute Rejection at 6 Months (%)
Low Immunologic Risk				
CSA/AZA/Pred		4 mg/kg/day	1.5-2 mg/kg/day	36
CSA/AZA/Pred	IL-2Ra	Not stated	Not stated	22
CSA/MMF/Pred		150-300 ng/ml × 3 mo, 100-200 ng/ml	1 g bid	24
CSA/MMF/Pred	IL-2Ra	125-400 ng/ml × 3 mo, 100-300 ng/ml	1 g bid	12
TAC/AZA/Pred	OKT3 or Atgam	5-14 ng/ml	1.5 mg/kg/day	32
TAC/MMF/Pred	OKT3 or Atgam	5-14 ng/ml	1 g bid	7
TAC/MMF/Pred	IL-2Ra	7-16 ng/ml × 3 mo, 5-15 ng/ml	1 g bid	4
CSA/SRL/Pred		200-350 ng/ml × 1 mo, 200-300 ng/ml × 1 mo, 150-250 ng/ml	2 mg/day	17
TAC/SRL/Pred		8-16 ng/ml × 3 mo, 5-15 ng/ml	4-12 ng/ml	13
High Immunologic Risk				
CSA/SRL/Pred	IL-2Ra or rATG	200-300 ng/ml 0-14 days 150-200 ng/ml	10-15 ng/ml	14*
TAC/SRL/Pred	IL-2Ra or rATG	10-15 ng/ml 0-14 days 5-10 ng/ml	10-15 ng/ml	17
Drug Minimization or Avoidance				
CSA (low)/MMF/Pred	IL-2Ra	50-100 ng/ml	1 g bid	23
TAC (low)/MMF/Pred	**IL-2Ra**	**3-7 ng/ml**	**1 g bid**	**12**[47]
TAC/MMF	**IL-2Ra or rATG**	**10-20 ng/ml × 3 mo, 5-15 ng/ml**	**1.5 g bid × 14 days 1 g bid**	**9**[43]
SRL/MMF/Pred	IL-2Ra	N/A	SRL 4-8 ng/ml MMF 1 g bid	38
Bela/MMF/Pred	**IL-2Ra**	**N/A**	**1 g bid**	**22 (MI) 17 (LI)**[48,49]*
CNI → SRL/MMF/Pred	IL-2Ra or rATG or OKT3	N/A	SRL 5-10 ng/ml MMF 1-1.5 g bid	7.4*
CSA → EVL/MMF/Pred	IL-2Ra	N/A	EVL 6-10 ng/ml MMF 1 g bid	15*

*Acute rejection rate at 12 months.
Bold, Suggested regimens by the authors based on available data.

consideration of patients for belatacept therapy be limited to those who fall into this immunologic category. A post hoc analysis of patients included in both the BENEFIT and BENEFIT-EXT (the latter including patients receiving extended-criteria donor kidneys) showed significantly lower blood pressure, serum lipids, and incidence of new-onset diabetes (NODAT) in those randomized to belatacept regimens compared with CsA.[50] Thus patients with pretransplant metabolic profiles at risk for post-transplant metabolic complications in particular may benefit from belatacept-based CNI-free immunosuppression.

In contrast to their use in complete CNI avoidance strategies, mTOR inhibitors have achieved relative success when used in CNI withdrawal[51,52] and conversion protocols. In one study, patients receiving a CNI, MMF, and prednisone were randomized to continue this regimen or undergo CNI conversion to sirolimus at 1 to 6 months after transplant with statistically similar rates of acute rejection and comparable renal function at 2 years.[53] Another study, employing a similar approach of CNI conversion to everolimus at 4 to 5 months post-transplant, demonstrated equivalent rates of acute rejection (15% in both groups) and significantly improved estimated GFR (eGFR) at 12 months in the conversion group (72 ml/min vs. 62 ml/min in the CNI continuation arm).[54] A recent meta-analysis that included 23 studies comparing CNI conversion to mTOR inhibitors found a modest improvement in renal function with no difference in rates of rejection or graft loss.[55] Widespread acceptance of CNI to mTOR inhibitor conversion strategies has been hindered because of mTOR inhibitor–related side effects and reluctance to alter immunosuppression in stable transplant recipients.

Acute rejection rates by treatment regimen reported in recent multicenter clinical trials are shown in Table 104.4. These rates are often higher than rates reported to registries (see Fig. 104.1) because of the more rigorous follow-up and mandatory reporting within the context of clinical trials.

TREATMENT

Acute T Cell–Mediated Rejection

Treatment of T cell–mediated acute rejection is often directed by the findings on biopsy and the clinical response to pulse corticosteroids. For the patient with graft dysfunction and biopsy-proven rejection, treatment with intravenous methylprednisolone 3 to 5 mg/kg (250 to 500 mg/d) for 3 to 5 days is often effective if the histologic injury is tubulointerstitial (Banff class IA or IB). Remarkably few studies of the clinical response to corticosteroids in the treatment of acute rejection have been performed under modern immunosuppression, but prior data suggest that 60% to 70% of patients will respond with improved urine output and decreasing serum creatinine within 5 days. If there is inadequate response after corticosteroid pulse therapy or if there is vascular involvement (Banff class IIA, IIB), corticosteroids often must be supplemented with T cell–depleting antibody therapies in a similar dosing strategy but longer treatment course compared with their use for induction (see Table 104.1). Most studies have used these agents in 7- to 14-day treatment courses, with no clinical trials investigating the efficacy of shorter courses versus longer courses. For patients who are on a maintenance regimen that is not tacrolimus based, tacrolimus conversion may be considered in the setting of rejection with an inadequate response to corticosteroids,[56] whereas for patients on a corticosteroid-free regimen, reinstitution of maintenance prednisone may be warranted.[57] For patients who do not respond adequately to corticosteroids, T cell–depleting agents are required. A typical course of rATG for T cell–mediated rejection is 1.5 mg/kg for 4 to 14 days dictated by clinical response and absolute lymphocyte counts, again with no controlled study comparing one treatment regimen versus another.

Acute Antibody-Mediated Rejection

Treatment of acute humoral rejection is indicated when the triad of graft injury, evidence of antibody/endothelium interaction, and circulating donor-specific antibody is present, but also should be considered in high-risk circumstances (prior desensitization or known donor-specific antibody) even if all three criteria are not met. High-quality randomized trials investigating treatment options for acute humoral rejection are lacking,[58] and strategies are generally dictated by center experience. Traditionally, treatment has entailed plasma exchange (to remove the pathogenic immunoglobulin[s]) and IVIG (to inhibit/suppress antibody production). In general, at least five plasma exchange treatments should be administered with 1 to 2 g/kg total dose IVIG. IVIG is removed by plasma exchange, so a common strategy is to administer IVIG 100 to 200 mg/kg after each exchange. For refractory acute humoral rejection, rituximab may be considered despite targeting B cells at an earlier phase of maturation than the antibody-producing plasma cell line.[59] The largest randomized clinical trial of rituximab treatment for antibody-mediated rejection to date found no difference between the treatment group and placebo when added to plasma exchange and IVIG for a composite end-point of early improvement in renal function at 12 days after treatment and graft loss at 1 year. However, the study was limited by a small sample size ($n = 38$) and significant crossover between groups with 42% of subjects in the placebo arm receiving rescue doses of rituximab.[60] In contrast, the proteosome inhibitor bortezomib directly inhibits antibody-producing plasma cells and has been reported in single-center case series as a potential treatment for refractory antibody-mediated rejection, usually in combination with other modalities such as plasma exchange and IVIG.[61] Eculizumab is a humanized monoclonal antibody that blocks terminal complement activation and has been shown to significantly reduce the risk for acute humoral rejection, as well as subsequent transplant glomerulopathy in patients who have undergone positive crossmatch kidney transplant[62]; however, feasibility of this approach is limited by high cost. Finally, there are case reports of splenectomy for refractory acute humoral rejection.[63] These therapies are typically coupled with targeted T cell therapy such as high-dose steroids and/or depleting antibody therapy, because histologic evidence of mixed T cell rejection is often present and helper T cell function may contribute to an enhanced B cell response. Agents used for treatment of acute humoral rejection are summarized in Table 104.2.

Chronic Rejection (T Cell–Mediated and/or Antibody-Mediated)

T cell–mediated or antibody-mediated injury in a graft without features of acute tissue injury remains a therapeutic dilemma in kidney transplantation. No specific intervention has been proven effective in reversing the chronic tissue injury; however, consideration should be given to optimizing or enhancing the maintenance immunosuppression by transitioning to tacrolimus/MMF therapy or increasing the dose of these agents if CNI nephrotoxicity is not identified.[64] Any intervention should be weighed against the potential for risk for enhanced immunosuppression and the lack of any long-term data describing the impact of enhancing immunosuppression. This topic is discussed in greater detail in Chapter 107.

PROGNOSIS

Episodes of acute rejection may predispose to chronic graft dysfunction, with increased histologic findings of chronic rejection and/or interstitial fibrosis and tubular atrophy and clinical findings of reduced graft survival. The clinical response to antirejection therapy appears to be critical in this regard, because the change in renal function from 6 and 12 months post-transplant is more predictive of long-term graft survival than the occurrence of prior episodes of acute rejection.[65] Two analyses (one examining the U.S. experience[66] and another examining the Australia/New Zealand experience[67]) have shed light on risk factors for graft loss after episodes of acute rejection. In general, acute T cell–mediated rejection that responds to therapy with return to near baseline renal function does not portend worse graft survival. However, vascular rejection, late rejection (after 3 months), and rejection that does not respond to within 75% of baseline serum creatinine is associated with worse graft outcomes. Although the risk for acute rejection has fallen significantly over the past decade, the likelihood of graft survival has not improved in parallel; one explanation for this finding is that the rejection now identified tends to be less responsive to therapy, with fewer cases achieving near-baseline serum creatinine levels. The long-term prognosis after episodes of acute antibody-mediated rejection has not been fully defined in prospective analyses. However, from single-center and retrospective studies, it appears that episodes of acute humoral rejection likely affect long-term graft survival. For example, a retrospective analysis of 302 patients with biopsy-proven acute rejection (192 with T cell–mediated rejection and 110 with antibody-mediated rejection) found a threefold to ninefold increased risk for graft loss at 5 years associated with antibody-mediated rejection compared with T cell–mediated rejection.[10] Similarly, the emergence of de novo HLA antibodies at any time after transplant has been shown to be associated with a 5% worse graft survival per year compared with those who do not form anti-HLA antibodies.[68] For this reason, patients who have had episodes of acute rejection must be rigorously monitored with optimization of baseline maintenance immunosuppression. Remaining questions include the value of escalated immunosuppression such as longer term scheduled antibody therapy and additional IVIG treatment for those without adequate clinical response or with persistently elevated titers of HLA antibodies.

SUMMARY AND RECOMMENDATIONS

The incidence of acute rejection has decreased over time, but it remains an important cause of graft dysfunction and progressive graft loss, particularly when antibody-mediated forms of injury are identified. Higher risk patients benefit from induction therapy with lymphocyte-depleting agents for the prevention of rejection. Although many maintenance immunosuppressive regimens have been used to minimize the incidence of rejection and side effects, the most effective maintenance immunosuppressive regimen for the prevention of rejection is a three-drug regimen consisting of tacrolimus, mycophenolate, and prednisone. Alternative immunosuppressive strategies may be considered for side effects or toxicities related to immunosuppressive agents, which in clinical practice has led to a myriad of treatment combinations (see Table 104.4). Steroid minimization and belatacept-based CNI-free immunosuppression have been associated with adequate short- and intermediate-term outcomes but should be limited to those patients at lower immunologic risk for acute rejection. Until there is an accurate means of determining an individual patient's degree of immune function, suppression, or graft-specific immunity, the clinician must determine the best treatment regimen based on potency (potential to minimize rejection) and tolerability.

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SELF-ASSESSMENT QUESTIONS

1. According to the Banff Working Classification of Renal Allograft Pathology, which of the following patterns would be recognized as acute antibody-mediated rejection?
   - **A.** Circulating donor-specific antibodies, severe tubulitis, interstitial inflammation
   - **B.** Peritubular capillary C4d deposition, peritubular capillaritis, interstitial inflammation
   - **C.** Circulating donor-specific antibodies, mild-moderate large vessel intimal arteritis, moderate interstitial fibrosis
   - **D.** Peritubular capillary C4d deposition, circulating donor-specific antibodies, peritubular capillaritis.
2. Which of the following statements is true regarding induction immunosuppression for the prevention of acute rejection?
   - **A.** Rabbit antithymocyte globulin is a monoclonal antibody directed against the CD3 subunit of the T cell receptor associated with a significant innate immune response resulting in a cytokine release syndrome.
   - **B.** Lymphocyte-depleting agents are more effective in preventing acute rejection compared with IL-2 receptor antibodies in patients at high immunologic risk.
   - **C.** The risk for post-transplant lymphoproliferative disorders is higher in patients treated with IL-2 receptor antibodies than in those treated with lymphocyte-depleting agents.
   - **D.** Patients at low immunologic risk experience higher early (<12 months) rates of acute rejection when treated with anti-CD52 therapy (Campath) compared with IL-2 receptor antibody therapy.
3. Which of the following is the most effective maintenance immunosuppressive regimen for the prevention of rejection:
   - **A.** Sirolimus, mycophenolate mofetil (MMF), prednisone
   - **B.** Tacrolimus, MMF, prednisone
   - **C.** Belatacept, MMF, prednisone
   - **D.** Tacrolimus, MMF, prednisone withdrawal at 7 days post-transplant
4. A 47-year-old man treated with tacrolimus, MMF, and 5 mg of prednisone after undergoing deceased-donor kidney transplant 5 months prior presents with an elevated serum creatinine of 5.2 mg/dl (recent baseline 1.3 mg/dl) and mild graft tenderness. Renal ultrasound is nondiagnostic, a workup for infectious causes is negative, and an assay for donor-specific antibody is negative. Allograft biopsy is performed and reveals severe tubulitis with vascular intimal arteritis without evidence of peritubular capillary C4d deposition. The most appropriate initial therapy consists of:
   - **A.** Increasing the dose of maintenance prednisone to 60 mg/day for 7 days followed by a dose taper back to 5 mg
   - **B.** 3-5 days of intravenous methylprednisolone at 500 mg/day
   - **C.** Rabbit antithymocyte globulin (rATG) 1.5 mg/kg intravenously for 7 to 14 days
   - **D.** Plasmapheresis followed by 100 to 200 mg/kg immune immunoglobulin for a total of five session

105

Medical Management of the Kidney Transplant Recipient

Infections and Malignancies

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INFECTIOUS DISEASES

Infection follows cardiovascular (CV) disease as the second most common cause of death with a functioning graft in kidney transplant recipients. Most deaths attributable to CV disease are in patients with diabetes, whereas infection and malignancy are more commonly the cause of death among those without diabetes. Predisposing risk factors for infectious complications include immunosuppression, increased recipient age, indwelling Foley or vascular catheters, surgical drains, drug-induced leukopenia, and metabolic derangement. Epidemiologic exposures, shifts in nosocomial flora associated with repeated antimicrobial exposures (antimicrobial resistance), and improvement in molecular diagnostic assays also contribute to the emergence of novel infections and changes in the epidemiology of infections.[1]

Immunizations Before and After Transplantation

All kidney transplant candidates should receive immunization for hepatitis B, pneumococcus, and other standard immunizations appropriate for age and the presence of end-stage kidney disease. Vaccinations should be administered at least 4 to 6 weeks before transplantation to achieve optimal immune response and minimize the possibility of live vaccine–derived infection in the post-transplantation period. Household members, close contacts, and health care workers should also be fully immunized. A minimum of 4 weeks should elapse between live virus vaccine administration and transplantation. Live virus or live organism vaccines should be avoided after transplantation. In addition, exposure to persons who have chickenpox or herpes zoster should be avoided until the lesions have crusted over and no new lesions are appearing. Immunizations using inactivated or killed microorganisms, components, and recombinant moieties are safe for transplant recipients. Most centers restart vaccinations 3 to 6 months after transplantation. Vaccination during the first 3 months after transplantation may result in suboptimal response and protection because of heavy immunosuppression. Seasonal influenza vaccine is safe and effective, and no conclusive evidence exists for a link between vaccination and allograft dysfunction. For recommendations for prophylaxis or vaccination for transplant recipients who travel to countries where endemic infections such as malaria are present, refer to reference 2. Recommended immunizations before and after transplantation are listed in Table 105.1. Ensuring adequate response to hepatitis B vaccination is important to prevent transmission of donor-derived infection.

Infectious Causes

Both the type and occurrence of infections in the immunocompromised transplant recipient follow a “timetable pattern” (Box 105.1). However, the timing of infections may be altered by the intensity of immune suppression, use of target antibiotic prophylaxis, and patient exposures.

Risk Factors for Post-Transplant Infectious Complications

Risk factors for post-transplant infectious complications include active or latent infections in the donors, net state of immunosuppression, surgical instrumentation, wound, abdominal fluid collections, reactivation of latent infections, epidemiologic exposure, metabolic conditions (e.g., diabetes, uremia), infections with immunomodulating viruses, and hypogammaglobulinemia, among others. Severe hypogammaglobulinemia (immunoglobulin [Ig] G <400 mg/dl) during the first year post-transplantation is associated with a significant increase in the risk for cytomegalovirus (CMV) infection, fungal and respiratory infections, and 1-year all-cause mortality among recipients of solid organ transplantation.[3] Although prospective controlled trials are lacking, post-transplant monitoring of IgG levels and Ig replacement therapy to keep IgG level greater than 700 to 800 mg/dl may reduce infection rates in patients with hypogammaglobulinemia.

Donor-Derived Infections

Donor-derived infections include bacterial, fungal (*Candida* spp.), viral (HIV, hepatitis B and C [HBV and HCV], CMV), and parasitic infections (malaria, *Babesia* and *Balamuthia* infections, amebic meningitis). Allograft-transmitted infections with unusual viruses such as lymphocytic choriomeningitis virus, West Nile virus, and rabies also have been described. Despite routine surgical prophylaxis, transmission of resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and azole-resistant *Candida* spp. occurs with increased frequency. Donor-derived carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections are associated with high morbidity and mortality. Donation of organs that are directly involved in CRKP infection should be avoided (e.g., kidneys from donors with CRKP urinary tract infection [UTI], lungs from donors with CRKP airway infection or colonization).[4] All organ procurement organizations in the United States perform nucleic acid testing (NAT) to increase the likelihood of detecting HIV and hepatitis infections among donors at increased risk. If a donor is identified as being at increased risk for HIV, HBV, and HCV transmission according to the U.S. Public Health Service Guidelines, recipients of such kidneys should undergo protocol surveillance, including HIV RNA by NAT (or HIV Ab/Ag combination assays), HBsAg (or quantitative HBV DNA), and quantitative HCV RNA pretransplant and at 6 weeks post-transplant. Repeat testing for HBsAg (or HBV by NAT), anti-HBsAb, and anti-HBcAb should be performed at 12 months after transplant.

TABLE 105.1 Recommended Immunizations Before and After Transplantation

Vaccine	Before TX	After TX (≥3 Months Post-Tx)	Comments (Vaccinations <3 Months Post-Transplant May Result in Suboptimal Response and Protection)
Measles-mumps-rubella	Y	Contraindicated	
Diphtheria-tetanus-pertussis	Y	See comments	Diphtheria and tetanus: Booster every 10 years.
Varicella-live	Y	Contraindicated	Should be administered ≥4 weeks before transplant.
Poliovirus	Y	Inactivated polio	For travelers to endemic areas (e.g., some parts of Asia, Africa).
Haemophilus influenzae type b	Y	Y	
Inactivated influenza vaccine Influenza A and B	Y	Y	Annually All patients who are >3 months post-transplant should receive seasonal influenza vaccine. May be administered in the immediate post-transplant period during an outbreak.
Live-attenuated influenza (nasal spray flu vaccine)	Contraindicated	Contraindicated	
Pneumococcal conjugate PCV13	Y	Y	For those who have not received either *Pneumococcus* vaccine, PCV13 should be administered first, followed 8 weeks later by PPSV23. Patients who have already received 1 dose of PPSV23 should receive PCV13 at least 1 year after PPSV23.
Pneumococcal polysaccharide PPSV23	Y	Y	Recommended post-transplant if not administered pretransplant. Patients who have already received 1 dose of PPSV23 should receive an additional dose 5 years after the first dose of PPSV23.
Hepatitis A	Y	Y	Recommended post-transplant if not administered pretransplant. For travelers to endemic areas.
Hepatitis B	Y	Y	Recommended post-transplant if not administered pretransplant. Monitor titers for response to vaccination and repeat vaccination series if needed.
Human papillomavirus (HPV)	Y	—	Nonpregnant female candidates ages 11-26, males ages 11-21.
Neisseria meningitides	Y	Y	Recommended for patients with properdin terminal component deficiencies or receiving eculizumab therapy, or those with functional or anatomic asplenia. *Others:* Military members, travelers to high-risk areas, college freshman living on campus.
Zoster-live (Zostavax)	Y	Contraindicated	Should be administered ≥4 weeks before transplant.*

*If inadvertently given within 4 weeks before transplant, consult infectious disease specialist and administer acyclovir to prevent reactivation of vaccine-strain virus.
TX, Transplant; *Y,* yes.

Month 1 After Transplantation

In the first month after transplantation, donor- and recipient-derived infections with common nosocomial bacterial microorganisms and *Candida* spp. predominate. Infections caused by multidrug-resistant bacteria are center specific. Despite the advent of potent broad-spectrum antimicrobial agents, infections caused by multidrug-resistant bacteria, including gram-positive bacteria (MRSA, VRE), extended-spectrum β-lactamases, and gram-negative bacilli and multidrug-resistant nonfermentative gram-negative bacilli, including CRKP, continue to be important causes of morbidity and mortality.

Most bacterial infections during this period involve wounds, catheters, and drainage sites. Aspiration pneumonia and UTIs are common. Most UTIs are caused by gram-negative bacteria (*Escherichia coli,* Enterobacteriaceae, *Pseudomonas*) and gram-positive bacteria *(Enterococcus)*. Preventive measures for UTIs include early urethral catheter removal and antibiotic prophylaxis. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis (or ciprofloxacin for patients with sulfa allergies) during the first 3 to 6 months after transplantation may reduce the risk for UTIs and eliminate urosepsis unless anatomic or functional derangement of the urinary tract is present. In a series of 20 kidney transplant recipients with CRKP, antimicrobial prophylactic therapy with agents other than TMP-SMX was found to be a risk factor for the development of CRKP bacteriuria.[5] Strict aseptic surgical techniques and perioperative use of first-generation cephalosporins reduce the incidence of wound infections. Except for herpes simplex virus (HSV), viral infections are uncommon during this period.

Months 1 to 6

During months 1 to 6, unconventional or opportunistic infections secondary to immunosuppression are most common. Viral infections such as CMV, HSV, varicella-zoster virus (VZV), Epstein-Barr virus, HBV, and HCV may occur from exogenous infection or reactivation of latent disease. Reactivation or de novo HCV infection is an important cause of morbidity and mortality after transplantation because of the historical lack of effective treatments and the risk for precipitating acute allograft rejection with interferon therapy. The advent of the interferon-free, protease inhibitor–based regimen (e.g., sofosbuvir/ledipasvir) may improve outcomes in HCV-positive kidney transplant recipients. Repeated courses of antibiotics and corticosteroid therapy increase the risk for fungal infections, whereas viral infections not only may result from immunosuppression but may further impair immunity and increase the risk for additional opportunistic infections. TMP-SMX prophylaxis eliminates or reduces the incidence of *Pneumocystis* infection, *Listeria monocytogenes* meningitis, *Nocardia* spp. infection, and *Toxoplasma*

BOX 105.1 Timetable of Infections

FIRST MONTH AFTER TRANSPLANT

Common nosocomial bacterial pathogens and *Candida* spp. predominate.

Bacterial (Sites and Sources)

Urinary tract
Respiratory
Bacteremia
Surgical wound or intraabdominal sources (lymphoceles, hematomas, urine leak)
Vascular access or instrumentation (catheters, drains, urinary stents)
Anatomic or functional genitourinary tract abnormalities (ureteral stricture, vesicoureteric reflux, neurogenic bladder)
Clostridium difficile or center-specific multidrug-resistant species

Viral

Uncommon except for HSV

Fungal

Candida spp. predominate (recipient pretransplant colonization or donor-derived)

Organisms Transmitted with Donor Organs

MONTHS 1 to 6

Unconventional or opportunistic infections secondary to immunosuppression.

Viral

CMV, HSV, VZV, EBV, HBV, HCV, BK virus (exogenous infection or reactivation of latent disease as a result of immunosuppression)
Others: HHV-6, HHV-7, influenza, parainfluenza, RSV, adenovirus

Fungal

Aspergillus spp., *Cryptococcus,* agents of mucormycosis

Bacterial

Recurrent urinary tract infections or pyelonephritis
Nocardia, Listeria, Mycobacterium spp. (tuberculous and nontuberculous), *Legionella*

Parasitic

Pneumocystis jiroveci, Toxoplasma and *Strongyloides* spp., leishmaniasis, *Trypanosoma cruzi*

AFTER 6 MONTHS

Infection risks associated with duration and intensity of immunosuppression and epidemiologic exposures.

Stable Patients on Low-Dose Immunosuppressants

Community-acquired respiratory and GI viral pathogens

History of Multiple Rejection Episodes Requiring Intensification of Immunosuppression

Viral infections (invasive CMV such as CMV colitis or pneumonitis, VZV, parvovirus B19), late opportunistic infections *(Pneumocystis, Cryptococcus, Listeria, nocardiosis),* tuberculosis

Persistent Infections

HBV, HCV,* papillomavirus, BK virus

Geographically Restricted

For example, coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis)

Deep-Seated Infections

For example, osteomyelitis, paravertebral abscess
Predisposing risk factors: Chronic skin infections, long-standing poorly controlled diabetes, peripheral vascular disease

Associated With Malignancies

EBV (PTLD), papillomavirus (squamous cell carcinoma), HSV (cervical cancer), HHV-8 (Kaposi sarcoma)

*Incidence may decrease with the use of the newer interferon- and ribavirin-free anti-HCV protease inhibitor combination therapy.
CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HSV,* herpes simplex virus; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HHV-6,* human herpesvirus-6; *HHV-7,* human herpes virus-7; *PTLD,* post-transplant lymphoproliferative disease; *RSV,* respiratory syncytial virus; *VZV,* varicella zoster virus.

gondii. Reactivation of latent infection such as *Mycobacterium tuberculosis, Trypanosoma cruzi, Leishmania* spp., *Strongyloides stercoralis, Cryptococcus neoformans, Histoplasma capsulatum,* and *Coccidioides* and *Paracoccidioides* spp. may be observed. Community-acquired respiratory viruses are a common hazard in these vulnerable immunocompromised patients during this period, whereas BK virus infection remains an important cause of allograft loss (discussed later).

After 6 Months

After 6 months, the infection risk is largely a function of chronic maintenance immunosuppression, exposure to T cell–depleting agents, graft function, and epidemiologic exposures. Patients can be arbitrarily divided into three categories in terms of infection risks.

The first category consists of most transplant recipients (70% to 80%), who have satisfactory or good allograft function, relatively low doses of immunosuppressants, and no history of chronic viral infection. The risk for infection is similar to that of the general population, with community-acquired respiratory viruses constituting the major infective agents. Opportunistic infections are unusual unless environmental exposure has occurred.

The second group (~10% of patients) consists of those with chronic viral infection that may include HBV, HCV, CMV, Epstein-Barr virus (EBV), BK virus (BKV), or papillomavirus. In the setting of immunosuppression, such viral infections may lead to the development of progressive liver disease or cirrhosis (HBV, HCV), BK nephropathy (BKV), post-transplant lymphoproliferative disorder (EBV), or squamous cell carcinoma (papillomavirus). Alemtuzumab (a humanized monoclonal antibody directed against CD52 found on T and B cells) is associated with increased risk for late invasive viral and fungal infections because of its profound and prolonged effect on pan–T cell depletion. New infections occurring in this time period often reflect new exposures (e.g., *L. monocytogenes* [dietary ingestion], Lyme disease [tick exposure], and malaria [travelers to endemic areas]).[1]

The third group (~10% of patients) consists of those who experience multiple rejection episodes requiring repeated exposure to heavy immunosuppression. These patients are the most likely to develop chronic viral infections and superinfection with opportunistic infections. Causative opportunistic pathogens include *Pneumocystis, Listeria, Nocardia, Cryptococcus,* and geographically restricted mycoses (coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis). We advocate lifelong antifungal prophylaxis in high-risk transplant recipients such as those with a history of infection or who live in endemic areas. Environmental exposure (primarily avoidance of pigeons and areas of active building construction) should be minimized.

MANAGEMENT AND PROPHYLACTIC THERAPY FOR SELECTED INFECTIONS

Suggested prophylactic therapy in kidney transplant recipients is shown in Table 105.2.

Cytomegalovirus Infection

CMV infection may cause primary infection in a seronegative recipient (donor seropositive, recipient seronegative), reactivation of endogenous latent virus (donor seropositive or seronegative, recipient seropositive) or superinfection with a new virus in a seropositive recipient (donor seropositive, recipient seropositive). Primary CMV infection is usually more severe than reactivated infection or superinfection.

Clinical Manifestations

CMV infection may be asymptomatic, manifesting as a mononucleosis-like syndrome, an influenza-like illness with fever and leukopenia or thrombocytopenia, or a severe systemic disease. Any organ system may be affected by CMV. Clinically, patients may present with hepatitis, esophagitis, gastroenteritis, pneumonia, carditis, chorioretinitis, and even otitis. Clinical manifestations usually occur 1 to 4 months after transplantation except for chorioretinitis, which occurs later in the transplant course. Results of quantitative CMV assays of serum in patients with invasive colitis and gastritis or neurologic disease, including chorioretinitis, are often negative. Diagnosis in such patients may require invasive testing and biopsies.

TABLE 105.2 Post-Transplant Antimicrobial Prophylaxis

Prophylaxis	Regimen	Comments
Pneumocystis jiroveci	*First line:* TMP-SMX × 6 months* *Second line (sulfa allergies):* Atovaquone, dapsone, or aerosolized pentamidine†	TMP-SMX also reduces the incidence of *Toxoplasma gondii, Listeria monocytogenes,* and *Nocardia asteroides* and reduces the incidence of UTI in kidney transplant recipients. Check glucose-6-phosphate dehydrogenase before initiation of dapsone.
Fungal	Nystatin S&S (×1 months) or fluconazole (×3-6 months)‡ (see comments)	Fluconazole recommended in high-risk recipients (e.g., combined liver-kidney or pancreas-kidney transplant recipients, history of coccidioidomycosis, patients who live in endemic areas).
CMV	Acyclovir, valganciclovir, ganciclovir (see Box 105.2)	Acyclovir for HSV and VZV prophylaxis for patients not on CMV prophylaxis.

*Restart TMP-SMX prophylaxis ×6-12 mo after any solumedrol pulse or antibody treatment.

†Listed in order of preference. Consider adding fluoroquinolones or other agents for antibacterial activity.

‡We advocate lifelong therapy in patients with history of coccidioidomycosis or in those who live in endemic areas.

CMV, Cytomegalovirus; *HSV,* herpes simplex virus; *TMZ-SMX,* trimethoprim-sulfamethoxazole *VZV,* varicella zoster virus.

Immunomodulating Effects of Cytomegalovirus Infection

CMV infection is associated with immune modulation and dysregulation of helper and suppressor T cells. It may be a risk factor for acute and chronic allograft rejection, secondary infection with opportunistic agents (e.g., *Pneumocystis, Candida, Aspergillus*), and reactivation of human herpesvirus 6 (HHV-6) and HHV-7 and may favor development of post-transplant lymphoproliferative disorder. CMV infection is also associated with acceleration of HCV infection and the development of post-transplantation diabetes mellitus (also known as *new-onset diabetes after transplantation*, see Chapter 106). Detection of CMV virus in blood may indicate that the patient's cellular immune response is impaired secondary to immunosuppression.

Risk Factors for Cytomegalovirus Infection

Donor and recipient serostatus (donor CMV seropositive, recipient CMV seronegative) and the use of blood products from CMV-seropositive donors are well-established risk factors for CMV infection. Other risk factors include the use of antilymphocyte antibodies, prolonged or repeated courses of antilymphocyte preparations, comorbid illnesses, concomitant HHV-6 and HHV-7 viral infections, neutropenia, lack of CMV-specific $CD4^+$ and $CD8^+$ T cells, and acute rejection episodes. Mycophenolate mofetil (MMF) may increase the risk for CMV viremia and disease, especially in patients receiving more than 3 g/day. Although the cause-and-effect relationship of CMV infection and allograft rejection remains hypothetical, several studies suggest that one may increase the risk for the other, possibly because of the release of inflammatory cytokines. Prevention of CMV infection, for example, results in a lower incidence of graft rejection. In addition, even with modern regimens for screening and prophylaxis, asymptomatic CMV viremia and even donor seropositivity and recipient seronegativity (D +/R–) in the absence of detectable CMV viremia or disease is associated with increased incidence of graft rejection.[6]

Prevention

Prophylactic therapy begins in the immediate postoperative period. Preemptive therapy involves treatment of those who are found to seroconvert by quantitative laboratory assays of the blood, such as CMV DNA polymerase chain reaction (PCR) or pp65 antigenemia during surveillance studies. The former assay is highly specific and sensitive for the detection of CMV viremia. Currently, with the widespread availability of NAT, antigen-based methods have largely been replaced by CMV DNA testing. Universal prophylaxis for CMV is recommended over initiation of preemptive treatment after detection of CMV viremia or antigenemia for patients in the highest risk group (D +/R–). Oral acyclovir is necessary for HSV and VZV prophylaxis in patients not receiving anti-CMV prophylaxis or treatment. Oral or intravenous ganciclovir or oral valganciclovir provides superior prophylactic or preemptive therapy against primary CMV infection or CMV reactivation. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest oral ganciclovir or valganciclovir in CMV D +/R– or D +/R+ for at least 3 months after transplantation and for 6 weeks after treatment with T cell–depleting antibodies. Seronegative individuals who receive organs from latently infected seropositive donors are at greatest risk for primary infection and severe CMV disease. Delayed-onset CMV disease developing soon after completion of antiviral prophylaxis occurs in 15% to 38% of high-risk CMV D +/R– solid organ transplant recipients who received 3-month CMV prophylaxis and is associated with poor patient and graft survival. Other suggested risk factors for delayed-onset CMV disease include allograft rejection, overimmunosuppression, and lack of CMV-specific immunity. A suggested CMV prophylaxis protocol is shown in Box 105.2.

BOX 105.2 Suggested Cytomegalovirus Prophylaxis Protocol*

For CMV (–) recipient of a CMV (–) organ
- Acyclovir 400 mg twice daily (for herpes prophylaxis) × 3 months**
- CMV DNA q2wk × 3 months

For CMV (–) recipient of a CMV (+) organ:
- During antibody induction treatment: Ganciclovir 5 mg/kg/day IV**
- After antibody treatment: Valganciclovir 900 mg/day PO × 6 months**
- If no antibody treatment: Valganciclovir 900 mg/day PO × 6 months**
- CMV DNA q2wk × 3 months, then monthly up to 12 months

For CMV (+) recipient of a CMV (–) organ:
- During antibody induction treatment: Ganciclovir 5 mg/kg/day IV**
- After antibody treatment: Valganciclovir 900 mg/day PO × 6 months**
- If no antibody treatment[†]: Valganciclovir 900 mg/day PO × 3 months**
- CMV DNA q2wk × 3 months, then monthly up to 12 months

For CMV (+) recipient of a CMV (+) organ:
- During antibody induction treatment: Ganciclovir 5 mg/kg/day IV**
- After antibody treatment: Valganciclovir 900 mg/day PO × 6 months**
- If no antibody treatment[†]: Valganciclovir 900 mg/day PO × 3 months**
- CMV DNA q2wk × 3 months, then monthly up to 12 months

*Practice may vary among centers. Acyclovir, valganciclovir, ganciclovir: ****Dose adjustment for renal function necessary**

[†] May use acyclovir or valganciclovir (center-dependent).

Treatment

The 2013 AST Infectious Diseases Community of Practice guidelines recommend oral valganciclovir 900 mg orally every 12 hours, adjusted according to glomerular filtration rate [GFR]) for mild to moderate CMV disease, whereas intravenous ganciclovir 5 mg/kg every 12 hours, adjusted according to GFR) should be the initial therapy for patients with severe or life-threatening CMV disease, those with high viral load, those with questionable gastrointestinal (GI) tract absorption, or those who are intolerant of oral medication. Treatment should be continued until the following criteria are met: (1) resolution of clinical symptoms; (2) virologic clearance below a threshold negative value based on laboratory monitoring with CMV, quantitative CMV nucleic acid test (QNAT), or pp65 antigenemia; and (3) minimum 2 weeks of antiviral therapy. Reduction of immunosuppression should be considered in moderate to severe disease, in slow responders or nonresponders, and in those with high viral loads or leukopenia. Antiviral drug dose reduction because of side effects should be performed only for renal insufficiency, because dose reductions for leukopenia have been shown to be associated with development of antiviral resistance. Reduction or withholding of mycophenolic acid (MFA) products, azathioprine (AZA), or TMP-SMX should be considered before valganciclovir or ganciclovir dose reduction. Severe leukopenia (absolute neutrophil count <500 to 1000/mm^3) can be treated with granulocyte colony-stimulating factor. The beneficial effect of adding intravenous immunoglobulin (IVIG) or CMV Ig to existing antiviral treatment regimens remains unclear but may be considered adjunctive therapy in individuals with hypogammaglobulinemia, in life-threatening disease, in nonresponders to standard therapy, or in those with severe forms of CMV disease, such as pneumonitis.

Laboratory monitoring for CMV by PCR assays should be performed weekly during treatment, and CMV DNA should be negative before discontinuation of treatment. Secondary prophylaxis with valganciclovir 900 mg/day for 1 to 3 months should be considered. Alternatively, patients should have close clinical and/or virologic follow-up after discontinuation of treatment to assess the risk for relapse. Measuring anti-CMV cell–mediated immunity (using QuantiFERON-CMV assay to measure the level of T cell interferon-γ (IFN-γ) production after CMV exposure) to assess the risk for CMV infection or disease and to guide therapeutic response is a subject of ongoing clinical research.

Mutation in the viral kinase *UL97* gene that prevents phosphorylation of ganciclovir to its active form confers ganciclovir-resistance. Cidofovir and foscarnet should be reserved for those with clinically suspected ganciclovir-resistant strains because of their associated nephrotoxicity and potential synergistic nephrotoxicity with calcineurin inhibitors (CNIs). Mutation in the *UL54* gene, which encodes for CMV DNA polymerase (a target for all currently available systemic anti-CMV drugs) could lead to cidofovir or foscarnet resistance or cross-resistance among ganciclovir, foscarnet, and cidofovir. Concomitant *UL97* and *UL54* mutations often confers high-level ganciclovir-resistance and warrants infectious disease specialist referral.

Candida Infections

Candida infections are common in transplant recipients; *Candida albicans* and *Candida tropicalis* account for 90% of the infections. Risk factors include diabetes, high-dose corticosteroids, broad-spectrum antibacterial therapy, indwelling urinary tract device, and, rarely, donor-derived candidiasis. Fluconazole has historically been considered the drug of choice for the prevention or treatment of donor-derived candidiasis. Other azoles (such as voriconazole or itraconazole) and the echinocandins do not effectively get into the urine as active drugs and should not be used.

Superficial candidal infections involving the mouth or intertriginous areas can be treated with nystatin and topical clotrimazole, whereas candidal UTIs require systemic antifungal therapy (see Chapter 53). Whenever possible, bladder catheters, surgical drains, and urinary stents should be removed. Management of asymptomatic candiduria in immunocompromised patients is discussed in Chapter 53. Systemic antifungal therapy is indicated in the presence of any blood culture positive for *Candida* spp.

BK Virus Infection

The clinical spectrum of BKV infections include BK viruria, BK viremia, BKVN, and, less commonly, ureteral stenosis. The highest prevalence of BK viruria and viremia occurs at 2 to 3 months, and 3 to 6 months, respectively. Serum BK viral load of at least 10,000 copies/ml has been suggested to be predictive of BKVN. However, PCR assays are not standardized and the sensitivity and specificity of the assays may vary.

BKV is an important cause of allograft dysfunction and graft loss and commonly manifests with an asymptomatic rise in serum creatinine during the first post-transplantation year. However, BKVN may occur as early as the first week and as late as 6 years after transplantation. Diagnosis is made by allograft biopsy that demonstrates BK viral inclusions in renal tubular cell nuclei and occasionally in glomerular parietal epithelium (Fig. 105.1). Interstitial mononuclear inflammation, often with many plasma cells, degenerative changes in tubules, and focal tubulitis, may mimic acute rejection. BKV infection and acute rejection may occur simultaneously, and distinguishing between BKVN and acute rejection or the presence of both can be a diagnostic challenge.

Treatment strategies for BK viremia with or without BKVN vary, but immunologic containment of BKV replication is universally accepted as the mainstay of therapy.[7] Suggested strategies for reduction in immunosuppression include reduction or discontinuation of antimetabolites (MFA) derivatives or AZA, or reduction of CNIs or corticosteroid therapy. In one study, routine BKV surveillance and immunosuppression reduction alone on detection of significant viremia (defined as ≥10,000 copies/ml) effectively resolved viremia, preserved renal function, and prevented clinical BKVN and graft loss.[8] The effectiveness of immunosuppression reduction alone was also demonstrated by others.[9,10]

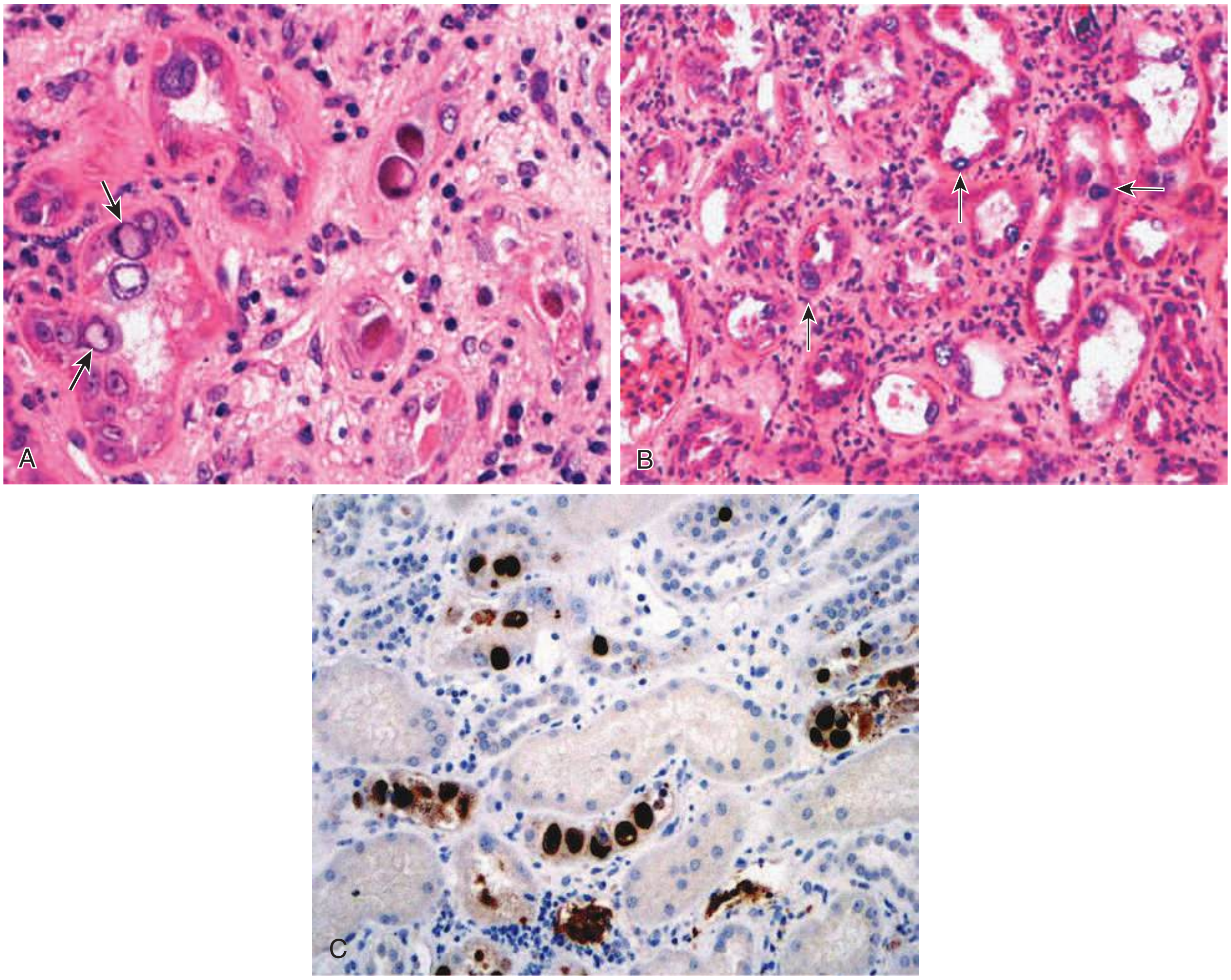

Fig. 105.1 BK virus nephropathy. (A) Prominent intranuclear viral inclusions are present within tubular epithelial cells *(arrows).* (Hematoxylin-eosin [HE] stain; original magnification ×400.) (B) Tubulointerstitial nephritis with diffuse intranuclear polyomavirus inclusions *(arrows).* (HE stain, original magnification ×200.) (C) Immunohistochemistry staining highlights intranuclear polyomavirus inclusions. (SV40 immunoperoxidase stain; original magnification ×200.) (Courtesy Charles Lassman and William Dean Wallace, David Geffen School of Medicine at UCLA, Los Angeles, California.)

Limited small case series demonstrated that tacrolimus to cyclosporine or sirolimus conversion therapy resulted in resolution of BKVN and viruria/viremia. Recent experimental studies demonstrated that sirolimus impairs BKV replication in renal tubular epithelial cells during viral early gene expression, but not during viral late gene expression by interfering with mammalian target of rapamycin (mTOR)-SP6-kinase activation. Cyclosporine was similarly shown to inhibit BKV replication, whereas tacrolimus activates BKV replication and reverses sirolimus inhibition, leading to increased BKV replication.[11] MMF to leflunomide or to sirolimus switch also has been suggested to be beneficial,[12] although this effect is probably linked more closely to discontinuation of MMF rather than direct antiviral effect of leflunomide therapy. In contrast to early studies, preliminary results of a single-center phase IV randomized trial evaluating the safety and efficacy of MMF to everolimus conversion versus 50% MMF dose reduction in the clearance rates of BK viruria and/or viremia at 3-months postrandomization showed no statistical significant differences in either primary or secondary end-point between the two treatment arms. The former was defined as a greater than 50% reduction of BK viruria and/or clearance of viremia at 3-months postrandomization and the latter as the percentage reduction in BK viremia at 3 months (www.clinicaltrials.gov, NCT01624948).

In BKV-associated disease refractory to immunosuppression reduction alone, the use of antiviral agents such as cidofovir, leflunomide, and fluoroquinolones has met with variable results and cannot be recommended (see Table 105.3).[7] There are only case series–level data regarding impact of IVIG. However, IVIG therapy may be considered for persistent BK viremia because it may have the added beneficial impact on limiting the negative effect of donor-specific antibodies, which may be seen arising in association with BK viremia.

In a small series of three pediatric kidney transplant recipients with biopsy-confirmed BKVN, ciprofloxacin to leflunomide conversion (if BK viremia did not decrease after 2 months of ciprofloxacin) and concomitant discontinuation of MMF resulted in complete resolution of BKVN.[13] In contrast, a meta-analysis of eight studies (two randomized controlled trials and six retrospective cohort studies) failed to show a beneficial effect of fluoroquinolone prophylaxis (for >1 month) in preventing BK viremia or BKVN at 1-year follow-up.[14]

Although small open-label case series demonstrated the possible beneficial effects of leflunomide, systematic review of 40 studies showed

TABLE 105.3 Therapeutic Interventions Targeting BK Virus Replication

Intervention	Proposed Mechanisms of Action	Adverse Effects	Eeefectiveness Comments
A. Manipulation of Immunosuppressive Therapy			
Reduction in immunosuppression	Reconstitution of BKV-specific immune response.	Acute/chronic rejection	Effective. Mainstay of therapy.
Tacrolimus to cyclosporine (CSA) switch	Experimental studies demonstrated that CSA may exert an antiviral effect on BKV via suppression of viral replication, whereas tacrolimus may activate BKV replication.		Cannot be recommended Further studies are needed.
Calcineurin inhibitor to mTOR inhibitor switch*	mTOR inhibitors inhibit phosphorylation of the 70-kDa ribosomal protein S6 kinase and reduce BK virus large T antigen expression. May promote differentiation of antiviral memory CD8 T-lymphocytes.		Effectiveness varies among studies. May have the added benefit of avoiding the long-term nephrotoxic effect of CNI therapy. [1] *"NCT01649609" clinical trial:* Substitution of tacrolimus for sirolimus vs. immunosuppression reduction for the treatment of BK viremia and prevention of BKVN (study completed. Results pending at the time of this writing).
Mycophenolate mofetil to mTOR inhibitor switch			[2] *Phase 4 clinical trial results:* MMF to everolimus switch *vs.* 50% MMF dose reduction in the clearance rates of viruria and/or viremia at 3 mo postrandomization shows no statistically significant differences in either first or second end-point between the two treatment arms (the former was defined as >50% reduction of BK viruria and/or clearance of viremia at 3-mo postrandomization and the latter as percent reduction in BK viremia at 3 mo). There was a nonstatistically significant trend toward improved clearance with everolimus conversion at 1 year
B. Antiviral Agents			May consider adjunctive antiviral agents in BKV-associated disease refractory to reduction or manipulation of immunosuppression although benefit is unclear.
Leflunomide	Tyrosine kinase inhibitor Inhibits BKV genome replication and early gene expression.	Anemia, hemolytic anemia, thrombocytopenia, thrombotic microangiopathy, transaminitis	Effectiveness varies among studies. [3] *Ongoing clinical trial (expected completion date March 2018):* Leflunomide in combination with orotic acid vs. standard of care in patients with high levels of BK viuria and absence of BK viremia.
Cidofovir	Inhibits BK viral replication by an unknown mechanism.	Potentially nephrotoxic Severe uveitis	Effectiveness varies among studies.
Fluoroquinolones	Inhibit BK DNA topoisomerase and SV40 large tumor antigen helicase.		No beneficial effect either as a prophylactic or therapeutic agent based on recent clinical data and two randomized trials. Authors' opinion: Not recommended
Intravenous immunoglobulins (IVIG)	BKV neutralizing antibodies. *Others:* Steric hindrance to receptor binding, complement-dependent cytotoxicity, viral agglutination, and antibody facilitated phagocytosis.		Effectiveness varies among studies. IVIG may be beneficial in patients with concomitant rejection and BKVN or in those with histopathologic changes that are indistinguishable from those of rejection.
C. Antiviremic and Antifibrotic Combination Therapy			
Leflunomide and sirolimus combination therapy			*Ongoing clinical trial (expected completion date 31/3/18):* The BK: KIDNI Trial (Standard immunosuppression reduction alone vs. replacement of antimetabolite with leflunomide and sirolimus in patients with BK viremia).

*Ongoing clinical trial www.clinicaltrials.gov NCT01289301. CNI to everolimus switch in kidney transplant recipients with biopsy-confirmed BKN (expected completion date: October 2018).

www.clinicaltrials.gov [1]NCT01649609, [2]NCT01624948, [3]NCT1620268.

BKVN, BK nephropathy; *CNI,* calcineurin inhibitor; *IVIG,* Intravenous immunoglobulins; *MMF,* mycophenolate mofetil.

no graft survival benefit of adding cidofovir or leflunomide to immunosuppressive reduction for the management of BKVN.[15] Whereas some studies demonstrated that therapeutic response to leflunomide generally correlates with blood levels between 40 and 100 mcg/mL,[16] other studies have not observed a similar association.[17] One single-center study demonstrated that simultaneous administration of three different anti-BKV agents (leflunomide, IVIG, ciprofloxacin) added no benefit to long-term outcome in patients with BKVN (follow-up 7.3 ± 4.99 years). In contrast, graft survival was significantly improved among those treated conventionally with immunosuppression reduction.[18]

Although reduction in immunosuppression is the mainstay of therapy in BK viremia/BKVN, it is not universally effective, suggesting that the balance between viral replication and virus-specific immune surveillance determines the clinical course of BKV-associated clinical syndromes. In recent years, BKV-specific T cell immunity has increasingly been recognized to play an important role in the containment of BKV infection.[19,20] In a series of 10 patients with BKVN, a strong cytotoxic T-lymphocyte response was associated with decreased BK viruria or viremia and low anti-BK antibody viral titers, whereas a low or undetectable cytotoxic T-lymphocyte response correlated with viral persistence and high anti-BK antibody titers.[19]

In the absence of conclusive evidence that any particular immunosuppressive agent has a specific advantage in terms of the risk for BKV replication, and the unclear benefit of antiviral agents, intensive monitoring of serum BKV using PCR in all kidney transplant recipients and immunologic containment of BKV replication should remain the mainstay of therapy in BKV-associated clinical syndromes.[7] Monitoring for plasma BKV alone appears to be cost-effective because BKVN is unusual in the absence of BK viremia. A proactive, preemptive approach often leads to resolution of viruria and/or viremia and halts the progression of BK viremia to BKVN. The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommend reduction in immunosuppression when BKV plasma NAT results are persistently greater than 10^4 copies/ml. However, in the authors' opinion, steadily rising plasma BKV DNA copies on serial measurements irrespective of BK copy levels warrants judicious immunosuppression reduction because early intervention prevents progression to BKVN. Patients with biopsy-proven BKVN and concurrent acute rejection should be treated with antirejection treatment, with subsequent reduction in immunosuppression. In patients with sustained high-level BK viremia despite reduction or manipulation of immunosuppressive therapy, antiviral agents may be considered, although the effectiveness of currently available antiviral agents is of uncertain benefit. In nearly all case series reported, adjuvant antiviral agents were initiated in conjunction with immunosuppression reduction. Furthermore, although antiviral therapy may reduce viral load, viral clearance may require continuous immune control. Optimal reduction of immunosuppressive therapy may allow sufficient reconstitution of BKV-specific T cells to control BKV replication while maintaining adequate immunosuppression to prevent allograft rejection. The routine recommendations of antiviral therapy or immunosuppression class switching in the prevention or treatment of BKV-related clinical syndromes await results of large prospective randomized trials. Therapeutic interventions targeting BK virus replication and suggested mechanisms of action of various antiviral agents are shown in Table 105.3.[7] Anecdotal reports suggested that IVIG may be effective in treating corticosteroid-resistant rejection. Its use may be beneficial in patients with concomitant BKVN and acute rejection (acute antibody-mediated or cellular rejection) or in those with histopathologic changes that are indistinguishable from those of rejection. Development of T cell or antibody-based vaccines against BKV is a subject of future research.[21] Suggested guidelines for post-transplant screening and monitoring for BKV replication are shown in Fig. 105.2.

Other Infections

Tuberculosis (TB) is an important cause of morbidity and mortality in solid organ transplantation with an estimated mortality rate of 20% to 30%. Over two thirds of reported cases of active TB in solid organ transplant recipients occur in the first post-transplant year (median 6 to 11 months). Although TB commonly results from inhalation of airborne bacilli, it more commonly emerges from the reactivation of dormant lesions in the setting of immunosuppressive therapy. Hence, all potential kidney transplant candidates should undergo a purified protein derivative (PPD) skin test or preferably the IFN-γ release assays before transplantation to diagnose latent TB. A positive skin test or IFN-γ release assay result or a history of TB mandates further evaluation to rule out active disease. Isoniazid (INH) prophylaxis for a total of 9 months is recommended for those who have a positive skin test or IFN-γ release assay result. Clinical, radiologic, or culture evidence of active TB infection is a contraindication to transplantation. INH prophylactic therapy should be considered in the following situations:

- Transplant candidates with a history of positive tuberculin skin test or IFN-γ release assay result
- Those with TB disease without adequate treatment
- Patients with evidence of old granulomatous disease on chest x-ray film and epidemiologic risk factors for TB
- Those with known prolonged exposure to a person with active TB
- Kidney transplant recipients in endemic areas
- Donor with positive tuberculin skin test or IFN-γ release assay result
- In highly endemic areas where TB transmission is common, universal INH prophylaxis for the first year post-transplant during the period of maximum immunosuppression is recommended by some transplant experts. However, in areas or countries where there is an increased prevalence of INH-resistance strain, such as in India, close monitoring and treatment of active infection is recommended over initiation of INH prophylaxis.
- In patients with a known history of adequately treated TB infection, we suggest secondary INH prophylaxis the first 9 months after transplantation in patients with a history of extensive disease such as positive blood cultures, visceral involvement, or recent treatment history (arbitrarily defined as <10 years before transplant). Others, however, have suggested that INH prophylaxis is not indicated for patients whose TB had been properly treated.

Strongyloides is a rare but important cause of infection in transplant patients, particularly those from endemic areas such as Southeast Asia. In the presence of immunosuppression, a "hyperinfection" syndrome may be observed with parasitic pneumonia and GI involvement.

GASTROINTESTINAL DISEASE

Post-transplantation GI complications are common. Selected complications are discussed.

Drug-Related Gastrointestinal Complications

MMF causes GI side effects, including nausea, vomiting, dyspepsia, anorexia, flatulence, and diarrhea. Dose reduction, temporary drug discontinuation, or administration of the drug in three or four divided doses often ameliorate the symptoms. A randomized, multicenter, open-label study demonstrated that switching from MMF to enteric-coated mycophenolate sodium (EC-MPS) may enable an increase in the maximum tolerated dose of MFA and reduce GI complications. Therefore conversion of MMF to EC-MPS should be considered in patients with GI intolerance associated with MMF use.

Proton pump inhibitor (PPI) use can reduce the dissolution of MMF by increasing gastric pH. In contrast to MMF, EC-MPS is not

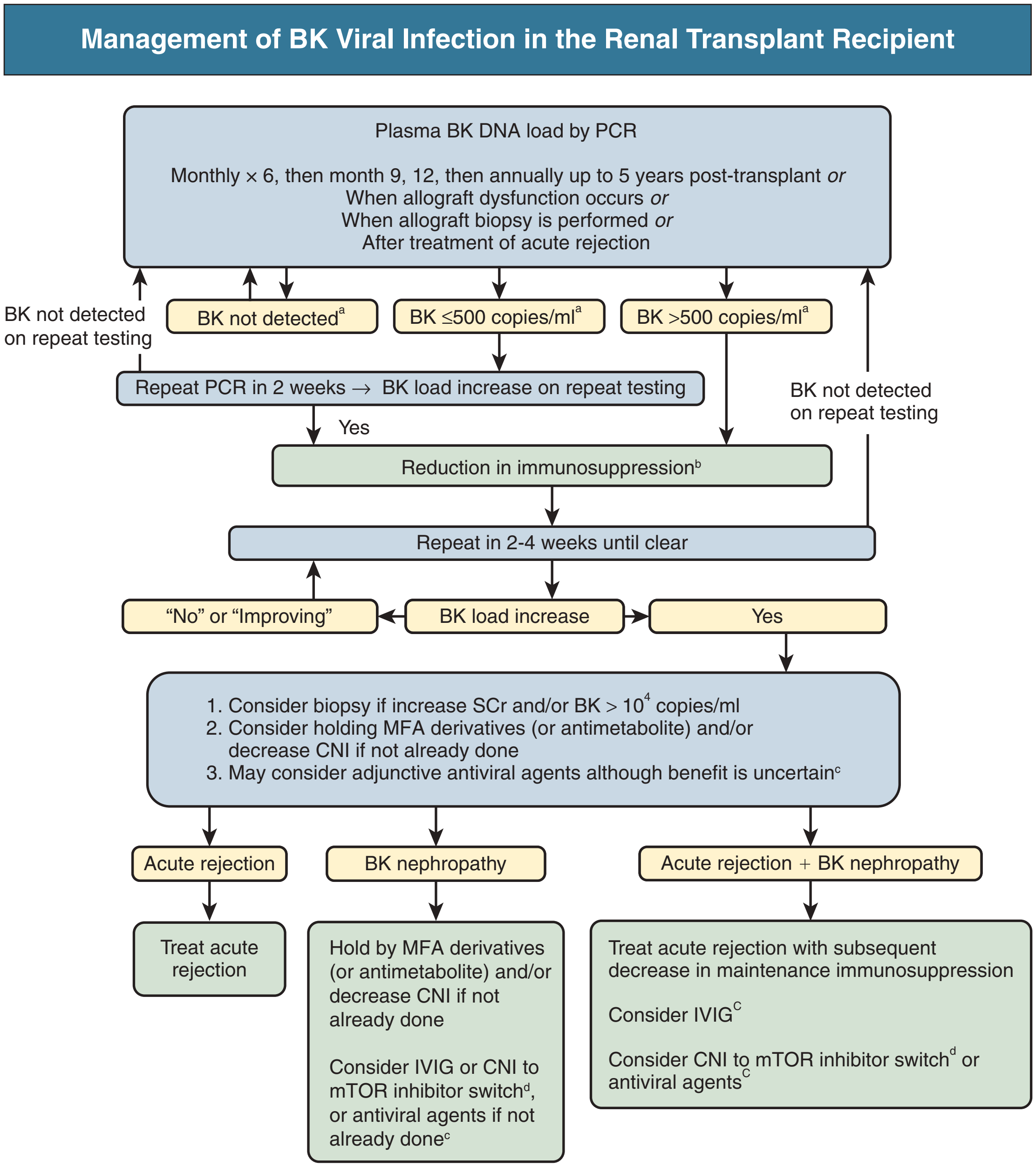
Management of BK Viral Infection in the Renal Transplant Recipient
Plasma BK DNA load by PCR
Monthly × 6, then month 9, 12, then annually up to 5 years post-transplant *or*
When allograft dysfunction occurs *or*
When allograft biopsy is performed *or*
After treatment of acute rejection
BK not detected on repeat testing
BK not detected[a]
BK ≤500 copies/ml[a]
BK >500 copies/ml[a]
Repeat PCR in 2 weeks → BK load increase on repeat testing
BK not detected on repeat testing
Yes
Reduction in immunosuppression[b]
Repeat in 2-4 weeks until clear
"No" or "Improving"
BK load increase
Yes
1. Consider biopsy if increase SCr and/or BK > 10^4 copies/ml
2. Consider holding MFA derivatives (or antimetabolite) and/or decrease CNI if not already done
3. May consider adjunctive antiviral agents although benefit is uncertain[c]
Acute rejection
BK nephropathy
Acute rejection + BK nephropathy
Treat acute rejection
Hold by MFA derivatives (or antimetabolite) and/or decrease CNI if not already done
Consider IVIG or CNI to mTOR inhibitor switch[d], or antiviral agents if not already done[c]
Treat acute rejection with subsequent decrease in maintenance immunosuppression
Consider IVIG[C]
Consider CNI to mTOR inhibitor switch[d] or antiviral agents[C]

Fig. 105.2 **Suggested approach for screening and management of *BK* virus (BKV)-associated clinical syndromes.** [a]No standardized polymer chain reaction *(PCR)* assays for BKV are currently available. Cut-off levels for viral detection should be based on PCR assays used at individual institutions. Viral load of 500 copied/ml is the lowest detection level at the author's institution. [b]Common practice: (1) Decrease or hold mycophenolic acid *(MFA)* derivatives (or antimetabolite) (2) Decrease (MFA + calcineurin inhibitor *[CNI]*) by 25% to 50%. (3) Decrease CNI. Less common practice: (1) Decrease prednisone ± decrease CNI (2) CNI to mTOR inhibitor switch ± decrease MFA. (3) Tacrolimus to cyclosporine switch. [c]See text and Table 105.3 (ongoing clinical trials). [d]Evidence-based recommendations are lacking (ongoing clinical trials). May avoid long-term nephrotoxic effect of CNI therapy. Not recommended in patients with baseline significant proteinuria (arbitrarily defined as >500 mg/24 h or at the discretion of the clinician). *IVIG,* Intravenous immunoglobulin; *MFA,* mycophenolate acid; *mTOR,* mammalian target of rapamycin; *SCr,* serum creatinine.

absorbed in the stomach and its bioavailability is not affected by PPIs. The latter formulation delays the release of MFA. Sirolimus may cause oral mucocutaneous lesions that may resemble HSV or CMV infection but are culture negative. Drug-related oral ulcers usually resolve after discontinuation of the offending agent. Sirolimus, everolimus, tacrolimus, and cyclosporine may cause diarrhea in some patients.

Infections

Post-transplantation infections of the GI tract may have a viral, fungal, or bacterial cause. Viral infections are most commonly caused by CMV and HSV; *C. albicans* and *C. tropicalis* are common opportunistic fungal infections. Leukoplakia and post-transplant lymphoproliferative disorders (PTLDs) may develop in patients with EBV infection (PTLD is discussed in a later section). Commonly encountered bacterial pathogens include *Clostridium difficile* and *Helicobacter pylori*.

Cytomegalovirus Infection

CMV can affect any segment of the GI tract. Patients may present with dysphagia, odynophagia, nausea, vomiting, gastroparesis, abdominal pain, diarrhea, or GI bleeding. Leukopenia and elevated transaminases are common. Persistent or unexplained symptoms of nausea, vomiting, or diarrhea, particularly in the early post-transplantation period or during intensification of immunosuppression, warrant further investigation with upper and lower endoscopies and biopsies. At the authors' institution, severe CMV and candidial gastritis/esophagitis were found in a patient who was heavily immunosuppressed with antithymocyte globulin and presented with intractable vomiting 4 months after transplantation. Histologic examination of the tissue obtained from the vomitus was compatible with foveolar gastric lining detachment (Fig. 105.3).

Herpes Simplex Virus Infection

HSV infection results primarily from reactivation of endogenous latent virus, causing clinical infection within the first 1 to 2 months after transplantation. Patients commonly present with oral mucocutaneous lesions or gingivostomatitis with or without odynophagia and dysphagia. HSV esophagitis has been noted to occur in patients receiving high-dose corticosteroids and antilymphocyte preparations for acute rejection. Limited oral mucocutaneous lesions are treated with oral acyclovir; extensive infections require intravenous acyclovir or ganciclovir. The routine use of acyclovir prophylaxis is recommended in the early post-transplantation period (see Box 105.2).

Fungal Infections

Candida stomatitis and esophagitis are common during the first 6 months after transplantation and are increased in patients with leukopenia, severe immunosuppression, diabetes, or concomitant infections. The use of prophylactic oral nystatin "swish and swallow" during the first month after transplantation is recommended. Fluconazole prophylaxis is warranted in high-risk candidates, including liver or pancreas transplant recipients and those receiving antilymphocyte antibody therapy.

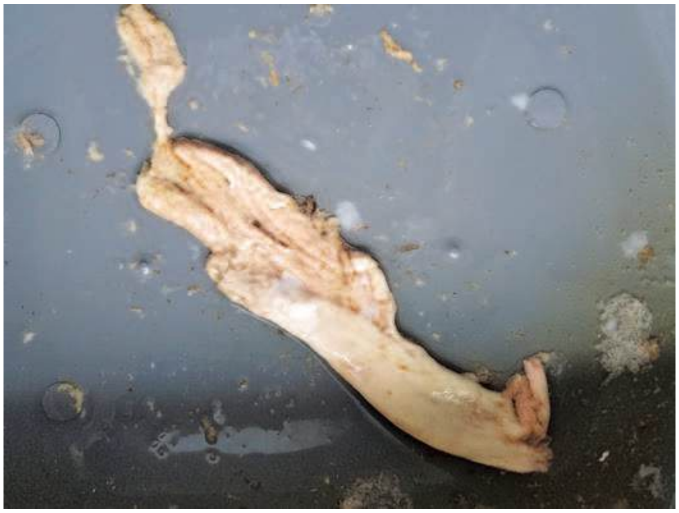

Fig. 105.3 Tissue obtained from patient's vomitus. Histologic examination of the necrotic tissue showed numerous fungal organisms (consistent with *Candida* spp.), and degenerated squamous epithelium with detached columnar (gastric foveolar type) epithelium. Occasional cells demonstrated enlarged nuclei and intracytoplasmic granular eosinophilic inclusions, consistent with cytomegalovirus viral inclusions.

Helicobacter Infection

H. pylori infection is associated with a wide range of GI complications including chronic gastritis, duodenal and gastric ulcers, mucosa-associated lymphatic tissue (MALT) lymphoma, and gastric carcinoma, both in the general population and in solid organ transplant recipients. Unexplained dyspeptic or reflux symptoms should be investigated further with endoscopy and biopsy to exclude malignancy. *H. pylori*–associated MALT lymphoma in kidney transplant recipients may be less aggressive than other lymphomas, and the disorder may be cured by eradication of *H. pylori*.

Diarrhea and Colon Disorders

Diarrhea is common after solid organ transplantation because of adverse drug effects (discussed in earlier section) and infectious pathogens. *C. difficile* is the most commonly encountered bacterial pathogen, and CMV is the most commonly encountered viral pathogen. In recent years, norovirus is increasingly recognized as a cause of diarrhea after solid organ transplantation. Although norovirus often causes acute self-limited illness in immunocompetent individuals, it can cause both acute and chronic diarrhea in solid organ transplant recipients. Management is supportive and includes volume repletion, antimotility agents, and reduction in immunosuppression (inconclusive evidence). Anecdotal case reports suggest that nitazoxamide is effective in treatment of norovirus-associated diarrhea. In a series of three orthotopic heart transplant recipients treated with nitazoxanide, diarrhea resolved in two of three patients.[22] However, in both cases treatment was initiated in conjunction with reduction in immunosuppression.

Diverticulitis and colonic perforations may be life-threatening and difficult to diagnose after transplantation because symptoms may be masked by immunosuppressive therapy, particularly in the early postoperative period. Diverticulitis complicated by perforation, abscess formation, phlegmon, or fistula has been reported in 1% of kidney transplant recipients, and its incidence may be increased in patients with polycystic kidney disease. Early post-transplantation colonic perforations are largely caused by high-dose corticosteroids, diverticulitis, CMV colitis, and intestinal ischemia; perforations occurring late or years after transplantation are commonly caused by diverticulosis or malignant disease.

TRANSPLANT-ASSOCIATED MALIGNANCY

The overall incidence of de novo malignancies is twofold to fourfold greater in solid organ transplant recipients compared with the general population.[23] Among long-term survivors after kidney transplantation (>20 years), cancer was the most common cause of death with a functioning graft followed by CV disease.[24] The intensity and duration of immunosuppression as well as the ability of these agents to promote replication of various oncogenic viruses are important risk factors. Table 105.4 provides a summary of the incidence of cancers related to infections in solid organ transplant recipients.[25]

Skin cancers are the most common de novo post-transplant tumors in the adult transplant population and occur with increasing frequency with time. Among nonskin malignant neoplasms, PTLDs are the most common type of post-transplantation malignancy. The mean time to diagnosis of different neoplasms varies with the type of organ involved. Kaposi sarcoma, PTLD, testicular cancer, cancer of the small intestine, and thyroid cancer occur early after transplantation (<800 days after transplantation). By 20 years after kidney transplant, nearly 50% have one or more skin cancers and 10% to 27% have nonskin cancers.[23] Renal cell carcinoma (RCC) occurs mainly in native kidneys and is associated with acquired cystic kidney disease and dialysis duration. A bimodal distribution is observed with the highest incidence occurring

TABLE 105.4 Meta-Analysis Standardized Incidence Ratios for Cancers Related to Infections in Transplant Recipients

Cancers	Meta-analysis SIRs
EBV-Related Cancers	
Hodgkin lymphoma	3.89 (2.42-6.26)
Non-Hodgkin lymphoma	8.07 (6.40-10.2)
HHV-8–Related Cancer	
Kaposi sarcoma	208.0 (114-369)
HBV- and HCV-Related Cancer	
Liver	2.13 (1.16-3.91)
HPV-Related Cancers	
Cervix uteri	2.13 (1.37-3.30)
Vulva and vagina	22.8 (15.8-32.7)
Penis	5.8 (5.79-34.4)
Anus	4.85 (1.36-17.3)
Oral cavity and pharynx	3.23 (2.40-4.35)
Nonmelanocytic-related skin	28.6 (9.39-87.2)

Modified from reference 24.

EBV, Epstein-Barr virus; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HHV,* human herpes virus; *HPV,* human papilloma virus.

in the first year and a second peak 4 to 15 years after transplant.[26] RCC occurring early after transplant is thought to reflect undetected or malignant transformation of preexisting cysts that developed during the course of end-stage renal disease. Common cancers in the general population, including cancers of the breast, colon, prostate, lung, bladder, stomach, and pancreas, were found to occur more frequently in kidney transplant recipients in some but not all studies. The KDOQI guidelines suggest an individualized screening plan for each kidney transplant recipient, considering the patient's medical and family history, tobacco use, and competing risk for death. In patients with compensated cirrhosis, annual hepatic ultrasound and measurement of α-fetoprotein level is recommended. Screening for cervical, breast, prostate, and colon cancer should follow local guidelines for the general population. In recipients with a history of preexisting malignant neoplasms, close monitoring for recurrences is mandatory. Suggested guidelines for tumor-free waiting periods for common pretransplant malignant neoplasms are shown in Box 105.3.

Post-Transplant Lymphoproliferative Disorder

PTLD encompasses a wide spectrum of lymphoid proliferations ranging from reactive polyclonal lesions to frank malignant monoclonal lymphomas. The World Health Organization (WHO) classification of PTLD is shown in Box 105.4. Most PTLDs are non-Hodgkin lymphoma of B cell origin, 80% to 90% of which are linked to EBV infection. However, the incidence of EBV-negative PTLD has increasingly been reported.

PTLD commonly occurs in the first year after transplant, although the cumulative incidence increases with time after transplantation. Registry studies and the United Network for Organ Sharing/Organ Procurement and Transplantation (UNOS/OPTN) database demonstrated that PTLD occurred at a median of 18 to 18.5 months after transplantation. Notably, EBV-negative PTLD generally manifests later after transplant (>5 years) and has been suggested to account for the bimodal distribution pattern of PTLD occurrence, with early cases being

BOX 105.3 Malignancy and Kidney Transplantation[1]

Most tumors: Wait time ≥2 years
No waiting time if cure at the time of transplantation
Incidental renal cell carcinoma
In situ carcinoma of bladder
In situ carcinoma of cervix
Basal cell carcinoma
Squamous cell carcinoma (skin) [2,3]
Waiting time ≥2-5 years[2]
Melanoma[2,4] 5 y
Wilms tumor 2 y
Renal cell carcinoma
  2 y if <5 cm
  5 y if >5 cm
Breast carcinoma[5] 2-5 y
Lymphoma 2-5 y
Colorectal carcinoma 2-5 y
Invasive bladder 2 y
Uterine body 2 y
Invasive cervical carcinoma 2-5 y

[1] Certain cancers may recur despite a tumor-free waiting period.
[2] Oncology evaluation or consultation with the Israel Penn International Transplant Tumor Registry at www.ipittr.org may be invaluable.
[3] Surveillance.
[4] In situ melanoma may require a shorter waiting period of 2 years (dermatology consultation is probably warranted).
[5] Early in situ (e.g., ductal carcinoma in situ) may require only 2-year wait. Individuals with advanced breast cancer (stage III or IV) should be advised against transplantation.

BOX 105.4 World Health Organization Classification of Post-Transplant Lymphoproliferative Disorder

1. **Early lesions**
   Plasmacytic hyperplasia
   Infectious mononucleosis
   Florid follicular hyperplasia
2. **Polymorphic PTLD**
3. **Monomorphic PTLD**
   B Cell Neoplasms
      Diffuse large B cell lymphoma
      Burkitt lymphoma
      Plasma cell myeloma
      Plasmacytoma-like lesion
      Other
   T Cell Neoplasms
      Peripheral T cell lymphoma, NOS
      Hepatosplenic T cell lymphoma
      Other
4. Classic Hodgkin lymphoma-type PTLD

NOS, Not otherwise specified; *PTLD*, post-transplant lymphoproliferative disorder.

predominantly EBV positive and late cases being EBV negative.[23,27] A French PTLD registry study suggests that late-occurring PTLD (8 to 10 years) is less likely to be due to EBV lymphoproliferation and more likely to be a consequence of aging and duration of immunosuppression exposure.[28]

Risk Factors

Risk factors for PTLD can be classified into those associated with the type of organ transplant, recipient age, type and intensity of immunosuppression, infectious agents, and human leukocyte antigen (HLA) mismatch.

Type of organ transplant. PTLD occurs in 1% to 2% of patients after kidney transplantation; 1% to 4% after liver transplantation; 2% to 3% after pancreas or simultaneous kidney-pancreas transplantation; 2% to 10% after heart, lung, and heart-lung transplantation; and up to 33% after small bowel and multivisceral transplantation. The high incidence of PTLD in bowel and multiorgan transplants has been attributed to the use of more intensive immunosuppression and the amount of donor-derived lymphoid tissue transferred at organ transplantation.

Age. PTLD is the most common malignancy in children, whereas in adults it is the second most common malignancy after skin cancer. The higher incidence of PTLD in children compared with adults has been attributed to the pretransplant EBV-naïve status of children.

Type of immunosuppression

Calcineurin inhibitors. Cyclosporine and tacrolimus may enhance the development of EBV-associated PTLD by directly promoting survival of EBV-infected B cells, presumably via the inhibition of EBV-transformed cells from apoptosis. Although single-center retrospective studies demonstrated that tacrolimus increased the risk for PTLD by twofold to fivefold compared with cyclosporine,[29] tacrolimus use has not been consistently shown to be associated with increased PTLD risk compared with cyclosporine.[30]

mTOR inhibitors. Sirolimus has a strong antiproliferative effect on PTLD-derived B cell lines. Experimental studies suggest that mTOR inhibitors may be beneficial in reducing the incidence of PTLD in high-risk patients or as an alternative method of immunosuppression in patients with established PTLD. However, a higher incidence of PTLD associated with the use of sirolimus-containing regimens compared with no sirolimus has been described. The UNOS/OPTN database demonstrated that in EBV-negative recipients, mTOR inhibitor–tacrolimus combination therapy was associated with a 1.4-fold increased PTLD risk, compared with MMF-tacrolimus combination therapy.[31] Analysis of 719 patients with PTLD similarly demonstrated that de novo sirolimus was associated with a 1.2-fold increased risk for PTLD in EBV-negative kidney transplant recipients.[32] In contrast, in a case series of 13 kidney transplant recipients with PTLD, immunosuppression reduction in conjunction with initiation of sirolimus alone was effective in induction of remission in 4 patients after a median time of 12 weeks (all 4 patients presented with extranodal disease and had histologic and immunophenotyping evidence of diffuse large B cell lymphomas).[33] Studies evaluating the association of sirolimus and PTLD risk may have yielded conflicting results because of differences in methodologies and overall intensity of induction and maintenance immunosuppression among studies. Limited studies suggest that high-dose mTOR inhibitor maintenance therapy may carry an increased PTLD risk.[34]

Antimetabolites. The use of antimetabolites such as AZA and MMF has not been consistently shown to be associated with an increased risk for PTLD.

Induction agents. Whereas induction therapy with muromonab CD3/OKT3 (removed from U.S. market in 2010) or antithymocyte globulin may increase PTLD risk, the use of interleukin-2 (IL-2) receptor inhibitors (daclizumab and basiliximab) or anti-CD52 antibody (alemtuzumab) induction has not been reported to increase PTLD risk. Analysis of the UNOS/OPTN database demonstrated that thymoglobulin was associated with significantly increased PTLD risk, whereas alemtuzumab, basiliximab, and daclizumab trended toward a protective effect ($P = .06$). In this study, maintenance therapy with an mTOR inhibitor was unexpectedly found to be strongly associated with PTLD, in contrast to earlier reports suggesting its beneficial effect on PTLD because of its antiproliferative and antiangiogenic effects. Although both alemtuzumab and thymoglobulin are T cell–depletional agents, the former has been shown to have a more pronounced B cell–depleting effect. It is speculated that depletional induction is not an independent risk factor for PTLD, but rather that maintenance drug selection and the balance between B cell and T cell depletion may be more relevant determinants of PTLD risk. Nonetheless, aggressive PTLD attributed to alemtuzumab induction has been reported.[35] It is conceivable that the overall intensity of immunosuppression increases PTLD risk by decreasing host cytotoxic T cells directed against grafted EBV-infected B lymphocytes.

Belatacept. Belatacept is a non–antigen-specific biologic agent that blocks T cell costimulatory signals, hence preventing T cell activation. Phase III clinical trials suggest that its use in transplant recipients with pretransplant EBV seronegativity is associated with an increased risk for PTLD.[36] However, the 2014 Cochrane Database systematic review suggested that belatacept use at different dosages and in patients who were EBV seronegative or seropositive before transplant confers no additional risk compared with CNI immunosuppression.[37] Nonetheless, the black box warning for belatacept use in EBV-seronegative transplant candidates remains, and its use should be avoided in transplant recipients with pretransplant EBV-seronegative or unknown EBV status. Further studies are needed.

Viral infection

Epstein-Barr virus. During primary infection, EBV is incorporated into B lymphocytes and establishes lifelong latency. Immunocompetent hosts mount an antibody response and, more importantly, an EBV-specific cytotoxic T cell immune response. EBV-naïve transplant recipients lack both virus-specific antibodies to neutralize the virions released by infected donor-derived B cells and EBV-specific T cells to control the outgrowth of subsequently infected recipient B cells. Hence, an EBV-negative recipient with an EBV-positive donor is at greatest risk for developing PTLD.

Hepatitis C virus. Whereas HCV infection has been linked to increased risk for lymphoma among immunocompetent individuals, the association between HCV and PTLD after solid organ transplantation has not consistently been shown. A large transplant registry study failed to demonstrate the link between HCV and PTLD. However, the risk for PTLD was increased among 2.8% of patients with HCV who were reported not to have received immunosuppressive therapy. It is speculated that chronic antigenic stimulation of the intact immune system is necessary for the development of HCV-related lymphoproliferation.[38]

Miscellaneous. Other suggested risk factors for PTLD include history of CMV infection, fewer HLA matches, pretransplant malignancy, and infections with HHV-8 and simian virus 40.

Clinical Manifestations

PTLD may manifest with constitutional symptoms such as fevers, night sweats, malaise, and weight loss or with localized symptoms of the respiratory tract (infection or mass, including tonsillar or even gingival involvement), GI tract (diarrhea, pain, perforation, bleeding, mass), or central nervous system (CNS; headache, seizure, confusion). Other clinical manifestations may include lymphadenopathy or symptoms related to allograft dysfunction or compression of surrounding structures. Extranodal involvement occurs in more than two third of patients.[39] In contrast to lymphomas in the general population, the CNS is frequently involved in PTLD, occurring in up to 25% to 30% of patients, and can be the only site of disease. Early diagnosis requires a high index of suspicion in the appropriate clinical setting and radiologic findings. Although computed tomography and magnetic resonance imaging are the most commonly used imaging modalities in PTLD, 2-(fluorine-18) fluoro-2-deoxy-D-glucose positron emission tomography scan is superior to conventional imaging methods for detecting extranodal localization. Tissue sampling is necessary for a definitive diagnosis and subcategorization of PTLD.

Treatment

Reduction or discontinuation of immunosuppressive therapy, particularly cyclosporine, tacrolimus, or MMF, is the first-line treatment; prednisone can be continued to prevent allograft rejection. Although sirolimus has antiproliferative effects, there are insufficient data to recommend or refute its use in the treatment of PTLD. Suggested factors predictive of a poor response to reduction in immunosuppression alone include elevated lactate dehydrogenase (LDH), organ dysfunction at diagnosis, multiple organ involvement, bulky disease, advanced stage, and older age.

In patients who fail to respond to manipulation of immunosuppression alone, rituximab has been used with variable success. Suggested favorable predictive factors for response include EBV-positive PTLD, a shorter interval from transplantation to diagnosis of PTLD, a smaller number of involved sites, and a normal LDH level. Chemotherapy is often used in patients refractory to reduction in immunosuppression and rituximab, in those with aggressive disease at presentation, or in those with lesions not amenable to surgery. The treatment regimens are similar to those used to treat non-Hodgkin lymphoma. CHOP-based chemotherapy (cyclophosphamide, adriamycin, vincristine, and prednisone) with or without rituximab is the most widely used regimen. Adverse effects of chemotherapy include high mortality rates from sepsis and treatment-related toxicities. Surgical resection with or without adjunctive local radiation has been suggested for localized disease. Local radiation has been advocated as the treatment of choice for PTLD involving the CNS. Nonetheless, unless contraindicated, chemotherapy is still recommended by some experts in the field.[40] Acyclovir and ganciclovir are of unproven benefit because their activity is dependent on intracellular phosphorylation by virally encoded thymidine kinase. EBV-driven lymphomas do not express thymidine kinase. Adoptive immunotherapy using EBV-specific cytotoxic T lymphocytes or donor lymphocyte infusion (aiming to kill dividing B cells in EBV-associated PTLD) has emerged as a novel treatment strategies for PTLD.

Poor prognostic factors include multiple-site versus single-site involvement, tumor monoclonality, graft organ involvement, advanced age, CD20-negative large cell lymphomas, recipient EBV-negative serostatus, and the use of antilymphocyte globulin or antithymocyte globulin. Other poor prognostic factors include WHO performance status score of 3 or 4 (a score of 3 is defined as confined to bed or a chair for more than 50% of waking hours, and a score of 4 as completely disabled), late onset of disease (>1 year after transplant), elevated LDH, CNS disease, severe organ dysfunction, acute kidney injury at diagnosis, impaired kidney function, and T cell disease.[23,39,40]

Viral Load Monitoring and Preemptive Strategies

Limited studies in pediatric liver and kidney transplant recipients suggest that monitoring EBV load and preemptive immunosuppression reduction with or without ganciclovir in response to elevated EBV loads reduce the incidence of PTLD. Recent studies suggest that rituximab may prevent transmission of EBV to EBV-naïve transplant recipients. It is speculated that rituximab-mediated elimination of B cells may prevent transmission of EBV to the recipient, because EBV persistence requires the establishment of a latent infection in recipient B cells.[41]

The role of antiviral prophylaxis for the prevention of PTLD remains controversial. A systematic review of 31 studies showed no beneficial effect of antiviral prophylaxis on the incidence of PTLD in high-risk EBV-naïve transplant recipients. The findings were consistent across all types of solid organ transplants, age groups, prophylactic or preemptive therapy, duration of antiviral prophylaxis, or different antiviral agents (acyclovir, valacyclovir, ganciclovir, valganciclovir).[42]

Skin Cancer

Skin cancers are the most common de novo post-transplant tumors in the adult transplant population. Potential risk factors include light skin color, total sun burden and recreational sun exposure, genetic factors, history or present use of AZA, and duration of follow-up after transplantation. Whereas basal cell carcinoma is the most common type of skin cancer in the general population, squamous cell carcinoma has been reported to be two to five times more common than basal cell carcinoma in recipients of solid organ transplantation. In addition, immunosuppression in combination with enhanced sunlight exposure may induce malignant changes in papilloma-induced warts. Sirolimus may delay the onset or reduce the incidence of post-transplant skin and nonskin malignant neoplasms (discussed further later).

Management of Immunosuppressive Therapy in Post-Transplantation Malignancy

In principle, immunosuppression dose reduction improves immune surveillance against malignant cells. However, there are no systematic studies to demonstrate whether immunosuppression reduction or withdrawal might alter the natural history of established post-transplantation malignancy. In our opinion, a switch from CNI to sirolimus or CNI minimization in conjunction with sirolimus may be a viable therapeutic option in selected post-transplant malignancies (the antitumoral effect of sirolimus is discussed later). In patients with metastatic cancer, manipulation of immunosuppression is probably futile, and the risk for rejection and graft loss likely outweighs the benefit.

Studies suggest that immunosuppressive agents have different effects on cancer risk after transplantation. The carcinogenic effects of antithymocyte globulin, cyclosporine, tacrolimus, and AZA have been well documented. In contrast to AZA, MFA derivatives have been shown to have an antiproliferative effect and have been suggested to be protective of post-transplantation malignancy.[43] Analysis of more than 17,000 adult patients with preexisting diabetes indicated a significantly higher incidence of malignancy in AZA-treated than in MMF-treated patients (3.7% vs. 2.2%). In a nested case-control study to evaluate the association between immunosuppressive medications and squamous cell skin cancer risk among cardiac and kidney transplant recipients, an inverse association between MFA derivatives and squamous cell skin cancer was observed independent of tacrolimus use. MFA use was associated with a nearly 50% squamous cell skin cancer risk reduction compared with no MFA derivatives use. In contrast, AZA use was associated with a greater than twofold increase in squamous cell skin cancer risk compared with no AZA use.[44] The study findings suggest that the increased risk for squamous cell skin cancer historically associated with AZA is not seen in organ transplant recipients treated with newer immunosuppressants (e.g., MFA or tacrolimus). Whether MMF is protective of post-transplant malignancies warrants further exploration particularly because it is common practice among clinicians to reduce or discontinue MMF in the presence of malignancies because of the theoretical risk for net protumor effect of overimmunosuppression.

Both preclinical and clinical studies have demonstrated that sirolimus and everolimus have antiproliferative and antitumoral effects. There has been ample literature suggesting that mTOR inhibitor–containing regimen is associated with decreased nonmelanoma skin cancer risks, and its use is effective in both primary and secondary skin cancer prevention.[45-47] Furthermore, the earlier the conversion after an initial diagnosis of cutaneous squamous cell carcinoma, the greater is the efficacy.[46] It has been suggested that the protective effect of mTOR inhibitors against skin cancer is a result of its inhibition of several ultraviolet-induced mechanisms involved in skin carcinogenesis. The mTOR inhibitors also have been reported to be effective in inducing remission of Kaposi sarcoma in organ transplant recipients.[48,49]

Although sirolimus appears to provide satisfactory outcomes in primary and secondary skin cancer prevention, its use in the management of other malignancies after solid organ transplantation remains to be defined. A systematic review of 20 randomized controlled trials and two observational studies (n = 39,039 kidney transplant recipients) demonstrated that sirolimus use was associated with lower overall cancer incidence, driven by a reduction in nonmelanoma skin cancer incidence. The protective effect of sirolimus on nonmelanoma skin cancer (NMSC) risk was most notable in studies comparing sirolimus against cyclosporine (incidence rate ratio [IRR] = 0.19, 95% confidence interval [CI] = 0.04-0.84). After excluding NMSCs, there was no overall association between sirolimus and incidence of other cancers. Further analysis demonstrated that sirolimus use was associated with lower kidney cancer incidence (IRR = 0.40, 95% CI = 0.20-0.81), and higher prostate cancer incidence (IRR = 1.85, 95% CI = 1.17-2.91). The lower incidence of NMSC among sirolimus users was thought to be due in part to cyclosporine withdrawal. Overall, the study findings suggested that sirolimus may reduce kidney cancer risk but did not appear protective for other cancers (including non-Hodgkin lymphoma, Kaposi sarcoma, and lung cancers). In contrast, sirolimus use may increase prostate cancer risk.[50]

It is our current practice to start patients with newly diagnosed skin cancer or RCC (or those with a history of skin cancer or RCC) on sirolimus or everolimus in conjunction with discontinuation of antimetabolites (such as AZA or MFA derivatives) and reduction of CNI therapy tailored to each individual patient. Available data do not support the routine use of mTOR inhibitors in the management of other cancer types.

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SELF-ASSESSMENT QUESTIONS

1. Which one of the following statements regarding immunization before and after transplantation is correct:
   - **A.** Seasonal influenza vaccine is contraindicated in the early post-transplant period because it is associated with allograft dysfunction and acute rejection.
   - **B.** Intranasal influenza vaccine is safe and effective before and after transplantation.
   - **C.** Live virus vaccination should be administered at least 4 weeks before transplantation to minimize the possibility of live vaccine–derived infection in the post-transplantation period.
   - **D.** Vaccinations should be administered at least 2 weeks before transplantation to achieve optimal immune response.
2. Clinical manifestations and management of cytomegalovirus (CMV) infection include all of the following *except:*
   - **A.** The absence of CMV viremia does not rule out invasive CMV disease.
   - **B.** In high-risk candidates, CMV prophylactic therapy is recommended over initiation of preemptive treatment after detection of CMV viremia.
   - **C.** Primary CMV infection is usually more severe than reactivated infection or superinfection.
   - **D.** The American Society of Transplantation Infectious Diseases Community of Practice guidelines recommend that antiviral therapy be continued until resolution of clinical symptoms or for a minimum of 2 weeks, whichever comes first.
3. The most widely accepted mainstay of therapy in BK virus–associated clinical syndromes includes:
   - **A.** Leflunomide
   - **B.** Immunosuppression reduction
   - **C.** Ciprofloxacin in conjunction with immunosuppression reduction
   - **D.** Substitution of calcineurin inhibitor (cyclosporine or tacrolimus) for mTOR inhibitor (sirolimus or everolimus)

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Medical Management of the Kidney Transplant Recipient

Cardiovascular Disease and Metabolic Abnormalities

Phuong-Thu T. Pham, Son V. Pham, Phuong-Anh T. Pham, Gabriel M. Danovitch

CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is the most frequent cause of death with a functioning graft. The U.S. Renal Data System (USRDS) 2014 annual data report revealed that mortality from CVD among kidney transplant recipients (kidney alone or combined organ transplant) is nearly twice that observed for infection or malignancy. An analysis based on the Assessment of Lescol in Renal Transplantation (ALERT) trial suggested that major CV events could be predicted with a seven-variable model including age, previous coronary heart disease (CHD), diabetes, low-density lipoprotein (LDL), creatinine, number of transplants, and smoking.[1] CV risk factors in kidney transplant recipients encompass both conventional and unconventional risk factors. Although kidney transplantation ameliorates some CV risks by restoring renal function, it introduces new CV risks, including impaired glucose tolerance or diabetes mellitus, hypertension, and dyslipidemia, which are derived in part from immunosuppressive medications. Box 106.1 summarizes suggested CV risk factors in transplant recipients.[2] Selected risk factors will be discussed.[2]

CONVENTIONAL CARDIOVASCULAR DISEASE RISK FACTORS

Post-Transplantation Hypertension

Hypertension is present in 50% to 90% of kidney transplant recipients. In one single-center study (n = 94), ambulatory blood pressure (BP) measurements demonstrated that only 5% of kidney transplant recipients were normotensive (defined as BP <130/80 mm Hg).[3] Hypertension is a risk factor for both CV disease and kidney graft failure. The Collaborative Transplant Study registry study revealed a graded risk for graft failure with increasing levels of systolic BP (SBP) and diastolic BP (DBP).[4] The Kidney Disease: Improving Global Outcome (KDIGO) guidelines suggest a BP goal of less than 130/80 mm Hg for kidney transplant recipients irrespective of the level of albuminuria. However, such recommendations are based solely on epidemiologic data because no randomized trials demonstrate the optimal BP target in kidney transplant recipients.

Risk factors for post-transplantation hypertension include preexisting hypertension, cyclosporine (and to a lesser degree tacrolimus), corticosteroids, various donor-related factors (e.g., donor age, donor hypertension, donor family history of hypertension), delayed graft function, chronic allograft injury, high body mass index (BMI) or excess weight gain, acute rejection episodes, recurrent or de novo glomerulonephritis, and transplant renal artery stenosis. Sodium intake after transplantation and excess renin output from the native kidneys also may contribute in some patients. In kidney transplant recipients with severe hypertension refractory to medical therapy, bilateral native nephrectomy has been reported to ameliorate BP control.[5] In a retrospective study of 118 kidney transplant recipients with the primary renal disease autosomal dominant polycystic kidney disease, ipsilateral native nephrectomy at the time of allograft transplant (n = 64) was associated with a significant decrease in the number and daily dose of antihypertensive drugs needed for hypertension control compared with kidney transplantation alone at 12-, 24-, and 36-month follow-up. Subsequent contralateral native nephrectomy (n = 32) further improved BP control.[6]

Management of post-transplantation hypertension should include identification and treatment of the underlying cause, lifestyle modifications (see Chapter 35), and treatment of associated CV risk factors. The initial target BP goal is below 130/80 mm Hg; a BP goal below 125/75 mm Hg for patients with proteinuria is of uncertain benefit. Although there is a lack of controlled clinical trials related to selection of antihypertensive agent, we recommend perioperative β-blockers in transplant candidates with a history of coronary artery disease because they reduce CHD events. In the early post-transplantation period, nondihydropyridine calcium channel blockers (CCBs) and diuretics are frequently used, the former for their beneficial effect on intraglomerular hemodynamics and the latter to eliminate salt and water in patients who are volume expanded. The use of diltiazem and verapamil also permit calcineurin inhibitor (CNI) dose reductions of up to 40% and 30% to 50%, respectively. Although one retrospective cohort study[7] reported an unexpected association between the use of dihydropyridine CCBs and an increased risk for CHD, results of a large international cohort of kidney transplant recipients (n >14,000 from 10 centers worldwide) failed to show any significant association between any CV medication use (β-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], diuretics, CCBs, antiplatelet agents, and/or statins) and the risk for major cardiac events at 12 months,[8] and there is no contraindication to CCB use in the transplant setting. In contrast, most transplant centers use dihydropyridine CCBs for initial therapy because of their added benefit of antagonizing CNI-induced afferent arteriolar vasoconstriction, and their demonstrated efficacy in the general population irrespective of age, gender, and salt intake.[9]

ACE inhibitors and ARBs can cause acute changes in renal function as well as hyperkalemia and hence are usually not started until allograft function is stable. Transplant renal artery stenosis should be considered when serum creatinine rises to more than 30% above baseline. The National Kidney Foundation and KDIGO expert panel endorses the use of CCBs and drugs that block the renin-angiotensin system because of their potential unique advantages compared with other agents. Limited

BOX 106.1 Cardiovascular Risk Factors in Kidney Transplant Recipients

Conventional Risk Factors

Modifiable

- Hypertension
- Dyslipidemia
- Obesity or metabolic syndrome
- Smoking

Nonmodifiable

- Age
- Family history
- Pretransplant diabetes
- Male gender
- History of pretransplant and post-transplant cardiovascular disease
- Race/ethnicity (White race)

Unconventional Risk Factors

Modifiable or Potentially Modifiable

- Proteinuria
- Post-transplantation diabetes mellitus
- Left ventricular hypertrophy
- Inflammatory markers (e.g., inflammatory cytokines, C-reactive protein)
- Anemia
- Hyperuricemia
- Cytomegalovirus infection
- Delayed graft function
- Hyperhomocysteinemia
- Dialysis vintage
- Chronic kidney disease (post-transplant)
- Low albumin
- Obstructive sleep apnea
- Prothrombotic state
- Low physical activity

Nonmodifiable

Recipient Factors

- Prior acute rejection episodes
- Chronic kidney injury from any cause
- Preexisting coronary artery calcification
- Cardiac troponin T

Donor Factors (Donor Quality)

- Donor age
- Donor hypertension
- Donor recipient size mismatch
- Donor *APOL1* gene polymorphism (may be associated with early graft dysfunction)

studies in kidney transplant recipients suggest that renin angiotensin aldosterone system (RAAS) blockade reduces CV events and ameliorates CNI-induced interstitial fibrosis and tubular atrophy.[10] However, the beneficial effect of ACE inhibitors or ARBs on patient or graft survival has not been consistently demonstrated.[9]

Because of the lack of conclusive evidence that one class of antihypertensive agent is superior to another in the transplant setting, treatment should be individualized based on efficacy, tolerability, concomitant comorbidity, and drug-drug interactions with immunosuppressive agents. Potential advantages and disadvantages of different classes of antihypertensive agents in kidney transplant recipients are shown in Table 106.1.

Post-Transplantation Dyslipidemia

Dyslipidemia is common after transplantation, in part because of the hyperlipemic effect of corticosteroids, cyclosporine, tacrolimus, sirolimus, and everolimus. Mammalian target of rapamycin (mTOR) inhibitors, sirolimus, and everolimus are associated with the worst lipid profiles, followed by cyclosporine, and to a lesser extent tacrolimus. One single-center study demonstrated that the mean values of total cholesterol, LDL cholesterol, and triglycerides (TGs) and the incidence of CHD were higher among patients receiving mTOR inhibitors compared with those receiving calcineurin inhibitor-based immunosuppression (controls). However, the risk for CV events was not significantly higher among patients receiving mTOR inhibitors compared with controls at 4-year follow-up.[11] Subsequent studies similarly demonstrated that CV risk is not higher in transplant recipients treated with mTOR inhibitors.[12] The antiproliferative and cardioprotective effects of mTOR inhibitors and the reduction in CNI-related risk factors may offset the adverse effects of hyperlipidemia. Other potential etiologic factors for post-transplant dyslipidemia include age, diet, rapid weight gain, hyperinsulinemia, preexisting hypercholesterolemia, allograft dysfunction, proteinuria, genetic predisposition, and the use of β-blockers and diuretics.

Management of hyperlipidemia includes lifestyle changes (diet and exercise) and statins. In addition to their lipid-lowering effect, statins may protect against CVD via their antiproliferative and antiinflammatory properties and ability to reduce circulating endothelin-1, C-reactive protein levels, SBP and DBP, and pulse pressure. The benefits of statins in the general population have been demonstrated in several large randomized controlled trials (RCTs). There has been only one single prospective randomized trial in transplant recipients comparing statins (fluvastatin) with placebo—the ALERT trial. Results of the ALERT study suggest a beneficial effect of early initiation of fluvastatin on post-transplant CV outcome. Patients who received statin therapy within the first 4 years after transplantation had a risk reduction of 64% compared with 19% for those who received therapy after 10 years.[13] The 2014 Cochrane meta-analysis of 17 studies comparing statin with placebo or no treatment, and 5 studies comparing two different statin regimens demonstrated a trend toward reduction in major CV events, CV mortality, and fatal or nonfatal myocardial infarction. No association between statin use and all-cause mortality or stroke was observed.

The KDIGO expert panel on Clinical Practice Guideline for Lipid Management in chronic kidney disease (CKD) advocate statin therapy in all adult kidney transplant recipients, although supporting evidence was considered weak. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines indicate there is insufficient RCT evidence for guiding clinical recommendations for solid-organ transplant recipients and suggest clinical judgment weighing potential benefits, risks, and patient preferences. The KDIGO and ACC/AHA guidelines for the management of post-transplantation dyslipidemia are shown in Fig. 106.1. CVD risk reduction requires adherence to both medication and lifestyle regimens.

Statin Therapy

Kidney transplantation is regarded as risk factor for CHD similar to other conventional cardiac risk factors. Hence, despite the lack of evidence-based recommendations, most transplant centers assess and treat dyslipidemias aggressively with statin therapy in conjunction with lifestyle modification. The concomitant use of statins and CNIs, particularly cyclosporine, often results in a several-fold increase in statin blood level and an increased risk for myopathy and rhabdomyolysis. The risk is lowest with pravastatin and fluvastatin. In contrast, simvastatin appears to be particularly prone to drug-drug interactions compared with other statins because of its extensive metabolism by cytochrome

TABLE 106.1 Potential Advantages and Disadvantages of Different Classes of Antihypertensive Agents

Classes of Drugs	Advantages	Disadvantages
β-Blockers	Perioperative use: ↓ coronary heart disease events	↑ Risk for bradycardia when used with nondihydropyrine CCB Blunting of hypoglycemic awareness
CCBs	↓ CNI-induced vasoconstriction ↑ CNI level (diltiazem may permit CNI dose reduction by up to 40%, and verapamil by up to 30%-50%	
Diuretics	Beneficial in patients who are volume expanded	Hyperuricemia, gout
ACE inhibitors, ARBs	↓ Proteinuria Potential renoprotective and cardioprotective effects (the favorable impact on patient and graft survival has not been consistently demonstrated) Beneficial in post-transplantation erythrocytosis	Potential worsening anemia ↓ GFR, hyperkalemia
Aldosterone receptor blockers	May improve outcomes in heart failure	Severe hyperkalemia when used in combination with ACE inhibitor or ARB in patients with poor kidney function
α-Blockers	Benign prostatic hypertrophy Neurogenic bladder	
Direct vasodilators		Tachycardia
Central α-agonist		Depression

ACE inhibitors, Angiotensin-converting enzyme inhibitor; *ARBs*, angiotensin receptor blockers; *CCB*, calcium channel blocker; *CNI*, calcineurin inhibitor; *GFR*, glomerular filtration rate.

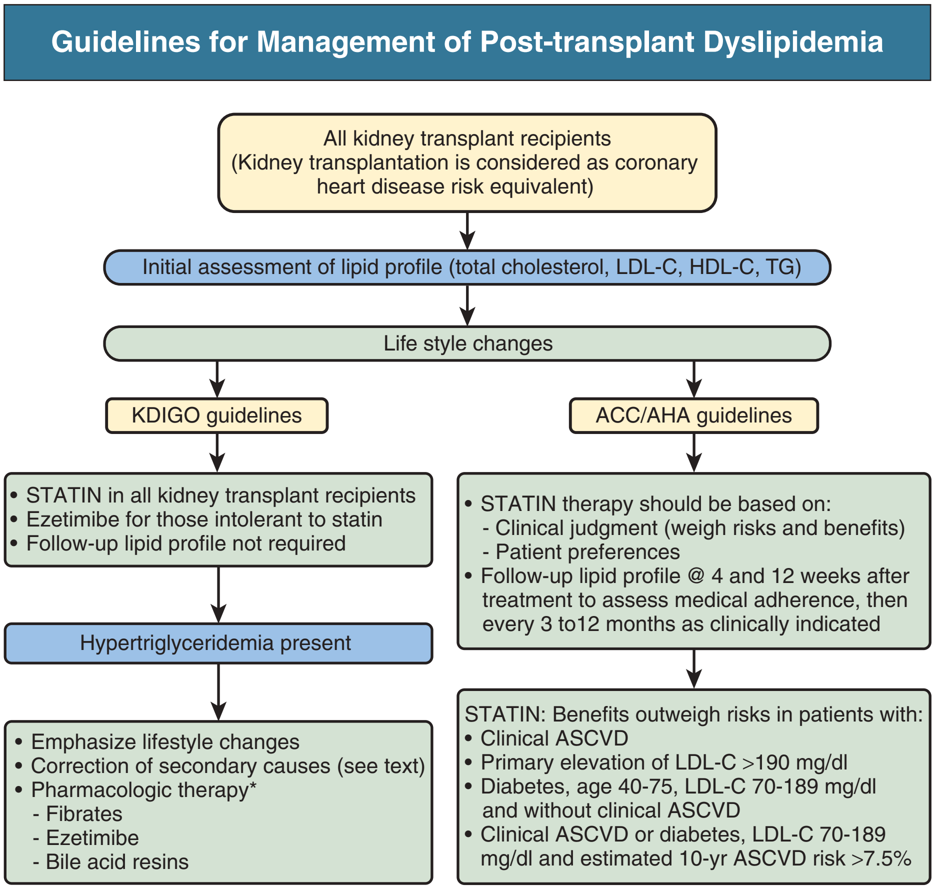
Guidelines for Management of Post-transplant Dyslipidemia
All kidney transplant recipients
(Kidney transplantation is considered as coronary heart disease risk equivalent)
Initial assessment of lipid profile (total cholesterol, LDL-C, HDL-C, TG)
Life style changes
KDIGO guidelines
ACC/AHA guidelines
• STATIN in all kidney transplant recipients
• Ezetimibe for those intolerant to statin
• Follow-up lipid profile not required
• STATIN therapy should be based on:
- Clinical judgment (weigh risks and benefits)
- Patient preferences
• Follow-up lipid profile @ 4 and 12 weeks after treatment to assess medical adherence, then every 3 to12 months as clinically indicated
Hypertriglyceridemia present
• Emphasize lifestyle changes
• Correction of secondary causes (see text)
• Pharmacologic therapy*
- Fibrates
- Ezetimibe
- Bile acid resins
STATIN: Benefits outweigh risks in patients with:
• Clinical ASCVD
• Primary elevation of LDL-C >190 mg/dl
• Diabetes, age 40-75, LDL-C 70-189 mg/dl and without clinical ASCVD
• Clinical ASCVD or diabetes, LDL-C 70-189 mg/dl and estimated 10-yr ASCVD risk >7.5%

Fig. 106.1 **Suggested guidelines for the management of post-transplantation dyslipidemia.** *Currently no data suggest that adding fibrates to statin is superior to adding ezetimibe to statin. See text for authors' opinion. *ACC*, American College of Cardiology; *AHA*, American Heart Association; *ASCVD*, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglyceride.

P450 (CYP3A4). Coadministration of simvastatin and cyclosporine should be avoided. Rhabdomyolysis associated with tacrolimus and statin use is generally seen in patients on concomitant diltiazem therapy.

Nonstatin Drug Therapy

Ezetimibe and statin combination therapy has been suggested to improve cholesterol control because of their complementary mechanisms of action. Ezetimibe blocks intestinal absorption of dietary cholesterol, whereas statin inhibits hepatic cholesterol synthesis. Results of The SHARP trial in which CKD patients were randomized to receive simvastatin 20 mg plus ezetimibe 10 mg (n = 4650) or placebo (n = 4620) demonstrated that simvastatin and ezetimibe combination therapy conferred a 17% CV risk reduction compared with placebo at a median follow-up of 4.9 years.[14] Limited studies suggest that statin and ezetimibe combination therapy is safe and effective in the treatment of dyslipidemia in kidney transplant patients who are refractory to statin therapy. In a single-center study consisting of 67 patients with post-transplantation hyperlipidemia resistant to statins, treatment with ezetimibe alone or with ezetimibe and statin significantly reduced total cholesterol and LDL cholesterol by 25% and 34%, respectively, during the first month of treatment.[15] To date, no data support the routine addition of nonstatin drug to statin therapy for CVD risk reduction in the general population or in the transplant setting. Nonetheless, based on the safety and efficacy data of ezetimibe use among CKD patients, ezetimibe is a second-line treatment option for high-risk kidney transplant recipients who are intolerant of statin or who are refractory to statin therapy. In the absence of evidence-based recommendations, adherence to lifestyle changes and to statin therapy should be reemphasized before adding a nonstatin lipid-lowering agent to statin therapy.

Management of Hypertriglyceridemia

Initial management should include lifestyle changes, increased physical activity, weight reduction, dietary counseling (carbohydrate restriction), smoking cessation, and correction of secondary causes. The latter may include untreated diabetes mellitus or excess alcohol intake or may be drug induced. Severe hypertriglyceridemia (TG level >500 mg/dl or 5.65 mmol/l) may occur with the use of sirolimus and everolimus. Management includes dose reduction, pharmacologic therapy, and, in refractory cases, switching of mTOR inhibitors to mycophenolic acid derivatives or tacrolimus.

Drug therapy for Hypertriglyceridemia

Fibrates. Fibrates have the most pronounced effect on lowering plasma TG levels of available lipid-lowering agents.[16] For patients with fasting TG levels above 1000 mg/dl (11.3 mmol/l), the Adult Treatment Panel (ATP) III recommends a diet very low in fat (<15% total calories), medium-chain TGs, and fish oils to replace some long-chain TGs. The National Kidney Foundation expert panel recommends gemfibrozil as the fibrate of choice. However, fibrates should be avoided in those with CKD stage 5. Of the major fibric acid medications (bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil), the first three can increase serum creatinine in cyclosporine-treated patients. Although all fibrates in combinations with statins have been associated with creatinine kinase elevations with or without overt rhabdomyolysis and myopathy, gemfibrozil may have a greater risk for the development of myopathy compared with fenofibrate or bezafibrate. Fenofibrate is contraindicated in patients with an estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73 m^2. Data on the safety of gemfibrozil in patients with advanced CKD is lacking.

Ezetimibe. Limited studies demonstrated that ezetimibe has TG-lowering effects and is safe and effective in the transplant settings.[17]

Bile acid resins. Bile acid sequestrants must be used with caution because of their potential interference with the absorption of CNIs and mycophenolic acid derivatives. Coadministration of bile acid sequestrants and mycophenolic acid products is not recommended. Studies in the general population suggest that bile acid sequestrants may increase TG levels. Their use is contraindicated in individuals with TGs greater than 400 to 500 mg/dl.[16]

Niacin. Niacin lowers TG and LDL-C levels and has pronounced effects on increasing high-density lipoprotein (HDL) concentration. Niacin monotherapy has not been reported to cause myopathy, but its combined use with lovastatin, pravastatin, or simvastatin may be associated with rhabdomyolysis.

Summary

Statins should be the first-line therapy for the treatment of non–high-density lipoprotein (non-HDL) cholesterol because of their well-established safety and efficacy in preventing CVD in randomized trials in the general population. We recommend atorvastatin or rosuvastatin for patients with mixed dyslipidemia. Ezetimibe should be considered in those intolerant to statins despite dose reduction or despite switching to another statin. There are currently no data to suggest that adding fibrates to statin therapy is superior to adding ezetimibe to statin therapy in the treatment of post-transplantation hypertriglyceridemia. In the our opinion, adding ezetimibe to statin therapy seems reasonable in mild to moderate hypertriglyceridemia (TG <500 mg/dl or 5.65 mmol/l). However, fibrate is the preferred therapy in patients with TG levels above 500 to 1000 mg/dl (5.65 to 11.3 mmol/l) because it has a more pronounced TG-lowering effect than ezetimibe. Nonetheless, the choice of one agent over the other should be based on adverse effects and potential drug-drug interactions. Simvastatin and gemfibrozil combination therapy is associated with an increased risk for rhabdomyolysis and should be avoided.

Suggested guidelines for pharmacologic treatment of dyslipidemia are summarized in Fig. 106.1.

POST-TRANSPLANTATION DIABETES MELLITUS (NEW-ONSET DIABETES AFTER TRANSPLANTATION)

Post-transplantation diabetes mellitus (PTDM) occurs in 4% to 25% of kidney transplant recipients. Variations in incidence may result from differences in definition, duration of follow-up, and the presence of both modifiable and nonmodifiable risk factors. Over the years, PTDM has undergone changes in nomenclatures including steroid diabetes, PTDM, new-onset DM, transplant-associated hyperglycemia, and new-onset diabetes after transplantation (NODAT).[18] In 2014 the International Expert Panel recommended changing the terminology NODAT back to PTDM, excluding transient post-transplantation hyperglycemia.[19] Using the term NODAT is thought to be misleading because it seemingly excludes patients with pretransplant diabetes. Preexisting diabetes is often undiagnosed because of the effect of CKD on insulin metabolism and clearance and the lack of effective pretransplant screening.

Risk Factors

PTDM may arise from both transplant-related and traditional risk factors. The diabetogenic effect of corticosteroids, CNIs (tacrolimus > cyclosporine), and mTOR inhibitors have been well-described. Neither azathioprine nor mycophenolic acid derivatives are diabetogenic. Risk factors for PTDM are summarized in Fig. 106.2. They can be loosely categorized into those that are nonmodifiable, potentially modifiable, and modifiable.

Management of Post-Transplantation Diabetes Mellitus

Although there may be differences in the pathogenesis and manifestation of PTDM compared with type 2 diabetes, management of PTDM

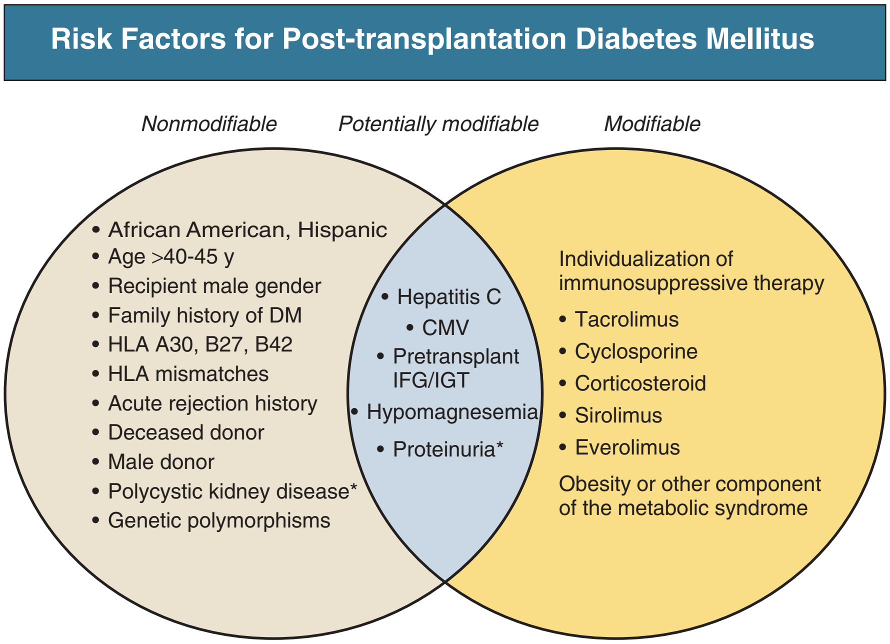
Risk Factors for Post-transplantation Diabetes Mellitus
Nonmodifiable
Potentially modifiable
Modifiable
• African American, Hispanic
• Age >40-45 y
• Recipient male gender
• Family history of DM
• HLA A30, B27, B42
• HLA mismatches
• Acute rejection history
• Deceased donor
• Male donor
• Polycystic kidney disease*
• Genetic polymorphisms
• Hepatitis C
• CMV
• Pretransplant IFG/IGT
• Hypomagnesemia
• Proteinuria*
Individualization of immunosuppressive therapy
• Tacrolimus
• Cyclosporine
• Corticosteroid
• Sirolimus
• Everolimus
Obesity or other component of the metabolic syndrome

Fig. 106.2 Risk factors for post-transplantation diabetes mellitus (PTDM). NOTE: Restoration of insulin metabolism by a functioning graft may unmask pretransplant IFG or diabetes mellitus. *The association between polycystic kidney disease (or proteinuria) and PTDM has not been consistently observed. *CMV,* Cytomegalovirus; *IFG,* impaired fasting glucose; *IGT,* impaired glucose tolerance.

should follow the conventional approach and clinical guidelines as established by well-recognized organizations. Medical management usually involves a multidisciplinary team approach involving patients (and frequently family members), transplant coordinators, transplant physicians, and diabetic educators. A shared decision-making approach by which clinicians and patients exchange information and reach a consensus on treatment decisions can be helpful.

The American Diabetes Association and European Association for the Study of Diabetes recommend a hemoglobin A_{1c} (HbA_{1c}) target of less than 7% in most patients to reduce the incidence of microvascular disease. More stringent control (HbA_{1c} 6.0% to 6.5%) might be considered in a subset of patients with short disease duration, long life expectancy, and no significant CV disease, if this can be achieved without significant treatment-related adverse effects.[20] For PTDM, the 2009 KDIGO clinical practice guidelines suggest a target HbA_{1c} level from 7.0% to 7.5%, not to fall below 6.0%, particularly if hypoglycemic reactions are common.

Therapeutic Interventions

Nonpharmacologic Management

Obesity treatment seems to be a reasonable target for intervention because higher pretransplant BMI correlates with insulin resistance after transplantation. We recommend promoting lifestyle modification in kidney transplant recipients, including moderation of dietary sodium (<2400 mg sodium per day) and saturated fat intake (<7% calories from saturated fats, 2% to 3% calories from *trans*-fatty acids), regular aerobic exercise, and weight reduction. Carbohydrate intake should be limited to 50% to 60% of caloric intake. The AHA guidelines in nontransplant recipients also suggest intake of at least 25 g of dietary fiber per day and two servings of fish per week. Dietary guidelines for vegetarians are lacking. Flax seeds (or flaxseed oil) and chia seeds are alternative sources of omega-3 fatty acid. Dietitian referral is recommended. Defining realistic goals such as a target weight loss of 5% to 10% of total body weight and a patient-centered approach to education may be invaluable in achieving success.

Modification of Immunosuppression

Although clinical trials comparing the incidence of PTDM in cyclosporine- versus tacrolimus-treated patients have yielded variable results, tacrolimus has more consistently been shown to have a greater diabetogenic effect than cyclosporine. Modification of immunosuppression including cyclosporine to tacrolimus conversion therapy or steroid avoidance or withdrawal has variably been shown to improve glycemic control. However, manipulation of immunosuppression is not without immunologic risk. In a meta-analysis of controlled clinical trials to assess the safety and efficacy of early steroid withdrawal or avoidance, steroid avoidance or steroid withdrawal after a few days was found to be associated with a decrease in PTDM incidence among cyclosporine- but not tacrolimus-treated kidney transplant recipients.[21] However, among cyclosporine-treated patients, acute rejection episodes were more frequently observed in steroid avoidance compared with conventional steroid-treated groups. In another study, the same group of investigators demonstrated no significant benefit of late steroid withdrawal (3 to 6 months after transplantation) on the incidence of PTDM. In the current era of immunosuppression, the beneficial effect of steroid avoidance or withdrawal on the incidence of PTDM has been questioned by experts in the field because rapid steroid taper and the use of lower target cyclosporine and tacrolimus levels are now common practice.[19] It should be noted that mycophenolate exposure is lower with cyclosporine than with tacrolimus immunosuppression; hence mycophenolate dosage adjustment or drug level monitoring may be necessary. Because of the lack of well-defined guidelines, modification of immunosuppression to alleviate the incidence of PTDM should be tailored to each individual patient. Reduction in immunosuppression should be weighed against the risk for acute rejection.

Pharmacologic Treatment

When lifestyle modification fails to achieve glycemic control, medical intervention is often necessary. Metformin is not widely used in transplant recipients because of the concern for lactic acidosis in the presence

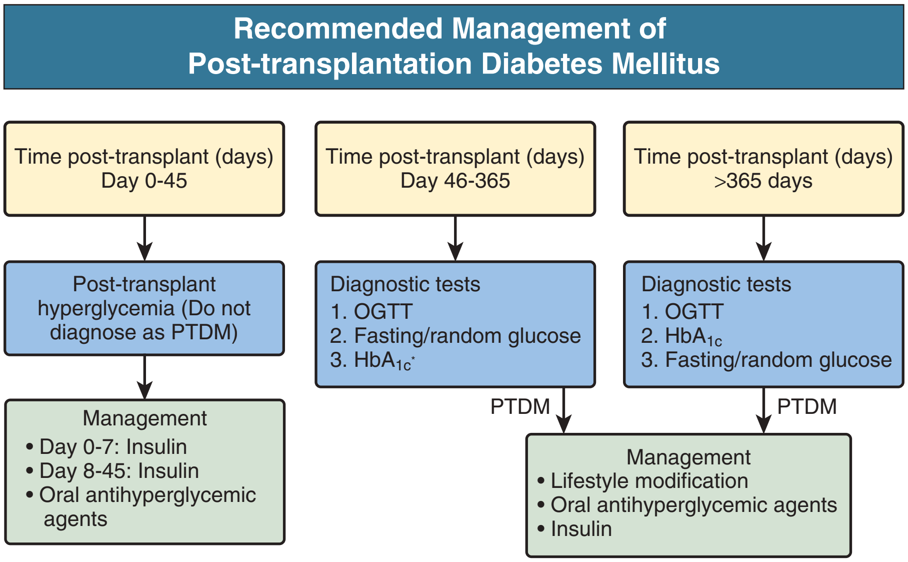
Recommended Management of
Post-transplantation Diabetes Mellitus
Time post-transplant (days)
Day 0-45
Time post-transplant (days)
Day 46-365
Time post-transplant (days)
>365 days
Post-transplant hyperglycemia (Do not diagnose as PTDM)
Diagnostic tests
1. OGTT
2. Fasting/random glucose
3. HbA1c*
Diagnostic tests
1. OGTT
2. HbA1c
3. Fasting/random glucose
PTDM
PTDM
Management
• Day 0-7: Insulin
• Day 8-45: Insulin
• Oral antihyperglycemic agents
Management
• Lifestyle modification
• Oral antihyperglycemic agents
• Insulin

Fig. 106.3 **The 2014 International Consensus Guidelines on Screening, Diagnosis, and Management of Post-Transplantation Diabetes Mellitus (PTDM).** Hyperglycemia in the first 45 days post transplant should not be diagnosed as PTDM. Hemoglobin A_{1c} alone less than 365 days may underestimate PTDM and require confirmatory testing. *OGTT,* Oral glucose tolerance test.

of dynamic kidney allograft function particularly in the early post-transplant period. However, the potential beneficial effects of metformin including weight neutral or weight loss, cardioprotection, and lack of significant drug-drug interactions renders metformin an attractive treatment option for solid-organ transplant recipients. Further clinical trials to assess the risk and benefit ratio of metformin are needed before it can be endorsed as the antihyperglycemic agent of choice in PTDM.[19] Experimental studies suggest that sulfonylureas are associated with beta cell apoptosis and beta cell exhaustion, raising theoretical concern about their use in PTDM, particularly in the early post-transplant period.[22] In contrast, the newer antihyperglycemic dipeptidyl peptidase-4 (DPP-4) inhibitors have been shown to preserve pancreatic beta cell function in diabetic animal models.[23] Limited clinical studies suggest that DPP-4 inhibitors are safe and effective in the treatment of PTDM.[24] There currently are no data on the use of sodium-glucose cotransporter type 2 (SGLT2) inhibitor in the transplant setting. However, SGLT2 treatment is associated with increased risks for urinary tract infection and genital candidiasis, potentially limiting its use in kidney transplant recipients.

Evidence-based studies recommending one oral antidiabetic agent over the other in the context of transplantation are currently lacking. Hence, the choice should be based on the potential advantages and disadvantages of different classes of agents. Failure to achieve glycemic control despite oral antihyperglycemic agent combination therapy necessitates initiation of basal-prandial insulin therapy. The 2014 updated international consensus guidelines on the screening, diagnosis, and management of early post-transplant hyperglycemia and PTDM is shown in Fig. 106.3. It should be noted that HbA_{1c} cannot be accurately interpreted within the first 3 months after transplantation because anemia and impaired graft function can directly interfere with the HbA_{1c} assay. Recent blood transfusion or the use of dapsone may alter HbA_{1c} levels.

Cigarette Smoking

As in the general population, cigarette smoking is associated with increased CV disease morbidity and mortality in kidney transplant recipients. Smoking cessation 5 years before transplantation reduces the risk for death by 29%.[25] Every effort should be made to encourage patients to stop smoking. A multifaceted approach including behavioral and pharmacologic strategies appears to be most effective.

Obesity

The prevalence of obesity (BMI ≥30 kg/m^2) among transplant recipients in the United States doubled between 1987 and 2001, and over the past decade the number of obese transplant candidates and recipients continues to rise.[26]

A high BMI at transplant is a significant independent predictor of congestive heart failure and atrial fibrillation.[27] The association between BMI and cardiac-related death is U-shaped, with an increase in the adjusted risk for cardiac death at both low and high BMI compared with a referent BMI of 22 to 24 (hazard ratio [HR], 1.3 for BMI <20; HR 1.2 for BMI 30 to 32; HR 1.4 for BMI >36).[28] The Scientific Registry of Transplant Recipients database demonstrated that obesity is also an independent risk factor for delayed graft function, graft failure, proteinuria, and acute rejection. Furthermore, the risk for adverse outcomes progressively increased with higher BMI categories.[26]

Management of post-transplantation obesity includes lifestyle and dietary modification. Corticosteroid reduction or withdrawal must be balanced against the risk for graft rejection and graft loss. The use of pharmacologic agents for weight reduction in the post-transplantation period is currently not recommended because of unknown potential drug-drug interactions. Data are inadequate regarding the safety and efficacy of post-transplantation gastric bypass surgery or adjustable gastric banding in ameliorating comorbid conditions such as hypertension, DM, and dyslipidemia. All studies reported to date were limited by lack of suitable comparison group, short follow-up, and heterogeneity in type of bariatric procedure and approach.[29] However, with the refinement in surgical techniques and advancement in postoperative care, post-transplantation bariatric surgery for morbid obesity should be explored.

UNCONVENTIONAL CARDIOVASCULAR DISEASE RISK FACTORS

Proteinuria

Proteinuria occurs in 9% to 40% of kidney transplant recipients with a functioning graft. Proteinuria from native kidneys typically decreases rapidly after transplantation and resolves within the first month after transplantation. Persistent or worsening proteinuria is usually indicative of allograft pathology. Hence, monitoring the urine protein-to-creatinine ratio at each clinic visit and allograft biopsy should be performed in kidney transplant recipients with persistent or worsening proteinuria and in those whose primary renal disease is focal segmental glomerulosclerosis, to monitor for disease recurrence. As in the nontransplant setting, post-transplantation proteinuria increases the risk for CV events, graft loss, and mortality. Controlled trials evaluating the beneficial effect of treating proteinuria in reducing CV risk in kidney transplant recipients remain limited. A Canadian double-blind RCT evaluating the effect of ramipril versus placebo in kidney transplant recipients with proteinuria greater than 0.2 g/day and eGFR greater than 20 ml/min/1.73 m^2 failed to show a beneficial effect of ramipril in ameliorating the composite primary end-point of reduction in doubling of serum creatinine, end-stage renal disease (ESRD), or death compared with placebo at a mean follow up of 48 months.[30] In contrast, in another RCT with 10-year follow-up, patients treated with an ACE inhibitor were found to have significantly better survival free of the composite end-point (death, major CV events, and renal graft loss or creatinine doubling) (P = .0102) and survival free of major CV events compared with those not receiving ACE inhibitors (controls), $P = .0027$. Furthermore, a significant increase in urinary protein excretion rate was observed only in controls. No significant differences in renal outcome were observed.[31] Although the routine recommendation of ACE inhibitor or ARB use in kidney transplant recipients with proteinuria awaits further studies, ACE inhibitors or ARBs should be considered in transplant recipients with proteinuria because of their well-established antiproteinuric and cardioprotective effects. The 2009 KDIGO clinical practice guidelines recommend an ACE inhibitor or ARB as first-line therapy for patients with hypertension and proteinuria of 1 g/day or greater.

Belatacept Use

Belatacept is a humanized fusion protein that inhibits the costimulatory pathway. Belatacept was developed to minimize CV risk and nephrotoxicity associated with CNI-based immunosuppression. Long-term follow-up of phase III RCTs comparing the safety and efficacy of belatacept-based versus cyclosporine-based immunosuppression in recipients of standard donor kidneys (BENEFIT study) and in those of extended-criteria donor kidneys (BENEFIT-EXT study) demonstrated that, compared with cyclosporine, belatacept-based regimens (1) resulted in lower BP, cholesterol levels, and incidence of PTDM, (2) significantly reduced death and graft loss, and (3) improved long-term renal function. Whether improvement in CV risk factor profile translates into reduction in CVD remains to be studied.

COMMON LABORATORY ABNORMALITIES

Anemia

In the immediate post-transplantation period, aggressive perioperative volume expansion may result in dilutional anemia. Refractory or severe anemia mandates aggressive evaluation to exclude the possibility of surgical postoperative bleeding, particularly in those with a rapid fall in Hb and hematocrit (Hct) levels.

Mild anemia is common in the early post-transplantation period when erythropoietin (EPO) therapy is typically discontinued, but usually improves within several weeks to months. Suggested etiologic factors for post-transplantation anemia include iron deficiency, impaired graft function, acute rejection episodes, recent infection, and medications (e.g., azathioprine, mycophenolic acid derivatives, sirolimus, everolimus, dapsone, ACE inhibitors, and ARBs).

Assessment of baseline iron stores at the time of transplantation may be invaluable because iron deficiency is common in the dialysis population. Profound iron deficiency should be treated with intravenous iron as tolerated. EPO therapy and darbepoetin alfa are effective in the treatment of anemic kidney transplant recipients. The 2012 KDIGO anemia guidelines recommend initiating an erythropoiesis-stimulating agent in CKD patients when Hb values are less than 9 to 10 g/dl, provided iron stores are adequate. A target Hb level of 10 to 11 g/dl is recommended. Large CKD anemia trials demonstrated a possible harmful effect of higher Hb levels and high epoetin doses. Observational studies in kidney transplant recipients similarly suggested that mortality may be increased with Hb levels above 12.5 g/dl. Although evidence-based recommendations in the transplant setting are lacking, management of post-transplantation anemia to keep Hb level in the range of 10 to 11 g/dl seems reasonable.

Refractory anemia or anemia that fails to rise gradually to a normal or near-normal level after the first few post-transplantation weeks can be a result of occult gastrointestinal bleeding, tertiary hyperparathyroidism, underlying inflammatory conditions, or parvovirus B19 infection. EPO-resistant anemia has been described in patients receiving sirolimus immunosuppression. In stable kidney transplant recipients, conversion from sirolimus to mycophenolic acid derivatives may help resolve anemia. Although uncommon, drug-induced hemolysis from agent such as dapsone should also be considered.

Leukopenia and Thrombocytopenia

Leukopenia and thrombocytopenia are most commonly related to adverse drug effects, including treatment with lymphocyte-depleting agents (e.g., thymoglobulin or alemtuzumab), azathioprine, mycophenolic acid derivatives, sirolimus, everolimus, and trimethoprim-sulfamethoxazole, among others. Withholding the offending agent or dose reduction generally corrects these hematologic abnormalities. Severe leukopenia may be safely treated with granulocyte-stimulating factor. Thrombotic microangiopathy (TMA) or cytomegalovirus (CMV) infection should be excluded. Parvovirus B19 infection may manifest with refractory anemia, pancytopenia, and TMA. Alemtuzumab can cause potentially fatal immune thrombocytopenia. Bortezomib, the first-in-class proteasome inhibitor introduced into clinical transplantation for the treatment of antibody-mediated rejection and desensitization protocols, has been reported to cause leukopenia and thrombocytopenia.

Erythrocytosis

Post-transplantation erythrocytosis (PTE) may develop within the first 2 years and generally affects those with good allograft function. Its incidence appears to have decreased to less than 10% concomitant with the more frequent use of ACE inhibitors and ARBs. Spontaneous remission is observed in one fourth of patients within 2 years from onset, whereas in the remaining three fourths erythrocytosis may persist for several years.[32] Risk factors for PTE include the presence of native kidneys, male gender, absence of rejection episodes, high baseline Hb before transplant, and hypertension. Smoking and diabetes have been shown to be risk factors for PTE in some but not all studies. Other suggested risk factors include polycystic kidney disease and glomerulonephritis as the cause of ESRD. Although transplant renal artery stenosis has not consistently been shown to be a risk factor for PTE, imaging studies to evaluate the iliac and renal arteries should be considered in patients with refractory PTE. In addition, the possibilities of renal cell carcinoma in the native or transplanted kidneys should be excluded.

Both hormonal systems and growth factors have been implicated in the pathogenesis of PTE. These may include defective feedback regulation of EPO metabolism, direct stimulation of erythroid precursors by angiotensin II, abnormalities in levels of circulating insulin-like growth factor 1 (IGF-1) and its binding proteins, and an increase in serum-soluble stem cell factors, which stimulates the growth of erythroid progenitor cells. Serum-soluble stem cell factors have been shown to correlate with both Hct values and the observed and expected EPO values in kidney transplant recipients with PTE.[33]

Treatment is generally recommended for an Hb level exceeding 17 to 18 g/dl or an Hct level over 51% to 52% because of the associated risk for thromboembolic complications, hypertension, and headaches. Hb and Hct treatment range may vary depending on gender and institutional reference range. Treatment with ACE inhibitors or ARBs is often sufficient, although phlebotomy may occasionally be necessary. Relapse is common and often necessitates long-term ACE inhibitor or ARB treatment. A negative association between the use of sirolimus and PTE has been reported. Nonetheless, modification of immunosuppressive medications to treat PTE is uncommon in clinical practice.

Hyperkalemia

Mild hyperkalemia is commonly encountered in kidney transplant recipients, particularly in the early post-transplantation period when higher doses of CNI are used. It is often associated with mild hyperchloremic acidosis, a clinical presentation reminiscent of that of type 4 renal tubular acidosis. Suggested mechanism(s) of CNI-induced hyperkalemia include hyporeninism, hypoaldosteronism, aldosterone resistance, and inhibition of cortical collecting duct potassium secretory channels. In patients receiving cyclosporine or tacrolimus immunosuppression, a potassium level in the range of 5.2 to 5.5 mmol/l is typical. Higher potassium levels, especially in the presence of concomitant use of drugs that may exacerbate hyperkalemia such ACE inhibitors, ARBs, and β-blockers, may require their discontinuation. Caution is needed when potassium-containing phosphorus supplements are prescribed. Although both high-dose and standard-dose trimethoprim can cause hyperkalemia via an amiloride-like effect, the routine use of low-dose trimethoprim-sulfamethoxazole prophylactic therapy is rarely the cause of severe or refractory hyperkalemia in kidney allograft recipients. Nonetheless, withholding of trimethoprim should be considered in patients with severe or refractory hyperkalemia. Treatment of hyperkalemia is discussed in Chapter 9. Sodium polystyrene sulfonate (Kayexalate) or calcium resonium enemas should be avoided in the early post-transplantation period to avoid colonic dilation and perforation. Although the newer cation exchanger patiromer is effective in the treatment of hyperkalemia, its use in kidney transplant recipients may be hindered by potential drug-induced hypomagnesemia. This adverse drug effect may exacerbate the electrolyte abnormalities commonly seen in the post-transplantation period (discussed later).

Hypophosphatemia

Hypophosphatemia is frequently encountered in the first months after transplantation. Concomitant hypercalcemia suggests post-transplantation hyperparathyroidism. In the absence of hypercalcemia, renal phosphate-wasting syndrome or malnutrition should be considered. Early after transplantation, hypophosphatemia has been attributed to a massive initial diuresis, particularly after a living-donor kidney transplant, defective renal phosphate reabsorption caused by ischemic injury, glucosuria (caused by hyperglycemia-induced osmotic diuresis), and corticosteroid use, the latter by inhibiting proximal tubular reabsorption of phosphate. Fibroblast growth factor-23 (FGF-23) has been suggested to play a major contributory role in the development of early post-transplantation hypophosphatemia independent of parathyroid hormone (PTH) level. FGF-23 is a phosphaturic hormone, and its levels are increased in the early stages of CKD and significantly elevated in dialysis patients. Pretransplant FGF-23 was found to be the main predictor of post-transplant phosphate levels.[34] In contrast to hypophosphatemia occurring in the early post-transplant period, persistent hypophosphatemia beyond 1 year after transplant is mainly due to persistent hyperparathyroidism rather than increased FGF-23 levels.

Hypercalcemia

Hypercalcemia is common after transplantation and is generally a result of persistent secondary hyperparathyroidism. The concomitant presence of severe hypophosphatemia, particularly in patients with excellent graft function, may exacerbate hypercalcemia through stimulation of renal proximal tubular 1α-hydroxylase. Resolution of soft tissue calcifications and immobilization are potential contributing factors. Hypercalcemia may be masked by high-dose corticosteroid therapy but may manifest during tapering. In about two thirds of patients, hypercalcemia resolves spontaneously within 6 to 12 months. However, spontaneous resolution occurs in less than half of those whose hypercalcemia existed before transplantation. Persistent hyperparathyroidism has generally been attributed to continued autonomous production of PTH from nodular hyperplastic glands, reduced density of calcitriol receptors, and decreased expression of the membrane calcium sensor receptors that render cells more resistant to physiologic concentrations of calcitriol and calcium. Persistently elevated FGF-23 levels after transplant may contribute to persistent hyperparathyroidism through inhibition of 1α-hydroxylase activity leading to low calcitriol levels. The risk for persistent hyperparathyroidism is increased with the duration of dialysis and the severity of pretransplant hyperparathyroidism. Severe and persistent hypercalcemia (≥11.5 to 12 mg/dl [2.87 to 3.0 mmol/l]) for longer than 6 months in the first post-transplant year requires further evaluation. Initial assessment should include an intact PTH level. Imaging studies, including neck ultrasound or parathyroid technetium-99m (^{99m}Tc)-sestamibi scan, are required to determine whether the clinically observed hyperparathyroidism arises from parathyroid adenoma, parathyroid gland hyperplasia, or hyperplastic nodular formation. Although therapeutic approaches differ across transplant centers, treatment with cinacalcet can be considered in kidney transplant recipients with hyperparathyroidism-associated hypercalcemia in the early post-transplant period. Serum calcium, phosphorus, and alkaline phosphatase should be monitored at each clinic visit. Because spontaneous resolution of hyperparathyroidism may not occur rapidly, it is generally advisable to delay any plan for parathyroidectomy to 1 year after transplant (see later for indication for parathyroidectomy). However, severe hypercalcemia associated with parathyroid adenoma often necessitates surgical parathyroidectomy.

Cinacalcet is commonly used off label by most U.S. centers to treat post-transplant hypercalcemic hyperparathyroidism. Subtotal parathyroidectomy is warranted in patients with tertiary hyperparathyroidism or persistent severe hypercalcemia (≥11.5 to 12 mg/dl [2.87 to 3.0 mmol/l]) for longer than 6 to 12 months, symptomatic or progressive hypercalcemia, nephrolithiasis, persistent osteitis fibrosa, calcium-related renal allograft dysfunction, or progressive vascular calcification and calciphylaxis.[35] In a retrospective cohort study of 83 kidney transplant recipients with tertiary hyperparathyroidism, parathyroidectomy resulted in a lower serum calcium level (9.28 mg/dl) compared with cinacalcet (10.20 mg/dl) ($P < .01$) at 6 weeks. One fourth of the observation group showed persistent hypercalcemic symptoms, compared with 7.7% in the cinacalcet and 0% in the parathyroidectomy group ($P < .01$).[36] In a more recent single-center study consisting of 59 stable kidney transplant recipients, the calcium-lowering effect of cinacalcet was found comparable to that of surgical parathyroidectomy at 8 weeks and at 1-year follow-up.[37] Subtotal parathyroidectomy was performed in patients with uncontrollable, long-standing, and marked osteitis fibrosa. Notably, 2 of 16 patients in the parathyroidectomy group were excluded from the study analysis because of surgical failures (defined as at least two of the three criteria including decrease in serum calcium, phosphorus, and PTH). Whether long-term calcimimetic use is safe and reduces the need for parathyroidectomy warrants further exploration. Although

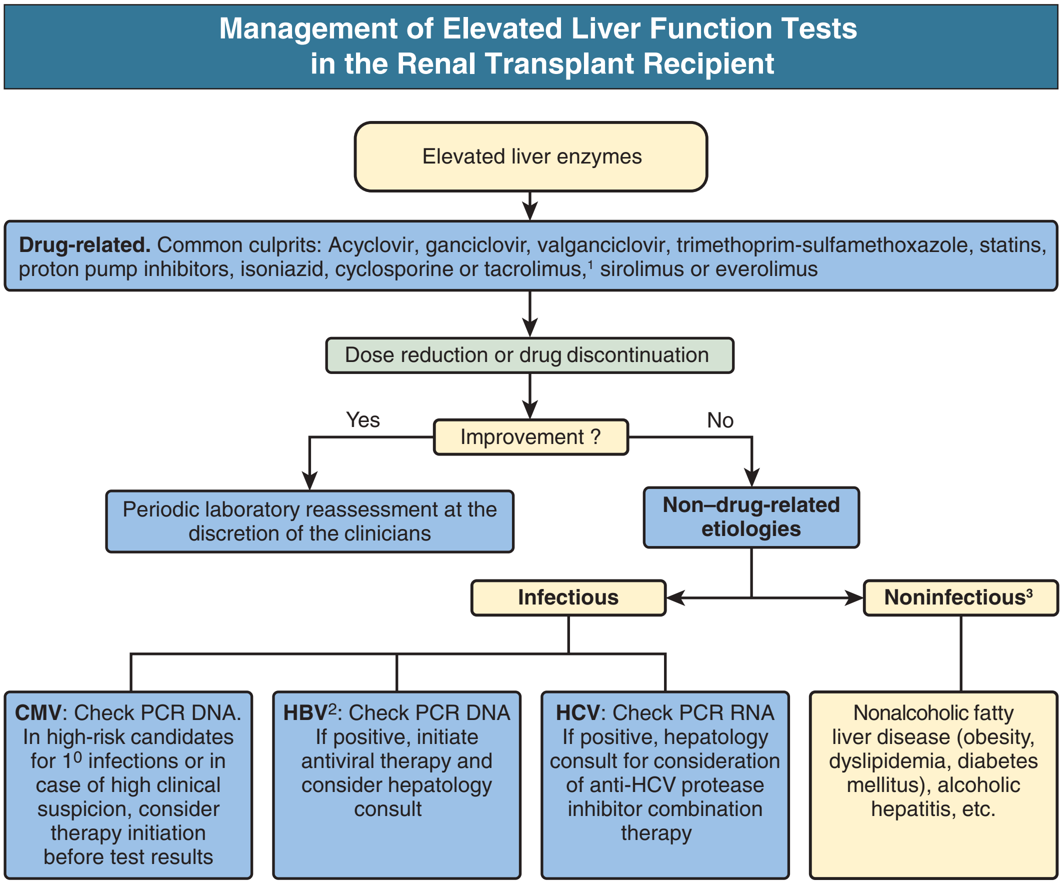
Management of Elevated Liver Function Tests in the Renal Transplant Recipient
Elevated liver enzymes
Drug-related. Common culprits: Acyclovir, ganciclovir, valganciclovir, trimethoprim-sulfamethoxazole, statins, proton pump inhibitors, isoniazid, cyclosporine or tacrolimus,1 sirolimus or everolimus
Dose reduction or drug discontinuation
Improvement ?
Yes
No
Periodic laboratory reassessment at the discretion of the clinicians
Non–drug-related etiologies
Infectious
Noninfectious3
CMV: Check PCR DNA. In high-risk candidates for 1⁰ infections or in case of high clinical suspicion, consider therapy initiation before test results
HBV2: Check PCR DNA If positive, initiate antiviral therapy and consider hepatology consult
HCV: Check PCR RNA If positive, hepatology consult for consideration of anti-HCV protease inhibitor combination therapy
Nonalcoholic fatty liver disease (obesity, dyslipidemia, diabetes mellitus), alcoholic hepatitis, etc.

Fig. 106.4 Algorithm for the management of elevated liver enzymes in kidney transplant recipients. [1]Cyclosporine and, less commonly, tacrolimus may cause transient, self-limited dose-dependent elevations of aminotransferase levels and mild hyperbilirubinemia secondary to defective bile secretion. [2]We advocate antiviral prophylactic therapy in all HBsAg-positive candidates at the time of transplantation. [3]Appropriate evaluation and management similar to those in nontransplant settings.

seldom reported, clinicians should remain vigilant for the potential development of nephrocalcinosis associated with the use of cinacalcet.[38]

Hypomagnesemia

Cyclosporine, tacrolimus, and sirolimus can cause hypomagnesemia by inducing urinary magnesium wasting. Other factors that may contribute to post-transplantation hypomagnesemia include loop diuretic therapy, recovery from acute tubular necrosis, postobstructive polyuria, and renal tubular acidosis. Hypomagnesemia may be more common in diabetics. In the first 3 months after transplantation, a magnesium level below 1.5 mg/dl (0.62 mmol/l) is common. Dietary magnesium intake is usually insufficient, and high-dose oral magnesium supplementation (i.e., 400-800 mg magnesium oxide three times per day) may be required. Intravenous magnesium should be considered in patients with severe hypomagnesemia (<1.0 mg/dl or 0.41 mmol/l), particularly patients with a history of CHD or cardiac arrhythmias and those taking digoxin.

Abnormal Liver Function Tests

Elevation of liver enzymes is common in the early post-transplantation period and is generally caused by drug-related toxicity (Fig. 106.4). Cyclosporine and less commonly tacrolimus may cause transient, self-limited, dose-dependent elevations of transaminase levels and mild hyperbilirubinemia secondary to defective bile secretion. Elevated liver enzymes caused by drug-related adverse effects generally improve or resolve after drug discontinuation or dose reduction.

Persistent or profound elevation in liver enzymes should prompt further evaluation to exclude infectious causes, including CMV, hepatitis B, and hepatitis C infections. Evidence of post-transplant HBV reactivation should be treated with entecavir or another nucleotide analogue. We advocate antiviral prophylactic therapy in all hepatitis B surface antigen (HBsAg)-positive candidates at the time of transplantation. Historically there was no effective treatment for chronic hepatitis C in kidney transplant recipients because of the increased risk for allograft rejection and graft loss associated with interferon-α therapy. With the advent of the new direct-acting antiviral agents, patients with evidence of post-transplant reactivation of hepatitis C should be referred to a hepatologist for consideration for interferon-free anti-HCV protease inhibitor therapy. A suggested algorithm for the management of kidney transplant recipients with elevated liver enzymes is shown in Fig. 106.4.

BONE AND MINERAL METABOLISM AFTER KIDNEY TRANSPLANTATION

Post-transplantation bone disease is a common and complex complication after kidney transplantation because of the adverse effects of immunosuppression (particularly corticosteroids), hypophosphatemia, and disturbances in the FGF-23–PTH–vitamin D axis. Corticosteroids act on the skeletal system by directly inhibiting osteoblastogenesis and inducing apoptosis of osteoblasts and osteocytes and by increasing bone resorption through osteoclast activation. Other adverse effects of corticosteroids on bone mechanical integrity include inhibition of intestinal calcium absorption, enhancement of renal calcium excretion, and direct suppression of gonadal hormone secretion. Low plasma calcidiol 25(OH) vitamin D level also may contribute to bone disease and is very common in kidney transplant recipients, with a reported prevalence of calcidiol deficiency of 30% and insufficiency of 81%. Suggested causative factors include nutritional deficiency, malabsorption, decreased sun exposure, and increased metabolism of calcidiol to calcitriol after a successful kidney transplant.

Other factors that have been suggested to contribute to post-transplantation bone loss include "normal" age-dependent osteoporosis, persistent metabolic acidosis, phosphate depletion, DM, hypogonadism, smoking, and CNI therapy. Experimental animal models suggest that CNIs may contribute to post-transplantation bone loss by stimulating bone resorption. Limited clinical studies demonstrated that CNI-based immunosuppression with low maintenance doses of corticosteroids induced slight bone formation but relatively potent, clinically relevant bone resorption. Nonetheless, the contributory role of CNIs in causing bone loss in kidney transplant recipients may be difficult to evaluate because of concomitant corticosteroid therapy. In a prospective study of 53 kidney transplant recipients randomly assigned to cyclosporine alone (n = 13), cyclosporine plus steroids (n = 20), or cyclosporine plus steroids plus azathioprine (n = 20), lumbar bone mineral density (BMD) increased significantly from transplant to 18 months after transplant among patients on steroid-free immunosuppression. In contrast, BMD significantly decreased among the two steroid-treated groups during the study period.[39]

Experimental studies suggest that mTOR inhibitors may have a bone-sparing effect. Sirolimus may interfere with the proliferation and differentiation of osteoblasts, and, more important, it may inhibit osteoclast formation. One small European study showed that sirolimus decreased serum level of bone resorption markers in patients treated with sirolimus compared with those receiving a CNI-based regimen.[40]

Osteoporosis

Post-transplantation decline in BMD is most pronounced in the first 6 months and correlates with higher corticosteroid exposure. This early rapid decrease in BMD is usually followed by a slower rate of bone loss, which reflects cumulative corticosteroid dose. BMD has been reported to decrease at a mean of 5.5% to 19.5% during the first 6 months after transplant, 2.6% to 8.2% from months 6 to 12, and 0.4% to 4.5% thereafter.[41] In recent years, the rates of post-transplantation bone loss and fractures appear to have decreased, in part, because of the use of lower corticosteroid doses or glucocorticoid-sparing regimen.[42]

Evaluation of patients for bone loss or osteoporosis relies on the measurement of BMD using dual-energy x-ray absorptiometry (DEXA) scan. The preliminary, revised 2016 KDIGO guidelines suggest BMD testing to assess fracture risk in kidney transplant recipients with CKD stage 1 to 5T (T indicating transplant patient) and risk factors for osteoporosis if the results alter therapy. Studies in the general population and limited studies in the transplant setting suggest that DEXA BMD predicts fractures across the spectrum of CKD severity. One retrospective cohort study of 238 kidney transplant recipients with CKD stage 1 to 5T demonstrated that osteopenia (HR 2.7, 95% confidence interval [CI] 1.6-4.6) and osteoporosis (HR 3.5, 95% CI 1.8-6.4) were associated with significantly increased hip fracture risk compared with normal BMD, independent of age, gender, and diabetes.[43] The mean eGFR at the time of DEXA testing was 48 ml/min (range 12 to 98 ml/min).

In patients with low BMD in the first 12 months after transplant, the KDIGO guidelines suggest that consideration should be given to treatment with vitamin D, calcitriol or alfacalcidol, or biphosphonates. The levels of calcium, phosphorus, PTH, alkaline phosphatase, and 25(OH) D may dictate the choice of therapy. Bone biopsy may be considered to guide treatment. Currently, data are insufficient to guide treatment after the first post-transplant year. Large prospective studies in kidney transplant recipients with CKD stages 1 to 5T to evaluate the utility of BMD testing and bone biomarkers as predictors of fractures are needed.

Avascular Necrosis

Post-transplantation avascular necrosis (AVN) occurs with an incidence of 3% to 16% and most commonly affects the femoral head and neck. Its prevalence appears to have decreased over the past two decades concomitant with the use of lower corticosteroid dose and rapid steroid tapering. AVN usually occurs within the first few years after transplantation and may affect other joints, including the knees, the shoulders, and less commonly the ankles, elbows, and wrists. Predisposing factors for AVN include greater exposure to intravenous corticosteroid pulse therapy, cumulative doses of more than 2 g for longer than 3 months,[42] low bone mass, hyperparathyroidism, increasing dialysis duration, excessive weight gain, hyperlipidemia, microvascular thrombosis, and a history of local trauma.

Early AVN of the femoral head commonly presents with hip or groin pain or referred knee pain. Magnetic resonance imaging is the most sensitive technique for early detection, and plain radiographs are of limited value. Corticosteroid dose reduction or discontinuation has little if any effect on altering the course of established AVN and may jeopardize graft function.

Prevention and Management of Post-Transplantation Bone Diseases

Management of post-transplantation bone disease has largely been based on studies involving postmenopausal osteoporosis and corticosteroid-induced osteopenia in nontransplant settings. Limited studies in solid organ transplantation have yielded variable and conflicting results, in part because of the complex pathophysiology of bone and mineral metabolism after transplantation, particularly in recipients of kidney transplants. Nonetheless, preventive measures to minimize post-transplantation bone loss should be initiated early after transplantation. Early ambulation and physical exercise should be encouraged. Adequate calcium supplementation (1000 mg/day) in nonhypercalcemic patients is recommended in the first post-transplantation year to prevent rapid bone loss resulting from corticosteroid-induced decreased intestinal calcium absorption. The KDIGO practice guidelines recommend measuring calcidiol levels and correcting vitamin D deficiency and insufficiency with use of treatment strategies recommended for the general population. In patients at increased risk for fracture, consideration should be given to rapid corticosteroid withdrawal or corticosteroid-free immunosuppressive protocols after weighing the risks and benefits of acute rejection. High pretransplantation PTH levels predict persistent hyperparathyroidism after transplantation, which may contribute to bone loss after transplantation. Hence, preexisting hyperparathyroidism associated with CKD should be treated according to the KDIGO guidelines.

In patients with preexisting secondary hyperparathyroidism, hypercalcemia and hypophosphatemia may develop after a successful kidney transplant because of the combined effect of persistent hyperparathyroidism and the newly elevated calcitriol level. The contributory role of FGF-23 in the development of post-transplant hypophosphatemia was previously discussed. Conservative management with phosphate replacement and suppression of hyperparathyroidism with cinacalcet has generally been recommended. Although no guidelines exist, phosphate supplementation should be considered in patients with a phosphate level of 1.5-1.7 mg/dl or less (0.5 mmol/l) to avoid complications associated with severe hypophosphatemia (e.g., rhabdomyolysis, left ventricular dysfunction, respiratory muscle weakness, and hemolysis). Treatment range may vary depending on institutional reference range. Patients should be encouraged to increase phosphate-rich food intake, and phosphate replacement should be discontinued when serum phosphate stabilizes at around 2.0 mg/dl (0.64 mmol/l). Overaggressive phosphate replacement is not recommended because it can result in hypocalcemia or persistent hyperparathyroidism and may increase the risk for nephrocalcinosis.

Bisphosphonates increase BMD in postmenopausal women and patients with corticosteroid-induced osteoporosis, particularly at the lumbar spine and trochanter. Studies evaluating the safety and efficacy of bisphosphonates in the treatment and prevention of bone disease after kidney transplantation have yielded mixed and even contradictory results, in part because of differences in study design, concomitant use of calcium or vitamin D, timing of treatment, duration of follow-up, and preexisting renal osteodystrophy, among others. The beneficial effect of bisphosphonates on BMD may be site-specific (e.g., lumbar spine and femoral neck but not hip) and gender-specific. In a single-center study of 42 living donor kidney recipients randomized to receive either 35 mg of risedronate weekly or placebo for 12 months, treatment with risedronate did not affect bone BMD in the overall cohort. However, subgroup analyses demonstrated a trend toward preservation of BMD in female but not male subjects. Protocol bone biopsy at the time of transplant and after 12 months of treatment showed no evidence for the development of adynamic bone disease.[44] In contrast, other studies have shown that bisphosphonate therapy significantly increases the risk for developing low-turnover bone disease. In a study of 72 kidney transplant recipients randomized to receive either pamidronate with vitamin D and calcium or vitamin D and calcium only (control group), preservation of bone mass was observed in pamidronate-treated patients at 6 and 12 months, whereas decreased vertebral BMD was seen in the control group during the study period. Bone biopsy in patients undergoing scheduled living donor kidney transplant revealed that 50% of the patients had low turnover bone at baseline. At 6-months, bone biopsy demonstrated adynamic bone disease in all pamidronate-treated patients compared with 50% in the control group[45] Whether an improved BMD with adynamic bone histology is useful in maintaining long-term bone health or reducing fracture risk in kidney transplant recipients remains to be studied.

Calcitonin inhibits osteoclastic action by a direct receptor-mediated signal. Similar to bisphosphonates, calcitonin is effective in postmenopausal patients as well as patients with corticosteroid-induced osteoporosis. The beneficial effects of calcitonin on bone loss have not consistently been shown in the transplant setting. Furthermore, calcitonin has no effect on fracture risk in kidney transplant recipients. Data are currently insufficient to recommend or refute the use of calcitonin in kidney transplant recipients.

Estrogen or androgen deficiencies also have been suggested to contribute to post-transplantation bone loss. However, no data support or refute the use of hormonal therapy to prevent post-transplantation–related bone loss in postmenopausal women or in men with hypogonadism; hence, treatment should be individualized.

The 2007 Cochrane Database Systematic Review of RCTs showed that no individual therapy (bisphosphonates, vitamin D sterol, or calcitonin) reduced fracture risk compared with placebo in RCTs. However, meta-analysis of all such trials combined demonstrated that any treatment (i.e., bisphosphonates by any route, vitamin D sterol, or calcitonin) was associated with a reduction in the relative risk of fracture (RR 0.51, 95% CI 0.27-0.99). A beneficial effect on lumbar spine BMD was seen with all individual agents. Bisphosphonates and vitamin D sterol also had a beneficial effect on the BMD at the femoral neck. It is suggested that treatment with a bisphosphonate, vitamin D sterol, or calcitonin after kidney transplantation may protect against immunosuppression-induced reductions in BMD and prevent fracture.[46,47] Few or no data were available for combined hormone replacement, testosterone, selective estrogen receptor modulators, fluoride, or anabolic steroids.

Denosumab is a humanized monoclonal antibody that binds to and prevents RANKL (receptor activator of nuclear factor kappa-β ligand) from activating its receptor (RANK) on the surface of osteoclasts and their precursors. Denosumab has been shown to increase BMD and decrease fracture risk in postmenopausal women and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of postmenopausal osteoporosis. Limited studies in kidney transplant recipients suggest that denosumab in combination with calcium and vitamin D may improve BMD compared with calcium and vitamin D alone.[48]

In summary, calcium supplementation, vitamin D, and bisphosphonates remain the backbone of treatment of abnormal bone and mineral metabolism after kidney transplantation. Persistent hyperparathyroidism or hypophosphatemia should be treated before considering additional therapies for osteoporosis. In the absence of evidenced-based recommendations, the use of bisphosphonates in the post-transplantation setting should be individualized. In our opinion, bisphosphonate therapy may be justifiable in high-risk individuals, including those with preexisting osteoporosis or documented overall low bone mass, those who are receiving high-dose corticosteroids or those with history of fractures, and those who are postmenopausal. Biphosphonates should be used with caution in patients with impaired kidney function and avoided in CKD stages 4 to 5. Biochemical markers of low bone turnover (serum PTH and bone-specific alkaline phosphatase levels below or at the lower limits of normal) may be used to guide therapy. In high-risk individuals who are intolerant of bisphosphonates, calcitonin, or denosumab can be used as an alternative treatment option. Profound hypocalcemia associated with the use of denosumab particularly in patients with low GFR has been reported and should not be overlooked.

GOUT

Potential risk factors for the development of post-transplantation hyperuricemia and gouty arthritis include pretransplantation hyperuricemia, graft impairment, obesity, diuretic use, and cyclosporine compared with tacrolimus. Cyclosporine has been suggested to impair renal excretion of uric acid secondary to decreased GFR, as well as increased net uric acid reabsorption by the proximal tubule.

Management of the acute gouty attack includes topical ice and rest of the inflamed joint. Pharmacologic treatments include colchicine, increased corticosteroid dose, or nonsteroidal antiinflammatory drugs (NSAIDS). The use of NSAIDS, however, should be avoided in the early post-transplant period and in patients with impaired allograft function. Temporary increase in corticosteroid dose is usually safe and effective (our experience). Progressive steroid tapering to low-dose maintenance antirejection therapy (usually over a 2- to 3-week period) is recommended to prevent rebound gout flare.

Management of chronic gout is directed at lowering uric acid levels. Allopurinol, a xanthine oxidase inhibitor, should be started at a low dose (100 to 200 mg/day), particularly in the presence of impaired allograft function, because renal impairment predisposes to severe allopurinol toxicity from retention of the metabolite oxypurinol. The dose can be increased by 50-mg increment (adjusted for renal function) every 4 weeks to maintain uric acid level below 6 mg/dl in symptomatic patients. We do not routinely recommend allopurinol therapy in asymptomatic patients based on uric acid level alone. In allopurinol-allergic patients, febuxostat (a nonpurine analogue xanthine oxidase inhibitor) can be used. It is administered as 40 or 80 mg/day, and the dosage is not modified in renal failure. Both allopurinol and febuxostat should be used cautiously in patients taking azathioprine because of the inhibition of azathioprine metabolism by xanthine oxidase inhibitors (e.g., when used in combination therapy with allopurinol or febuxostat, consider azathioprine dose reduction by 25% and close monitoring of complete blood counts). Alternatively, azathioprine to mycophenolic acid derivative conversion therapy may be considered. The latter does not interact with allopurinol or febuxostat. Recombinant pegylated uricase (pegloticase), which converts uric acid to the more soluble and readily excreted purine end-product allantoin, rapidly reduces uric acid levels in patients refractory to conventional therapy. The drug was approved by the FDA in 2010 for treatment of refractory gout. However, the development of high titers of antibodies to pegloticase is associated with loss of efficacy and infusion reactions.[49] Whether immunosuppressive therapy in the transplant settings might prevent antipegloticase antibody development and retain the urate-lowering efficacy among organ transplant recipients warrants further exploration.

OUTPATIENT CARE

We recommend that patients be seen two times a week for the first 4 weeks after transplantation and weekly for the next month. After the first 2 months, the frequency of outpatient visits depends on the complexity of the patient's early postoperative course. Patients with stable graft function and an uneventful postoperative course can return to work or their regular daily activities 2 to 3 months after transplantation. Laboratory assessment during the first month after transplantation should include serum creatinine and electrolyte values, fasting glucose level, liver enzymes, immunosuppressive drug levels, and complete blood count with platelets. Urinalysis and, if clinically indicated, urine culture, and urine protein-to-creatinine ratio (see proteinuria section) also should be performed. At our institution, the patient's care will generally be returned to the referring nephrologist after 3 months. However, continued annual follow-up at the transplantation center is recommended.

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SELF-ASSESSMENT QUESTIONS

1. Management of post-transplantation hypertension should include lifestyle modifications and which one of the following?
   A. An angiotensin-converting enzyme (ACE) inhibitor is the antihypertensive agent of choice after kidney transplantation because it improves patient and graft survival.
   B. The choice of antihypertensive agents should be individualized based on efficacy, tolerability, concomitant comorbidity, and drug-drug interactions.
   C. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest a blood pressure goal of less than 130/80 if albuminuria is present.
   D. Calcium channel blockers should be considered as first-line treatment.
2. Which one of the following statements regarding post-transplantation dyslipidemia is correct?
   A. The addition of ezetimibe to statin therapy reduces cardiovascular events compared with statin alone therapy.
   B. Fibrate should be considered as a second-line treatment option for high-risk kidney transplant recipients who are intolerant of statin.
   C. Ezetimibe should be considered as a second-line treatment option for high-risk kidney transplant recipients who are intolerant of statin.
   D. Among currently available immunosuppressive agents, calcineurin inhibitors are associated with the worst lipid profiles followed by mTOR inhibitors.
3. Which one of the following immunosuppressive agents has not been shown to play a contributory role in the development of post-transplantation diabetes mellitus?
   A. mTOR inhibitors (sirolimus and everolimus)
   B. Mycophenolic acid derivatives (mycophenolate mofetil or mycophenolate sodium)
   C. Calcineurin inhibitors (cyclosporine and tacrolimus)
   D. Corticosteroids

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Chronic Allograft Injury

Christian Morath, Martin Zeier

DEFINITIONS AND EPIDEMIOLOGY

The results after kidney transplantation have steadily improved over the last 30 years with a 1-year overall graft survival rate of about 94% and acute rejection rates within the first year after transplantation at 12%.[1] Loss of an allograft as a result of acute rejection has become a rare event and is predominantly found in patients who are presensitized against human leukocyte antigens (HLAs).[2] Today, most allografts are lost by chronic antibody-mediated rejection that is a consequence of (*de novo*) development of donor-specific HLA antibodies (DSAs). Every year, about 4% of kidney grafts are lost (Fig. 107.1). Only a decade ago, it was believed that nonimmunologic causes are the main factors leading to chronic allograft injury and graft loss.[3] However, our understanding has changed and HLA alloantibodies are today believed to be the main culprit, accounting for more than half of graft losses in the long term.[4] With the acknowledgment of alloantibodies as main factors that contribute to graft failure the term *chronic allograft nephropathy* had been replaced by more specific terminology in the Banff classification of renal allograft pathology (Table 107.1).[5,6]

Although immunologic causes are now believed to be mainly responsible for late allograft injury and graft failure, nonimmunologic causes still represent significant risk factors for (late) graft injury and graft loss. The donor graft may present with significant preexisting disease limiting long-term graft survival.[7] In addition, chronic interstitial fibrosis and tubular atrophy (IFTA) may result from early damage to the allograft such as ischemia/reperfusion injury or early acute rejection. Calcineurin-inhibitor (CNI) nephrotoxicity, recurrent or *de novo* glomerular disease, BK virus infection, and IFTA originating from other causes further contribute to graft damage and graft loss over the long term.

Whereas some allografts are lost because of one specific cause, others accumulate damage from several different causes with gradual loss of functioning nephrons. Main contributors to late graft injury and late graft loss are summarized in Box 107.1.

PATHOGENESIS: NONIMMUNOLOGIC FACTORS

Donor Age, Donor Gender, and Donor-Recipient Size Mismatching

Long-term graft survival is reduced in kidneys from older donors, an effect that is more pronounced in deceased compared with living kidney transplant recipients.[8] Impaired graft survival is attributed to a differential response of the older organ to injury, an impaired capacity to withstand stress, a limited ability to repair structural damage, or amplification of external injury as a result of preexisting structural abnormalities.[9]

Reduced nephron mass resulting in glomerular hyperfiltration and hypertension with accelerated senescence is also a postulated mechanism for a progressive decline in kidney graft function.[10] The effect of kidney size mismatching is thought to be related to insufficient numbers of nephrons within the donor kidney, which in turn leads to compensatory hyperfiltration.[11] Although there are experimental data to support this hypothesis, the extent to which an inadequate number of nephrons contributes to chronic injury in clinical transplantation is unknown.

Female donor gender has a negative impact on kidney graft survival, with reduced survival when female grafts are transplanted into male recipients (risk ratio, 1.22). This may be the result of reduced nephron mass of female donor kidneys (nephron underdosing). Other mechanisms may include possible differences in the immunogenicity of male and female grafts.[12,13]

Ischemia/Reperfusion Injury and Delayed Graft Function

Graft survival is lower in recipients with longer ischemia times, and longer cold ischemia time represents a risk factor for the development of IFTA at 6 months after transplantation.[14] Ischemia-reperfusion injury also may trigger immune-mediated injury because ischemia and oxidative injury resulting from reperfusion are associated with activation of the adaptive immune response, antigen-presenting cells and Toll-like receptors, and release of proinflammatory cytokines—all of which can lead to acute rejection and subsequent IFTA.[15] Pretreatment of the deceased organ donor with low-dose dopamine (aiming to reduce ischemia/reperfusion injury) reduced the need for dialysis early after kidney transplantation but failed to improve long-term kidney graft survival.[16,17] Similarly, therapeutic hypothermia compared with normothermia of the deceased organ donor was associated with reduced delayed graft function in the kidney transplant recipient (28% vs. 39%).[18] Another promising approach to reduce ischemia/reperfusion injury and improve early kidney graft function is the replacement of cold storage of kidneys by pulsatile machine perfusion during transportation that is currently being tested in clinical trials.

Delayed graft function, commonly defined by the need for dialysis in the first week after transplantation, is a risk factor for IFTA.[19] There are also independent associations between delayed graft function and late graft failure and between delayed graft function and graft failure that is mediated by acute rejection. Major risk factors for delayed graft function are prolonged cold ischemia time, donor age older than 50 years, and the presence of HLA alloantibodies.[2] Ischemia and oxidative injury resulting from reperfusion of an ischemic kidney may cause an upregulation of major histocompatibility complex (MHC) antigens or proinflammatory cytokines, predisposing to acute rejection.

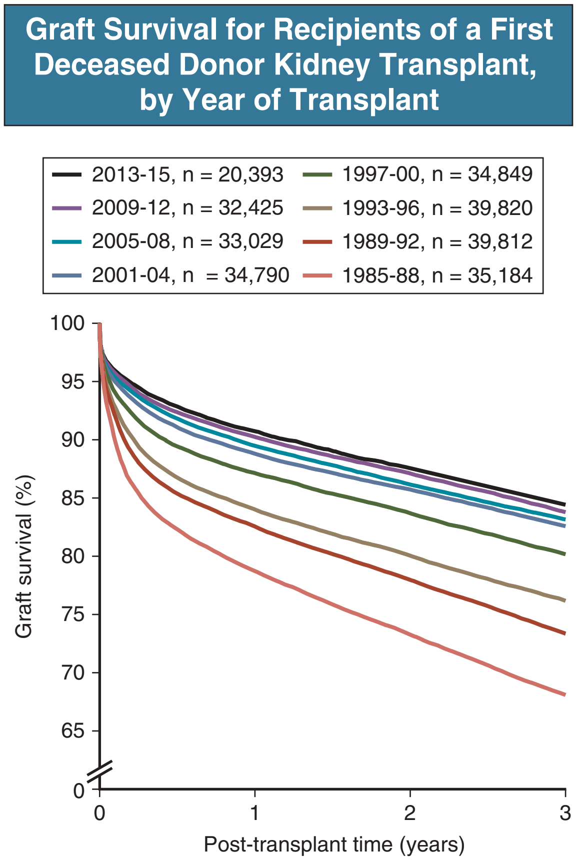

Fig. 107.1 Graft survival for recipients of a first deceased donor kidney transplant according to the year of transplantation. Graft survival has steadily improved over the past years but mainly as a result of reduction of early graft loss. (With permission from Prof. Gerhard Opelz, CTS Study).

BK Virus Nephropathy

BK virus is an endemic polyomavirus that is usually acquired during childhood and persists in the urinary tract. Although it is asymptomatic in the immunocompetent host, it becomes activated in the immunocompromised patient. Viremia may be found in 10% to 30% of patients within the first 6 months after transplantation with biopsy-proven BK virus–associated nephropathy in 1% to 10% of patients. BK virus–associated nephropathy mimics the pattern of interstitial cellular rejection but may be distinguished in immunohistochemistry by positive staining for the SV40 antigen. BK virus–associated nephropathy, if untreated, may lead to severe IFTA and graft loss in most patients. The mainstay of therapy is the reduction of immunosuppression.[20] The diagnosis and management of BK virus nephropathy are discussed further in Chapter 105.

Calcineurin Inhibitor Toxicity

CNI nephrotoxicity affects all histologic compartments of the transplanted kidney. Though not specific for CNI toxicity, CNI lesions include medial arteriolar hyalinosis, striped interstitial fibrosis, global glomerulosclerosis, and tubular microcalcification unrelated to other causes, such as tubular necrosis and hyperparathyroidism.[21,22] CNI-induced arteriolopathy is characterized by nodular hyaline deposits in the media of afferent arterioles sufficient to cause narrowing of the vascular lumen.[23,24] It is attributed to eosinophilic transformation and vacuolization of smooth muscle cells with subsequent necrosis. Arteriolar hyalinosis is the most reliable diagnostic marker of CNI nephrotoxicity. Confirmation of the diagnosis is made by exclusion of other causes, such as donor hyalinosis (which can be detected on the implantation biopsy specimen), diabetes, and hypertensive nephrosclerosis. Striped fibrosis is subjectively defined by a dense stripe of cortical fibrosis and atrophic tubules adjacent to normal cortex and is traditionally regarded as pathognomonic of CNI nephrotoxicity, but can be seen in any cause of fibrosis, especially those associated with microvascular injury. It is likely that the associated arteriolopathy and narrowing of the lumen contribute to development of fibrosis and atrophy after watershed infarcts within areas of ischemia. Local hypoxia leads to formation of free oxygen radicals, which promote cellular death by apoptosis. In addition, upregulation of transforming growth factor-β is considered an important etiologic factor in CNI toxicity.[22]

BOX 107.1 Main Factors Contributing to Late Graft Injury and Late Graft Loss

Donor Factors

- Deceased donor kidney (DBD or DCD)
- Older donor age, female donor
- Donor vascular disease
- Ischemia/reperfusion injury and long ischemia time
- Delayed graft function

Recipient Risks (Nonimmune)

- Obesity
- Urinary tract infection
- Transplant ureteral obstruction
- BK virus nephropathy
- Calcineurin inhibitor toxicity
- Recurrent renal disease or *de novo* glomerulonephritis
- Hypertension, dyslipidemia, smoking
- Diabetes (preexisting or post-transplantation)

Recipient Risks (Alloimmune)

- Child or adolescent recipient
- Variable medication trough concentrations from malabsorption or nonadherence
- HLA mismatches, presensitization status (donor-specific HLA alloantibodies)
- Acute rejection that is severe, corticosteroid resistant, vascular, antibody mediated, or late occurring
- Late *de novo* donor-specific antibodies and chronic (antibody-mediated) rejection

DBD, Donation after brain death; *DCD,* donation after cardiac death; *HLA,* human leukocyte antigen.

Today, CNI nephrotoxicity is believed to be responsible for only a small proportion of graft failures. The Study of Long-term Deterioration of Kidney Allograft Function (DeKAF) impressively demonstrated that 70% of patients with a primary or secondary histologic diagnosis of CNI nephrotoxicity had evidence of deposition of the complement split-product C4d and had DSA linking chronic graft failure to alloimmunity rather than CNI nephrotoxicity.[25,26]

Recurrent and *De Novo* Glomerular Diseases

Recurrent glomerulonephritis (GN) is diagnosed by exclusion of donor-transmitted disease and *de novo* GN. Its relative importance for graft loss increases as graft survival lengthens.[27] Given that it is a relatively common occurrence and has implications for treatment and retransplantation, recurrent GN should be looked for carefully in patients with a prior diagnosis of GN. Diagnosis and management of recurrent disease are discussed further in Chapter 108.

TABLE 107.1 Updated 2015 Banff Classification Categories

Category 1: Normal biopsy or nonspecific changes	
Category 2: Antibody-mediated changes	
Acute/active ABMR	All three features must be present for diagnosis. Biopsy samples showing histologic features plus evidence of current/recent antibody interaction with vascular endothelium or DSA, but not both, may be designated as suspicious for acute/active ABMR. Lesions may be clinically acute or smoldering or may be subclinical; it should be noted if the lesion is C4d positive or C4d negative, based on the following criteria: 1. Histologic evidence of acute tissue injury, including one or more of the following: • Microvascular inflammation (g >0 in the absence of recurrent or *de novo* glomerulonephritis and/or ptc >0) • Intimal or transmural arteritis (v >0)[*] • Acute TMA in the absence of any other cause • Acute tubular injury in the absence of any other apparent cause 2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following: • Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections or C4d >0 by IHC on paraffin sections) • At least moderate microvascular inflammation ([g + ptc] ≥2), although in the presence of acute TCMR, borderline infiltrate, or infection; ptc ≥2 alone is not sufficient, and g must be ≥1 • Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated 3. Serologic evidence of DSAs (HLA or other antigens) • Biopsies suspicious for ABMR on the basis of meeting criteria 1 and 2 should prompt expedited DSA testing
Chronic active ABMR[†]	All three features must be present for diagnosis. As with acute/active ABMR, biopsy samples showing histologic features plus evidence of current/recent antibody interaction with vascular endothelium or DSA, but not both, may be designated as suspicious, and it should be noted if the lesion is C4d positive or C4d negative, based on the criteria listed: 1. Histologic evidence of chronic tissue injury, including one or more of the following: • TG (cg >0), if no evidence of chronic TMA; includes changes evident by EM only (cg1a; Table 4) • Severe peritubular capillary basement membrane multilayering (requires EM)[‡] • Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no history of biopsy-proven TCMR with arterial involvement but are not required 2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following: • Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d >0 by IHC on paraffin sections) • At least moderate microvascular inflammation ([g + ptc] ≥2), although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥2 alone is not sufficient and g must be ≥1 • Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated 3. Serologic evidence of DSAs (HLA or other antigens): • Biopsy results suspicious for ABMR on the basis of meeting criteria 1 and 2 should prompt expedited DSA testing
C4d staining without evidence of rejection	All three features must be present for diagnosis[§]: 1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d >0 by IHC on paraffin sections) 2. g = 0, ptc = 0, cg = 0 (by light microscopy and by EM if available), v = 0; no TMA, no peritubular capillary basement membrane multilayering, no acute tubular injury (in the absence of another apparent cause for this) 3. No acute cell-mediated rejection (Banff 1997 type 1A or greater) or borderline changes
Category 3: Borderline changes suspicious for acute TCMR	• Foci of tubulitis (t1, t2, or t3) with minor interstitial inflammation (i0 or i1) or interstitial inflammation (i2, i3) with mild (t1) tubulitis; retaining the i1 threshold for borderline from Banff 2005 is permitted, although this must be made transparent in reports and publications • No intimal arteritis (v = 0)

TABLE 107.1 Updated 2015 Banff Classification Categories—cont'd

Category 4: TCMR	
Acute TCMR	IA. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2 or i3) and foci of moderate tubulitis (t2) IB. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2 or i3) and foci of severe tubulitis (t3) IIA. Mild to moderate intimal arteritis (v1) with or without interstitial inflammation and tubulitis IIB. Severe intimal arteritis comprising >25% of the luminal area (v2) with or without interstitial inflammation and tubulitis III. Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
Chronic active TCMR	Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neointima); note that such lesions may represent chronic active ABMR as well as TCMR; the latter also may be manifest in the tubulointerstitial compartment
Category 5: Interstitial fibrosis and tubular atrophy (IFTA)	Grade I. Mild interstitial fibrosis and tubular atrophy (≤25% of cortical area) II. Moderate interstitial fibrosis and tubular atrophy (26%-50% of cortical area) III. Severe interstitial fibrosis and tubular atrophy (>50% of cortical area)
Category 6: Other changes not considered to be caused by acute or chronic rejection	BK virus nephropathy Post-transplant lymphoproliferative disorders Calcineurin inhibitor nephrotoxicity Acute tubular injury Recurrent disease *De novo* glomerulopathy (other than transplant glomerulopathy) Pyelonephritis Drug-induced interstitial nephritis

From reference 5.

*These arterial lesions may be indicative of ABMR, TCMR, or mixed ABMR/TCMR. The v lesions are scored in arteries only having a continuous media with two or more smooth muscle layers.

†Lesions of chronic, active ABMR can range from primarily active lesions with early TG evident only by EM to those with advanced TG and other chronic changes in addition to active microvascular inflammation. In the absence of evidence of current/recent antibody interaction with the endothelium (those features in the second section of Table 3), the term "active" should be omitted; in such cases, DSAs may be present at the time of biopsy or at any previous time after transplantation.

‡Seven or more layers in one cortical peritubular capillary and five or more in two additional capillaries, avoiding portions cut tangentially.

§The clinical significance of these findings may be quite different in grafts exposed to anti–blood group antibodies (ABO-incompatible allografts), in which they do not appear to be injurious to the graft and may represent accommodation; however, with anti-HLA antibodies, such lesions may progress to chronic ABMR and more outcome data are needed.

ABMR, Antibody-mediated rejection; *cg,* glomerular double contours; *DSA,* donor-specific antibody; *EM,* electron microscopy; g, glomerulitis; i, inflammation; IF, immunofluorescence; IHC, immunohistochemistry; *ptc,* peritubular capillaritis; *t,* tubulitis; *TCMR,* T cell–mediated rejection; *TG,* transplant glomerulopathy; *TMA,* thrombotic microangiopathy; *v,* intimal arteritis.

Cardiovascular Risk Factors

The vasculopathy in chronic allograft injury resembles systemic vascular disease, raising the possibility that conventional cardiovascular disease risk factors may be implicated. Hypertension occurs in about 70% to 90% of transplant recipients and predisposes to graft failure.[28] Dyslipidemias, including raised total cholesterol, low-density lipoprotein cholesterol, and triglycerides, and cigarette smoking have also been associated with late graft failure. The management of CV risk factors in the transplant recipient is discussed in Chapter 106.

PATHOGENESIS: IMMUNOLOGICAL FACTORS

T Cell–Mediated Rejection

Acute T cell–mediated rejection, vascular or corticosteroid-resistant rejection, subclinical rejection, and late (chronic-active) T cell–mediated rejection all contribute to the burden of chronic allograft injury. Early acute T cell–mediated rejection (within 3 months of transplantation) that is adequately diagnosed and treated usually has no impact on long-term graft survival. But late chronic-active T cell–mediated rejection in which serum creatinine does not return to baseline usually translates into IFTA and/or vascular damage, contributing to graft injury. Multiple and severe late acute T cell–mediated rejection episodes are predictive of chronic graft dysfunction more than early cellular rejection and acute vascular rejection, which have stronger associations with acute graft loss.[29] There is some evidence from protocol biopsy studies that subclinical T cell–mediated rejection may be an important factor contributing to chronic graft injury.[30,31]

Besides the direct effects of T cell–mediated rejection on graft function, acute T cell–mediated rejection may be linked to the development of DSA and subsequent antibody-mediated rejection.[32]

Antibody-Mediated Rejection

Chronic antibody-mediated rejection is a leading cause of graft loss, together with death with a functioning graft, recurrent renal disease, and IFTA of unknown origin.[33]

For the diagnosis of antibody-mediated kidney graft rejection, histologic features of antibody-mediated rejection in the biopsy sample (Figs. 107.2 to 107.4), together with evidence of current or recent antibody

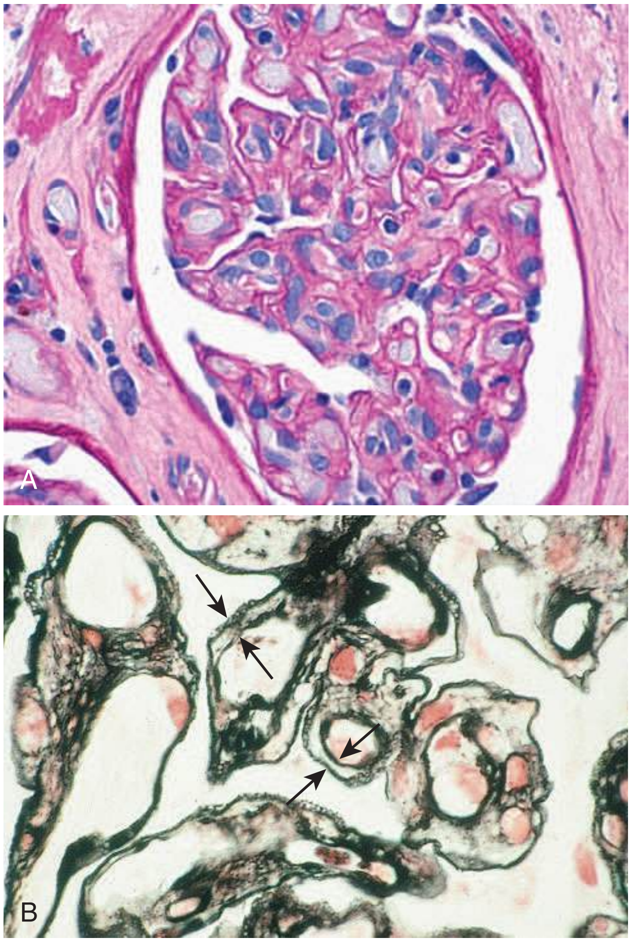

Fig. 107.2 Transplant glomerulopathy: light microscopy. (A) Note the mesangial expansion and thickening of the glomerular basement membrane (GBM). (B) Note the GBM reduplication in capillary loops *(between arrows).*

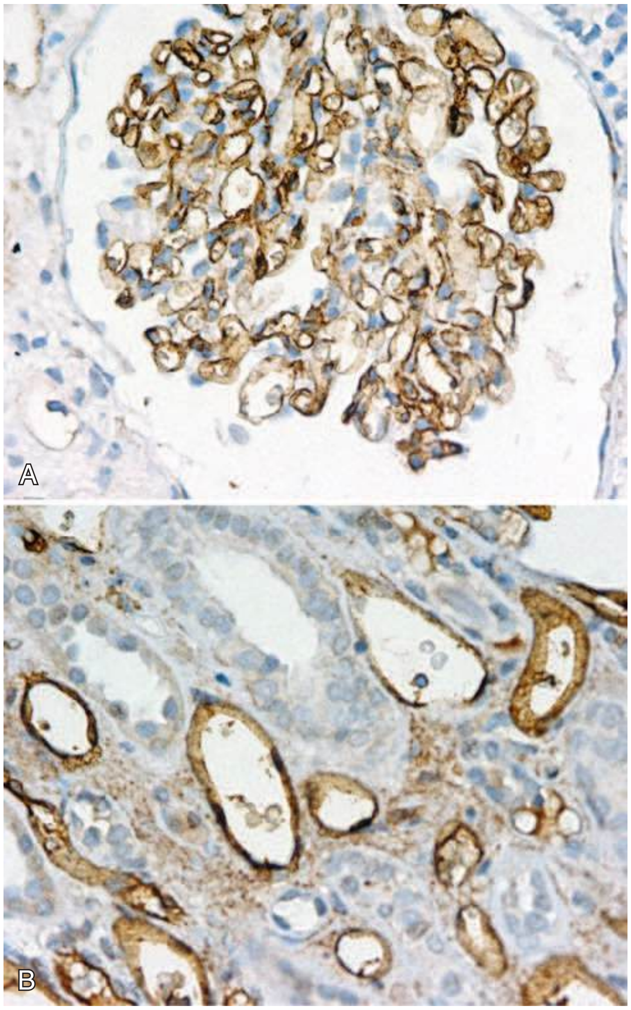

Fig. 107.3 C4d immunoperoxidase staining in association with chronic antibody-mediated rejection. Staining of glomerular capillaries (A) and circumferential staining of peritubular capillaries (B) are typical.

interaction with the vascular endothelium (see Fig. 107.3) and the detection of circulating DSA (either HLA or non-HLA) are required. Because C4d in peritubular capillaries is not detectable in more than 50% of patients with chronic antibody-mediated rejection, C4d-positivity is no longer a prerequisite for the diagnosis of antibody-mediated rejection.[6] This finding, together with the observation that chronic antibody-mediated rejection may occur in the absence of complement activation (e.g., the occurrence of transplant glomerulopathy in patients during effective therapeutic complement inhibition by eculizumab) led to the hypothesis that complement-independent mechanisms such as direct endothelial cell activation and infiltration of natural killer (NK) cells or monocytes may contribute to chronic antibody-mediated allograft injury. C4d-negative antibody-mediated rejection shares the same histologic and ultrastructural features as C4d-positive rejection. To improve the diagnosis of antibody-mediated rejection, a molecular microscope strategy was adopted in the 2013 update of the Banff classification.[34] This means that in the absence of C4d positivity or microvascular inflammation, antibody interaction with the vascular endothelium is also suggested by detection of an increased expression of specific gene transcripts in the biopsy tissue indicative of endothelial injury (the “molecular microscope”), though this approach still needs further validation.

Unrecognized DSAs, if strongly reactive and complement-activating, can cause hyperacute rejection or accelerated antibody-mediated rejections in the early phase after kidney transplantation. Acute antibody-mediated rejection in the early phase occurs in about 1% to 6% of patients overall, but in as much as 21% to 55% in patients who had detectable DSAs already before transplantation and who received desensitization therapy.[35-37] Weakly positive DSAs have been associated with rather subtle types of graft damage, often leading to delayed graft function.[2] Early damage can lead to chronic rejection, most probably because the structure of the endothelium is no longer intact and new antigenic epitopes are expressed on the surface of transplanted tissue. During later phases after transplantation, insufficient immunosuppression can facilitate the development of *de novo* DSAs against these new epitopes and result in chronic antibody-mediated rejection and failure of the transplanted organ. *De novo* DSAs, but to a lesser extent also persistence or reemergence of DSAs that were detectable before transplantation, are associated with poor allograft outcome.

Chronic antibody-mediated rejection is found more frequently in patients who are nonadherent to immunosuppressive medication or in whom immunosuppression was reduced for other reasons, such as conversion to CNI-free or steroid-free immunosuppressive protocols, recurrent infection, or malignancy.[38-40] In these patients, antibody-mediated lesions and T cell–mediated lesions are often found in kidney graft biopsy samples at the same time. Additional risk factors for the development of *de novo* DSAs and antibody-mediated rejection are HLA class II DR mismatches between donor and recipient, prior cellular

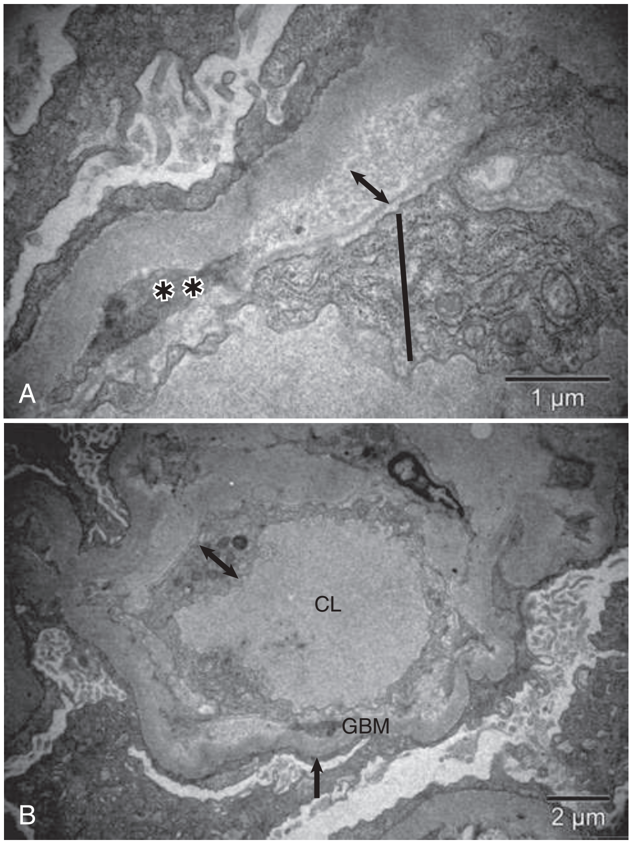

Fig. 107.4 **Transplant glomerulopathy: electron microscopy.** (A) Section of a glomerular capillary loop (×24,000) demonstrating mesangial interposition *(asterisks)*, subendothelial expansion and new lamina densa *(double arrow)*, and endothelial hypertrophy *(line)*. (B) A complete glomerular capillary loop *(CL)* with glomerular basement membrane *(GBM)* thickening *(single arrow)*, endothelial hypertrophy *(double arrow)*, expanded subendothelial space, and new lamina densa *(single arrow)*. Apparent GBM duplication is a result of mesangial interposition and formation of new lamina densa.

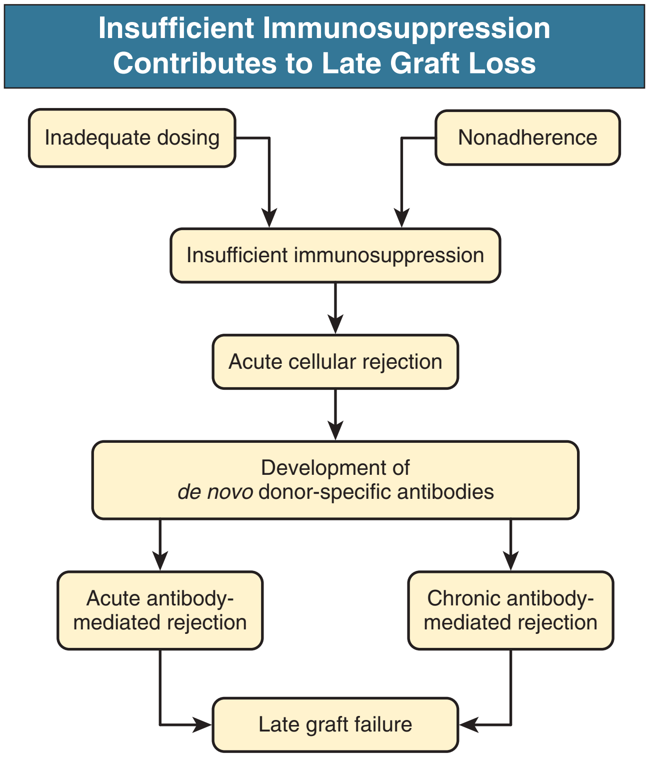
Insufficient Immunosuppression Contributes to Late Graft Loss
Inadequate dosing
Nonadherence
Insufficient immunosuppression
Acute cellular rejection
Development of de novo donor-specific antibodies
Acute antibody-mediated rejection
Chronic antibody-mediated rejection
Late graft failure

Fig. 107.5 Insufficient immunosuppression contributes to late graft loss.

rejection episodes and younger recipient age. In many patients with late antibody-mediated graft loss, even when HLA class I alloantibodies are detectable, HLA class II *de novo* DSAs are considered to be mainly responsible for rejection. In a recent study on the evolution of HLA alloantibodies after transplantation, *de novo* DSAs appeared at a mean of 4.6 years after transplantation, and the prevalence of *de novo* DSAs after 10 years was 20% in those adherent to the immunosuppressive regimen, compared with 60% in nonadherent graft recipients.[40] In another study, DSAs were found in 37% of patients who had an indication biopsy 7 days to 31 years after transplant.[4] *De novo* DSAs that were directed against HLA class II antigens had an especially strong association with strongly impaired graft survival. A recent development for the detection of harmful DSAs is the introduction of solid-phase assays into a clinical routine, which enables the distinction of complement-binding (C1q assay) HLA antibodies from antibodies that do not bind complement. It was recently demonstrated that the post-transplant occurrence of complement-binding DSA in a cohort of more than 1000 patients was associated with adverse events. The 5-year graft survival in patients with complement-binding antibodies was 54% compared with 93% in patients with DSAs that were not able to bind complement. The higher risk for graft loss in patients with complement-binding DSAs was attributable to a higher risk for chronic antibody-mediated rejection.[41] Recent preliminary data also suggest that DSAs of different immunoglobulin G subclasses may be associated with different distinct injury phenotypes in kidney allograft biopsies.

Other antibodies that may contribute to chronic antibody-mediated rejection are MHC class I–related chain A antibodies, angiotensin II type 1 receptor–activating antibodies, and other antiendothelial cell antibodies.[42,43]

Insufficient Immunosuppression and Nonadherence to Medication

The recognition that HLA alloantibodies are responsible for a great proportion of late graft losses[33,44] has focused attention on the role of insufficient immunosuppression and nonadherence to immunosuppressive medication as significant factors in chronic graft loss (Fig. 107.5).[38,45]

A retrospective analysis of more than 25,000 kidney transplant recipients showed that reduction or discontinuation of cyclosporine, tacrolimus, or mycophenolate mofetil after the first post-transplant year in patients with good graft function was associated with significantly reduced subsequent kidney graft survival.[38] In a recent study in which 64% of graft losses in a cohort with indication biopsies were attributable to (antibody-mediated) rejection, about half of the patients with rejection-associated allograft loss were identified as nonadherent.[45]

Young adults who are in transition from pediatric to adult nephrology care are at high risk for nonadherence. Other risk factors are previous nonadherence, psychiatric disorders, substance abuse, insufficient socioeconomic support, and adverse effects from immunosuppressive medication. Insufficient immunosuppression may also occur during immunosuppressive minimization (tapering) or CNI-avoidance trials. In a recent study, 14 of 61 patients (23%) who were converted from cyclosporine to everolimus at 3 to 4.5 months after transplantation developed DSA, compared with only 7 of 65 patients (11%) who continued on cyclosporine.[35] Eight patients on everolimus but only two patients on cyclosporine developed antibody-mediated rejection.

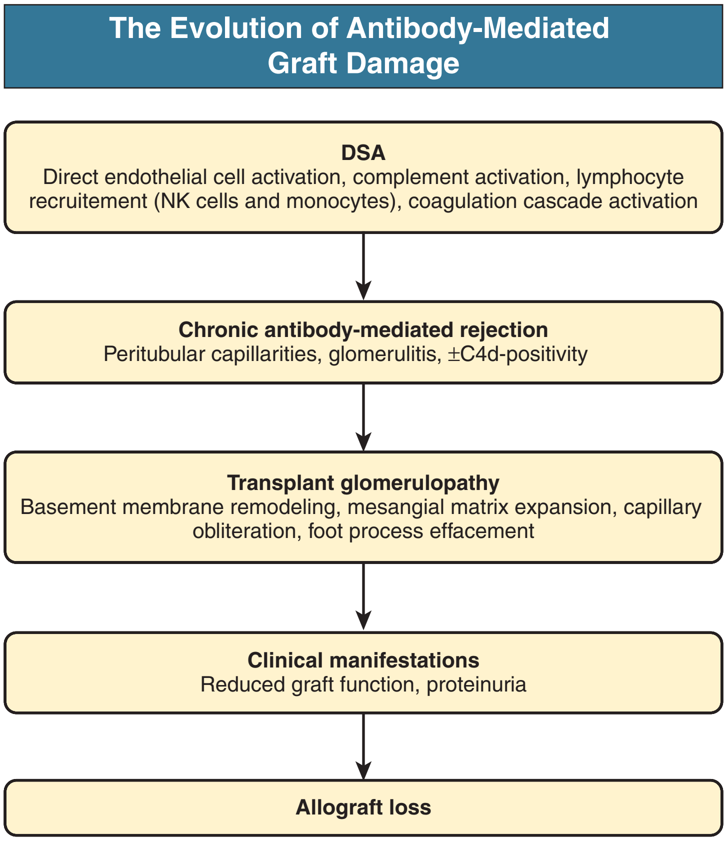
The Evolution of Antibody-Mediated Graft Damage
DSA
Direct endothelial cell activation, complement activation, lymphocyte recruitement (NK cells and monocytes), coagulation cascade activation
Chronic antibody-mediated rejection
Peritubular capillarities, glomerulitis, ±C4d-positivity
Transplant glomerulopathy
Basement membrane remodeling, mesangial matrix expansion, capillary obliteration, foot process effacement
Clinical manifestations
Reduced graft function, proteinuria
Allograft loss

Fig. 107.6 The evolution of antibody-mediated graft damage from the binding of DSA to graft loss. *DSA,* Donor-specific antibodies; *NK,* Natural killer.

Therefore these patient cohorts should be rigorously evaluated for the development of alloantibodies and antibody-mediated allograft injury according to Transplantation Society Guidelines (see later).[46]

CLINICAL MANIFESTATIONS

Routine laboratory evaluation of graft function does not facilitate the early diagnosis of chronic allograft injury. A rise in serum creatinine is a late marker of allograft dysfunction. Reduction in the glomerular filtration rate is usually estimated by equations such as the Modification of Diet in Renal Disease (MDRD) formula or the chronic kidney disease epidemiology collaboration (CKD-EPI) formula. However, substantial nephron loss may occur before a rise in serum creatinine becomes evident.

Persistent or worsening proteinuria is also a late sign of chronic allograft injury. Proteinuria greater than 1 g/day typically occurs with recurrent or *de novo* GN or with severe chronic antibody-mediated changes such as transplant glomerulopathy (see Figs. 107.2 to 107.4). A definite diagnosis of antibody-mediated rejection requires transplant kidney biopsy together with serologic testing for alloantibodies and viral disease such as BK virus or cytomegalovirus infection. So far, no noninvasive tests can reliably diagnose antibody-mediated rejection. The evolution of antibody-mediated graft damage from the binding of DSAs to graft loss is given in Fig. 107.6.

PATHOLOGY

Chronic IFTA (Fig. 107.7) represents the final pathway of nephron injury and is not specific for any graft disease. IFTA is found in most late graft biopsies, whether a result of early graft damage (e.g., tubular injury from ischemia reperfusion injury, overt or subclinical rejection, or even preexisting disease of the donor) or later graft damage (secondary to CNI toxicity, hypertension and hyperlipidemia, recurrent glomerular disease, or immune-mediated injury) or of unknown origin (IFTA).

Chronic antibody-mediated rejection is characterized by structural remodeling of glomerular basement membranes (GBMs) (so-called transplant glomerulopathy) and similar changes in the peritubular capillaries together with IFTA and fibrous thickening of arteries (see Figs. 107.2 to 107.4). Transplant glomerulopathy is characterized by duplication of glomerular capillary basement membranes and mesangial matrix expansion, in the absence of immune deposits. In addition, deposition of C4d in peritubular and glomerular capillaries can sometimes occur (see Fig. 107.3). Clinicopathologic studies suggest that transplant glomerulopathy is a manifestation of capillary injury occurring in conjunction with interstitial, peritubular capillary, and glomerular inflammation, although it also may occur independently of IFTA or transplant arteriopathy.[47] On electron microscopy, there is expansion of the subendothelial space with deposition of flocculent or fibrillary material, interposition of mesangial cell cytoplasm in the lamina densa, and mesangial matrix expansion (see Fig. 107.4). Electron microscopy may be used to diagnose transplant glomerulopathy at its earliest stages. Ultrastructural abnormalities characteristic of endothelial activation occur long before GBM duplication and graft dysfunction are evident, implying that endothelial injury is the initial insult that resulted in GBM remodeling.[48] An association between transplant glomerulopathy and peritubular capillary basement membrane duplication has been well described, suggesting that the process resulting in transplant glomerulopathy involves the entire glomerular and peritubular capillary

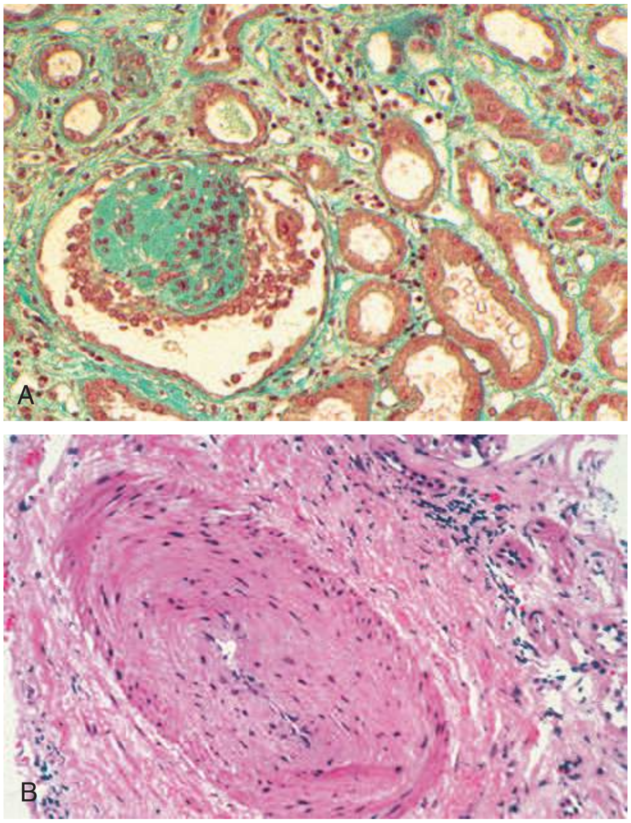

Fig. 107.7 Histologic features of chronic allograft injury and interstitial fibrosis–tubular atrophy with no evidence of specific cause. (A) Interstitial fibrosis and glomerulosclerosis. (Trichrome stain.) (B) Fibrointimal proliferation in an intrarenal artery. (Periodic acid–Schiff stain.)

beds.[49,50] It is currently debated whether transplant glomerulopathy represents scarring that is refractory to treatment.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

When chronic allograft injury has been identified by a gradual rise in serum creatinine and/or by new or worsening proteinuria, ultrasound should be performed to exclude ureteral or vascular problems and assess the Doppler resistive index. The Doppler resistive index gives an estimate of intrarenal (but also systemic) compliance and is most useful in longitudinal studies in the same patient to assess progressive graft vascular injury.

In addition, testing for BK virus in plasma is also advised during deteriorating graft function and for all kidney transplant recipients at 3-month intervals during the first 2 years after transplantation. Circulating HLA alloantibodies also should be documented during graft dysfunction and may further guide diagnostics and therapy. Many centers now perform routine HLA alloantibody screening in stable graft recipients at different time points after transplantation to facilitate early diagnosis of antibody-mediated rejection. According to the 2013 The Transplantation Society Consensus Guidelines, nonsensitized first kidney transplant recipients should be screened for DSAs at least once 3 to 12 months after transplantation.[46] In presensitized patients, more frequent screening is recommended. Although there is consensus that HLA alloantibodies are responsible for a significant proportion of late graft losses and that HLA antibodies in the context of deteriorating graft function are harmful, the significance of HLA alloantibodies that are detected solely during routine screening remains uncertain.[51,52]

Allograft biopsy is required to rule out a specific allograft pathology together with specific stainings, such as C4d, for detection of antibody-mediated allograft injury in all patients and SV40 if there is suspicion for BK virus nephropathy. Other specific examinations of the biopsy specimen for immunoglobulins, complement components, or electron microscopy may in addition be useful to rule out recurrence of primary renal disease or *de novo* GN. The role of protocol biopsies in the early detection of chronic allograft injury remains controversial.

Because the etiology of chronic allograft dysfunction is multifactorial, any specific diagnosis is made by combination of a biopsy with a review of the patient's history to identify important etiologic factors, such as preexisting donor disease, prior rejection, and high-titer anti-HLA antibodies, as well as issues not related to alloimmunity, such as CNI nephrotoxicity, *de novo* GN, or recurrent renal disease. Chronic allograft dysfunction is common and can have many causes. If it is left untreated, it can ultimately result in renal injury, which in turn will heal by scarring and interstitial fibrosis and progress to end-stage kidney disease.

Prevention of Antibody-Mediated Allograft Injury

In the absence of established treatments of circulating DSAs and chronic antibody-mediated rejection, only prevention of antibody-mediated allograft injury is effective in preventing future graft loss. Once harmful HLA antibodies such as C1q-binding DSA are detectable, it becomes very difficult to avoid allograft injury and decline of kidney function. Preventive measures include avoidance of sensitization by limitation of blood transfusions and poor HLA matching during first transplantations.[53,54] The introduction of erythropoietin about 20 years ago led to a dramatic decrease of recipient sensitization by a significant reduction in blood transfusions.[54] Sensitization should especially be avoided in young patients who may require retransplantation during their lifetime. New measures, such as matching for antibody epitopes in addition to whole HLA alleles may further help preventing sensitization.

When the patient is already sensitized, antibody-mediated allograft injury can best be prevented by transplantation of the patient with an organ against which the recipient has not developed HLA alloantibodies. This may be achieved by inclusion of patients in special programs such as Eurotransplant Acceptable Mismatch Program or by kidney-paired donation.[55,56] However, successful transplantation in patients with preexisting HLA alloantibodies usually requires desensitization in combination with other measures.[57]

After transplantation, chronic antibody-mediated allograft rejection is best prevented by conventional triple-drug therapy including a CNI (preferably tacrolimus), an antiproliferative agent (preferably mycophenolic acid–based therapy), and corticosteroids. Induction therapy, with an interleukin-2 receptor antagonist or antithymocyte globulin, should be used to prevent early acute cellular rejection.

Insufficient immunosuppression and nonadherence may lead, unless a patient is prone to tolerance, to cellular rejection and then, via development of *de novo* DSA, to antibody-mediated rejection and graft loss. Precise knowledge of the patient's alloantibody status before and after transplantation is a prerequisite for early diagnosis of allograft injury and early and targeted treatment to prevent antibody-mediated rejection and ensure long-term graft survival. HLA alloantibodies should be tested at least once after transplantation in all patients. In immunologically high-risk patients, desensitized patients, patients with suspected rejection, and during therapy of antibody-mediated rejection, antibodies need to be monitored more frequently with the goal of recognizing allograft injury in its early stages, and preventing its progression to chronic rejection.[46] Additional patient groups who may benefit from HLA alloantibody monitoring are patients who receive reduction, withdrawal, or change of immunosuppressive drugs, especially in the context of CNI- or steroid-free regimens. Protocol biopsies may

BOX 107.2 Strategies for the Prevention of Chronic Allograft Injury

- Avoid sensitization in future organ recipients (e.g., avoid blood transfusions, avoid poor HLA matching during first transplantation).
- Obtain complete donor and recipient typing and precise knowledge on HLA alloantibodies at time of transplantation.
- Minimize ischemia/reperfusion injury (e.g., short cold ischemia time).
- Avoid insufficient immunosuppression.
- Perform prophylaxis for CMV (first 3 to 6 months).
- Screen for BK virus after transplantation.
- Monitor donor-specific HLA alloantibodies after transplantation (at least in presensitized patients or during drug minimization).
- Perform protocol biopsies to detect subclinical rejection (at least in presensitized patients or during drug minimization).
- Review for nonadherence.

CMV, Cytomegalovirus; *HLA,* human leukocyte antigen.

BOX 107.3 Treatment of Chronic Allograft Injury

Treatment (Nonimmune)

- Treat hypertension (consider ACE inhibitors or AT_1 receptor antagonists)
- Lifestyle modification (stop smoking, control lipids)
- Control diabetes
- Prevention and treatment of urinary tract infection
- Target CNI toxicity by reduction or replacement of CNI (caveat: risk for insufficient immunosuppression)

Treatment (Alloimmune)

- Diagnose and treat early acute cellular rejection by steroids or antithymocyte globulin
- Diagnose and treat acute antibody-mediated rejection by means such as plasmapheresis or immunoadsorption ± anti-CD20 therapy
- Diagnose and treat chronic antibody-mediated rejection by means such as intravenous immunoglobulins ± anti-CD20 therapy
- Consider proteasome inhibitor or complement blockade (no clear evidence)

ACE, Angiotensin-converting enzyme; *AT_1,* angiotensin 1 receptor; *CNI,* calcineurin inhibitor.

further help in guiding post-transplant therapy at least in high-risk recipients, although definitive proof is lacking.

Strategies for the prevention of chronic allograft injury are summarized in Box 107.2.

Treatment of Chronic Allograft Injury

Although reduction of blood pressure to a target of less than 130/80 mm Hg is believed to be beneficial, the preferred agent for blood pressure reduction remains controversial; in particular the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers has not uniformly shown benefit.[58,59] Nor have there been specific studies confirming the benefits of reducing proteinuria in chronic allograft injury, although by extrapolation for other progressive proteinuric diseases, there is strong a priori evidence for the benefits of renin-angiotensin system blockade with dietary salt restriction.

A beneficial effect of treating dyslipidemia with statins in the transplant recipient also remains controversial,[60-62] and the adverse effects of statins such as rhabdomyolysis when used with CNIs must be considered. After a specific diagnosis had been established, targeted treatments can be initiated. These are summarized in Box 107.3.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is believed to be mainly responsible for late kidney graft loss?
   A. Hypertension and hyperlipidemia
   B. New-onset diabetes after transplantation
   C. Recurrence of primary disease
   D. Human leukocyte antigen (HLA) alloantibodies
   E. Calcineurin inhibitors
2. Chronic antibody-mediated rejection:
   1. May be C4d negative in graft biopsy samples
   2. Has specific histopathologic features
   3. Is found more often in patients nonadherent to immunosuppressive medication
   4. Can be mediated only by HLA alloantibodies
   5. Is targeted by reduction of immunosuppression
      A. Only 1 and 2 are correct.
      B. Only 1, 2, 3, and 4 are correct.
      C. Only 1, 2, and 3 are correct
      D. All answers are correct.
      E. No answer is correct.
3. Clinical manifestations of chronic antibody-mediated rejection are:
   1. A rise in serum creatinine
   2. A rise in protein excretion
   3. Specific for chronic antibody-mediated rejection
   4. Often late signs that occur after significant allograft damage has already occurred
      A. Only 1 is correct.
      B. 1 and 2 are correct.
      C. All answers are correct.
      D. 1, 2, and 3 are correct.
      E. 1, 2, and 4 are correct.

108

Recurrent Disease in Kidney Transplantation

Steven J. Chadban, Melanie Wyld

Kidney transplantation is a treatment, not a cure. Although transplantation may restore kidney function, it does not necessarily remove the cause of the original kidney disease. Glomerulonephritis (GN) and diabetes are the two leading causes of end-stage renal disease (ESRD) worldwide, and they are also the most common primary diseases of patients who undergo kidney transplantation. That both diseases can recur after transplantation is a source of concern for recipients and clinicians.

The longer that a graft remains in situ, the more likely it is to be affected by recurrence. As graft survival rates have increased over the past 30 years, the apparent incidence of recurrence has grown.[1] An analysis of U.S. Renal Allograft Disease Registry data examining GN recurrence demonstrated a prevalence of 2.8% at 2 years, 9.8% at 5 years, and 18.5% at 8 years of follow-up after transplantation, and such patients were twice as likely to experience graft failure compared with those without recurrence.[2]

Recurrence has a powerful impact on transplant survival and one that is increasingly apparent with time after transplantation. In an analysis of data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) including more than 1500 patients with biopsy-proven GN who received a kidney transplant, biopsy-proven recurrence was found to cause graft loss in 0.5% within 1 year after transplantation, 3.7% within 5 years, and 8.4% within 10 years after transplantation[3] (Fig. 108.1). This study and several others have found recurrent disease to be the third most common cause of graft failure beyond the first year after transplantation, behind death with a functioning graft and chronic rejection (CR), but substantially ahead of acute rejection[3] (see Fig. 108.1).

De novo GN and new-onset diabetes after transplantation (NODAT) may affect the transplanted kidney, although both are relatively uncommon causes of graft failure and may be difficult to distinguish from recurrence or from CR. Like recurrent disease, the prevalence of both appears to increase with time after transplantation. Given the high incidence of NODAT and increasing graft survival,[4] de novo diabetic nephropathy may become a significant clinical problem in the future. However, at present the major impact of NODAT in the first 10 years after transplantation is an increase in cardiovascular mortality with little impact on death-censored graft failure.[5]

DEFINITIONS

Diagnosis of recurrence requires histologic demonstration of the same disease involving both the native and transplanted kidneys. Diagnosis of recurrence causing graft failure requires a clinical decision that recurrence was the dominant contributor to graft loss (other contributors, such as CR, may be present).

The incidence of recurrent disease is probably underestimated because a histologic diagnosis of the primary kidney disease is not always obtained, and many transplant biopsies are not done with recurrent disease in mind, so immunohistologic and electron microscopic examination (mandatory for optimal diagnosis of recurrent disease) may not be undertaken.[1] In addition, a clinical diagnosis of CR is often made in patients with declining graft function and proteinuria, so that recurrent disease is not properly excluded.

Additional factors confound the available evidence. Many reports of disease recurrence are retrospective, single-center studies. Recall bias and incomplete documentation, changes in practice over time, and peculiarities of local patient populations and local practices may limit relevance to other populations. The most definitive reports have come from analyses of the large registry databases of Europe, the United States, and Australasia. Registries capture data on large numbers of patients but are still subject to bias because of factors including unit participation rates, quantity and type of data collected, accuracy, consistency of reporting, and reliability of data entry. How recurrence is defined and diagnosed and which outcomes are measured is crucial. For example, immunoglobulin A (IgA) nephropathy (IgAN) recurred in 58% of patients in one series in which all recipients underwent biopsy,[6] but in approximately 25% of cases in which biopsy was performed only when clinically indicated.[7] When graft loss from IgAN recurrence is the outcome measure, the risk decreased to approximately 10% at 10 years of follow-up.[3] Thus definition of recurrence, outcome measures, study design, era, and source of data all need to be considered in assessing the published literature.

RECURRENT GLOMERULONEPHRITIS

Virtually all GN may recur after transplantation; however, the rate and consequences of recurrence vary enormously. For example, anti–glomerular basement membrane (GBM) disease (Goodpasture disease) recurs only rarely, but when it does, it is likely to cause rapid graft loss. In contrast, C3 glomerulopathy (formerly known as dense deposit disease and/or type II membranoproliferative glomerulonephritis [MPGN]) recurs in more than 80% of patients; however, the disease tends to be very slowly progressive, and graft survival beyond 10 years is typical. Recurrence of focal segmental glomerulosclerosis (FSGS), IgAN, and membranous nephropathy (MN) are the most frequently encountered clinical problems (Fig. 108.2).

Several factors may influence the risk for recurrence in addition to the type of GN. Time since transplantation is clearly important and may be related to the duration of graft exposure to the nephritogenic factors responsible for GN.[1] Those grafts that survive long term are exposed to nephritogenic factors for longer and are more likely to develop

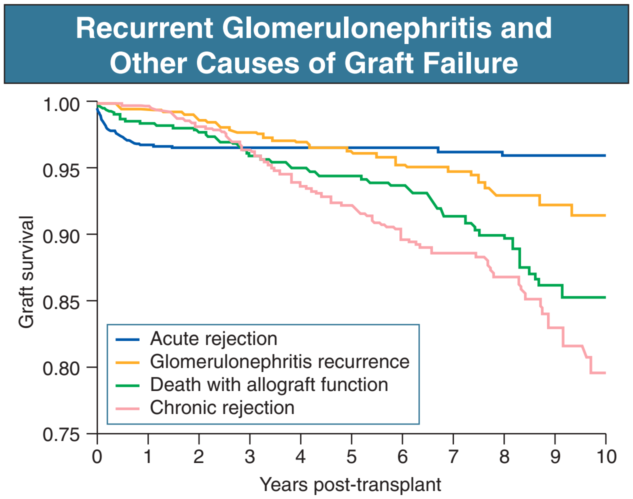

Fig. 108.1 Recurrent glomerulonephritis (GN) and other causes of graft failure. Kaplan-Meier analysis of the relative contributions of acute rejection, GN recurrence, death, and chronic rejection to graft loss during the first 10 years after transplantation among patients who underwent transplantation because of end-stage renal disease caused by GN. (Modified from reference 3.)

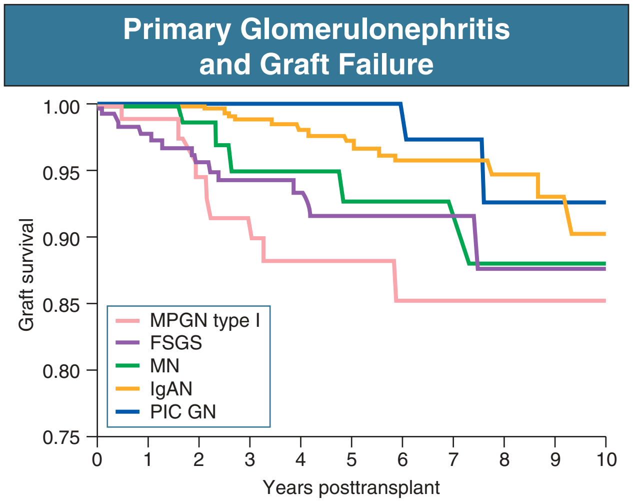

Fig. 108.2 Primary glomerulonephritis (GN) and graft failure. Kaplan-Meier analysis of freedom from graft loss caused by recurrent GN during the first 10 years after kidney transplantation among patients with a primary diagnosis of GN. *FSGS,* Focal segmental glomerulosclerosis; *IgAN,* IgA nephropathy; *MN,* membranous nephropathy; *MPGN,* membranoproliferative glomerulonephritis; *PIC GN,* pauci-immune crescentic glomerulonephritis. (Modified from reference 3.)

recurrent GN. Consistent with this, recipients of human leukocyte antigen (HLA)-identical transplants rarely experience rejection and enjoy prolonged graft survival but have a high rate of recurrent GN.[8] In one report of HLA-identical recipients, recurrent GN was present in 36% to 42% of those in whom biopsy was performed and resulted in 24% of graft losses, being the second most frequent cause of graft loss after death in this group.[8] Patients sustaining first graft loss from recurrent GN are also at higher risk for recurrence in a subsequent graft.

Improvements in immunosuppression over the past 40 years have led to reduced rates of acute rejection. Such improvements also may have had an impact on rates of graft loss from GN recurrence, which have declined by nearly 50% over the past 10 years according to one ANZDATA registry analysis.[9]

U.S. Renal Data System (USRDS) registry data failed to demonstrate superiority of any individual immunosuppressive agent on the incidence of recurrence.[10] Nevertheless, the immunosuppressive regimen may be important. For example, one small retrospective study found that induction therapy with rabbit antithymocyte globulin was associated with a lower risk for IgAN recurrence compared with either anti-CD25 antibodies or no induction.[11] Corticosteroid withdrawal may lead to increased rates of recurrence,[12] especially in recipients with IgAN, in whom a twofold increase in the risk for graft failure from recurrence of IgAN has been reported.[9] Similarly, inclusion or addition of cyclophosphamide to immunosuppressive regimens may treat recurrent vasculitis affecting the graft.[13] The use of sirolimus may result in proteinuria and renal dysfunction, especially in patients with underlying GN, suggesting that sirolimus may accelerate glomerular injury in the graft.[14] Effects of individual agents are likely to be disease-specific, but the necessary data remain sparse.

Strategies to reduce the risk for recurrence have been reported. Bilateral native nephrectomy to eliminate persistent antigenic stimulation appears unhelpful; indeed, nephrectomized patients experienced a higher incidence of recurrence compared with those with native kidneys left in situ in one large single-center, retrospective study.[15] Induction of disease remission before transplantation and prolonged time on dialysis pretransplantation (both aimed at permitting disease "burnout") do not appear to be effective except in the case of anti-GBM disease, in which a delay in transplantation until the patient has been serologically negative for at least 6 months virtually eliminates the risk for recurrence.[3] Avoiding living related donation to recipients with FSGS has been debated for years but overall appears not to have any impact on risk for recurrence.[16]

As with GN in native kidneys, proteinuria, hematuria, and deterioration in kidney function are the cardinal manifestations of recurrent GN. The pattern of renal and extrarenal manifestations is frequently similar to that of the native disease, except that, in our opinion, the overall rate of progression may be slower. Extrarenal features of the primary condition may recur, such as thrombocytopenia and hemolysis in hemolytic uremic syndrome (HUS) and extrarenal vasculitis in recurrent antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Serology may be helpful in some patients, such as anti-GBM antibody detection in those with Goodpasture disease, but not necessarily in others, such as those with recurrent lupus nephritis (LN).

The differential diagnosis of recurrent GN is clinically important because it may influence management (Table 108.1). CR and diabetic nephropathy, recurrent or de novo, may manifest with progressive graft dysfunction, proteinuria, and hypertension and may therefore be clinically indistinguishable from recurrence. De novo GN also should be considered. Viral diseases of the kidney should be considered (particularly BK nephropathy) because reducing immunosuppression and instituting antiviral therapy may provide benefit. Obstructive uropathy and tumors involving the graft should be excluded by an ultrasound scan. Finally, recurrence may coexist with CR or calcineurin inhibitor (CNI) toxicity. Indeed, every condition that can lead to chronic graft dysfunction should be considered in the differential diagnosis of recurrence (see Table 108.1 and Chapter 107).

Histologic evidence of recurrence is required in all patients. Biopsy can provide the diagnosis, exclude alternative diagnoses that may require different approaches to treatment, and provide important prognostic information pertinent to the affected graft and also relevant to any future consideration of retransplantation. Full evaluation of the biopsy specimen by light microscopy, immunohistology, and electron microscopy is desirable and in many patients essential

TABLE 108.1 Differential Diagnosis of Recurrent Glomerulonephritis

Diagnosis	Frequency and Timing	Clinical Features	Laboratory Features	Biopsy Features	Management
Recurrent glomerulonephritis	Common; variable timing, days to years	Proteinuria, hematuria, renal impairment, hypertension	Similar to primary glomerulonephritis; serology may be negative	Same as primary glomerulonephritis[4,5]	Disease specific
De novo glomerulonephritis	Uncommon; variable timing but typically later than recurrence	Proteinuria, hematuria, renal impairment	Type specific	Type specific[4,5,8]	Antiprogression strategies (see Chapter 79)
Chronic rejection	Very common; increasing incidence with time	Hypertension, proteinuria, renal impairment Calcineurin inhibitor exposure		Tubulointerstitial fibrosis, arteriolar hyalinosis, transplant glomerulopathy	Minimize calcineurin inhibitor and antiprogression strategies (see Chapter 79)
Graft pyelonephritis	Uncommon; typically early after transplantation	Fever, pyuria, renal impairment	Positive blood or urine cultures	Neutrophil infiltration	Antibiotics
BK nephropathy	Uncommon; typically 1-5 y after transplantation	Renal impairment, decoy cells in urine	Serum BK PCR positive	Tubulitis with tubular cell atypia and inclusions, normal glomeruli	Minimize immunosuppression and consider antiviral drugs
Acute rejection	Common; early	Renal impairment, oliguria	Nonspecific	Tubulitis with or without vasculitis[15]	Increase immunosuppression
Renal tumor/PTLD	Uncommon, rare; early or late	Renal impairment, renal mass	Anemia, EBV positive	Atypical cells, mitoses, monoclonality	Minimize immunosuppression, consider chemotherapy

EBV, Epstein-Barr virus; *PCR,* polymerase chain reaction; *PTLD,* post-transplantation lymphoproliferative disease.

to confirm recurrence.[17] Light microscopy and immunohistology are necessary to differentiate recurrent from de novo GN, rejection, and CNI toxicity. The presence of tubulitis should suggest acute rejection. CR may produce chronic interstitial inflammation and transplant glomerulopathy, which may be indistinguishable from MPGN on light microscopy (Fig. 108.3; see also Chapter 107). The use of immunohistology to define the immunoglobulin and complement component content of immune deposits and electron microscopy to establish the structure of basement membrane and location of deposits may clarify the diagnosis.[17] The risk for recurrence in common patterns of renal disease is summarized in Table 108.2.

RECURRENCE OF SPECIFIC GLOMERULAR DISEASES

Immunoglobulin A Nephropathy and IgA Vasculitis (Henoch-Schonlein Purpura)

IgA nephropathy is the most common form of GN leading to ESRD, and affected patients frequently become transplant recipients. Histologic recurrence is frequent and increases with time since transplantation. Published recurrence rates vary greatly (from 8% to 53%). Much of this variation appears to be due to study differences in biopsy indication (protocol or clinical) and length of post-transplant follow-up.[18] The highest published recurrence rates are from centers performing protocol biopsies in addition to those that are clinically indicated. This is likely because the early stages of IgAN recurrence are frequently not accompanied by clinical changes, such as proteinuria, hematuria, or graft dysfunction.[18]

Recurrence is difficult to predict. No large, prospective, multicenter cohort studies demonstrate risk factors for histologic and/or clinical recurrence. Single-center studies and registry analyses suggest that including younger age at transplantation, rapid progression of the native IgAN, degree of proteinuria, and donor factors (including HLA matching) may be associated with higher risk.[18] The suspicion that living donor grafts have higher rates of recurrence than deceased donors has not been confirmed.[18] Thus patients with IgAN should not be precluded from consideration for living donor transplantation. The number of HLA mismatches between donor and recipient also may have a role in recurrence rates. Two Australian registry studies have found that those with zero mismatch kidneys have higher rates of recurrence than those with one or more HLA mismatches.[9,19] Similarly, ABO-incompatible transplants have been found to have lower rates of recurrence, possibly because of differences in immunosuppression regimens.[20]

Choice of immunosuppression after transplantation is controversial. One large USRDS registry analysis suggested that individual drug choices did not affect the risk for graft loss attributed to recurrence.[10] In contrast, a retrospective analysis of ANZDATA found that continuation of corticosteroids was strongly associated with protection from graft loss caused by recurrence of IgAN, although not from other types of GN.[9] Observational data also suggest that induction with antithymocyte globulin may afford relative protection.[11]

The clinical expression of recurrent disease is variable and time dependent. Graft loss within the first 3 years after transplantation is uncommon (see Fig. 108.2), although it can occur, particularly when IgAN in the native kidney was rapidly progressive or after previous graft loss resulting from recurrence.[7] An Italian cohort study of 190 patients followed for 15 years recently reported that of their 22% of patients that developed recurrence, almost a third ultimately lost their graft because of IgAN recurrence during follow-up.[21] Death-censored

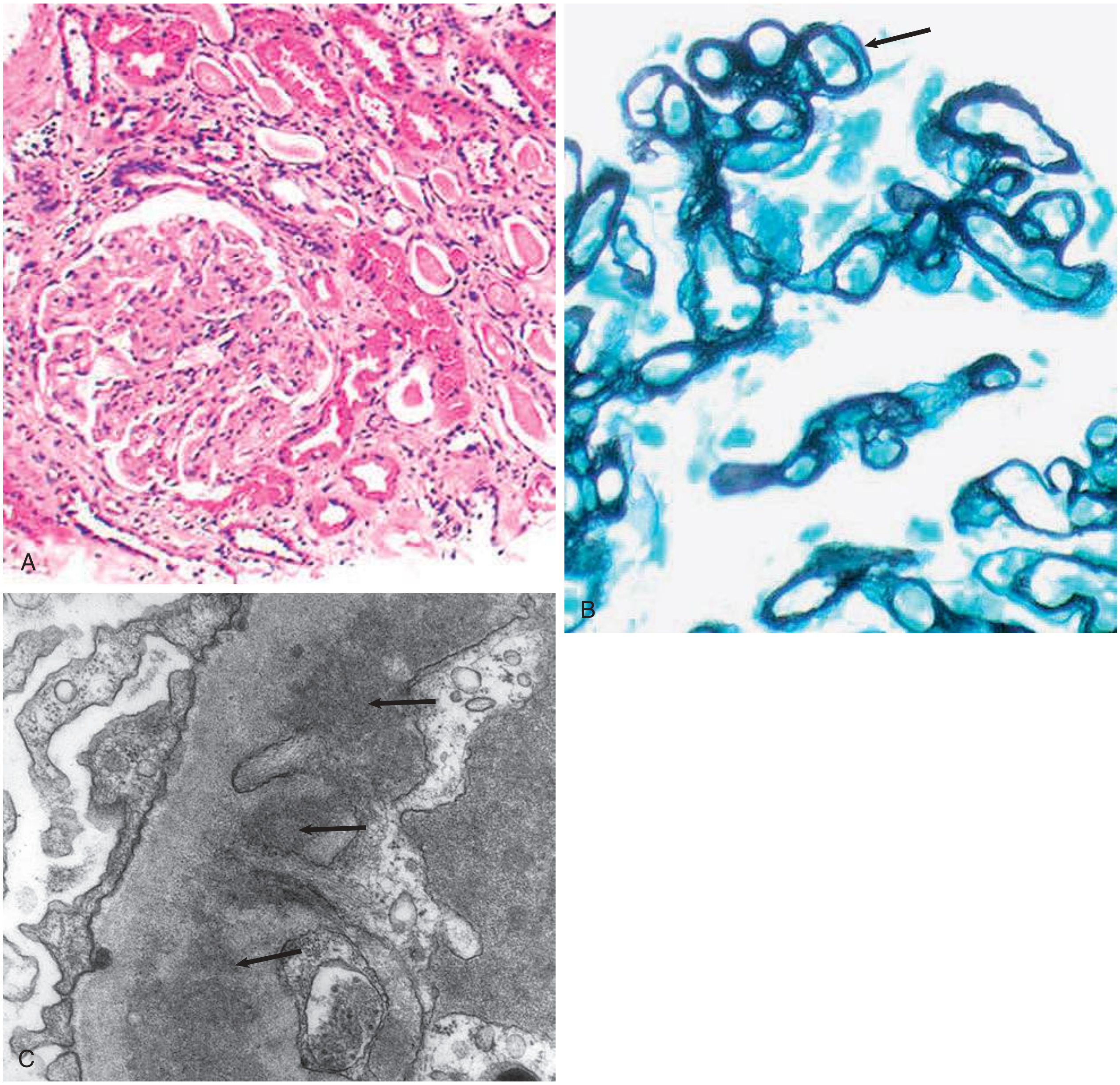

Fig. 108.3 **Transplant glomerulopathy and membranoproliferative glomerulonephritis (MPGN).** Transplant biopsy specimen from a patient with end-stage renal disease caused by biopsy-proven idiopathic MPGN type I, who received a kidney transplant and had a progressive reduction in glomerular filtration rate with proteinuria 1.5 g/day and hypertension. (A) Light microscopy. Glomerular hypercellularity and lobulation on a background of chronic interstitial inflammation and fibrosis, with protein casts within dilated tubules. (Hematoxylin-eosin stain; ×100.) (B) Subendothelial deposits and basement membrane reduplication *(arrow)*. (Methenamine silver stain; ×400.) (C) Electron microscopy showing subendothelial electron-dense deposits *(arrows)* (×7500). There were also prominent C3 deposits on immunofluorescence (not shown). Light microscopy was therefore suggestive of recurrent MPGN but was also consistent with chronic rejection (CR) with transplant glomerulopathy associated with CR. Immunofluorescence and electron microscopy (subendothelial deposits) confirmed recurrence of MPGN. (Compare Figs. 107.3 through 107.5.) (*A* and *B* courtesy Dr. Paul McKenzie, Royal Prince Alfred Hospital, Sydney, Australia.)

graft survival at 15 years was approximately 10% lower in patients who had IgAN than in controls, largely attributable to IgAN recurrence.[21]

Recurrence of IgA vasculitis (IgAV) is less well characterized but appears to be similar to IgAN. An analysis of the United Network for Organ Sharing (UNOS) database including 339 patients with ESRD caused by HSP who received a first kidney allograft reported a frequency of graft loss caused by recurrence of 13.6% and no difference in 10-year graft survival between recipients with IgAN (58.4%) or IgAV (59.3%) as their primary renal disease.[22]

Treatment of recurrent IgAN and IgAV has not been systematically evaluated. The addition of corticosteroid maintenance in corticosteroid-free patients with recurrence is unproven but reasonable. A change to mycophenolate mofetil (MMF) or the use of fish oil, antiplatelet agents, and tonsillectomy cannot be recommended. The use of nonspecific

TABLE 108.2 Recurrent Diseases in Renal Transplants and Effects on Graft Survival

Disease	Clinical Recurrence Rate (%)	Graft Loss in Recurrent Disease (%)
Primary focal segmental glomerulosclerosis	20-50 (children), 10-15 (adults)	40-50
Membranoproliferative glomerulonephritis type 1	20-30	30-40
Dense deposit disease	80	20, often late
Hemolytic uremic syndrome (HUS)		
Classic D + HUS	0-13	Uncommon
Atypical D – HUS	30-50	55-100
Familial HUS	57	Approaching 100
IgA nephropathy	30-40, increases with longer duration of follow-up (30%-60% histologic recurrence rate)	16-33
IgAV (Henoch-Schonlein purpura)	Rare (despite 50% histologic recurrence rate)	Rare
Membranous nephropathy	10-29 (histologic recurrence may be more common)	Up to 50
Systemic vasculitis, including Wegener granulomatosis and microscopic polyangiitis	10-20	20-50
Anti-GBM disease (Goodpasture disease)	<5	50
Systemic lupus erythematosus	1-30	Rare
Amyloidosis	25	10-20

GBM, Glomerular basement membrane; *IgA,* immunoglobulin A; *IgAV,* IgA vasculitis.

measures to prolong kidney survival is appropriate, including tight blood pressure control, renin-angiotensin system (RAS) blockade, and avoidance of nephrotoxins.

Membranous Nephropathy

Histologic recurrence of MN can be found in up to 40% of grafts,[23] and for those with documented recurrence, graft loss rates of over 50% at 10 years of follow-up have been reported.[24] Patients who have previously lost a graft to recurrence are at higher risk on retransplantation, but disease course, duration of dialysis, HLA genotype, graft source, and immunosuppression have not been found to predict recurrence risk.[24]

In 2009 M-type phospholipase A_2 receptor (PLA_2R) was identified as the antigen targeted in 70% to 80% of idiopathic MN.[25] This has spurred interest in the use of anti-PLA_2R antibody titers in monitoring disease activity and predicting recurrence. Recently a number of small, single-center and multicenter observational studies suggested a role for the adoption of PLA_2R measurement as a clinical tool in transplantation, with higher levels at transplantation associated with higher rates of recurrence.[26-29] The largest of these studies reported a recurrence rate of 57% among patients with primary MN, with a median time to recurrence of 4.1 months.[26] The positive predictive value of pretransplant anti-PLA_2R antibodies was 83% (10 of 12), and the negative predictive value was 42% (5 of 12).[26] Current data show that the presence of anti-PLA2R at the time of transplant increases the risk for recurrence; however, both sensitivity and specificity are imperfect and larger studies are required. At present there is insufficient evidence to recommend delaying transplantation until anti-PLA_2R antibody status is negative.

Management of recurrent MN is based on anecdotal reports and extrapolation of data on the management of native kidney MN. There has been some success with rituximab reported in small case series, but the findings await confirmation in a randomized trial. Spontaneous remission appears to be less common than is seen in MN affecting native kidneys. The cumulative exposure to immunosuppressive therapy should be considered because these patients may be at increased risk for lymphoma. Living donor transplantation appears warranted for first grafts but in our opinion should probably be avoided for second grafts if the first was lost early because of recurrence.

To diagnose recurrence requires a native kidney biopsy showing MN as well as a graft biopsy showing MN. This is especially important in MN, in which de novo MN has been reported in 2% to 15% of transplant recipients and tends to manifest more insidiously and later than recurrent MN.[30]

Focal Segmental Glomerulosclerosis

FSGS recurs in 20% to 30% of first transplants.[31,32] FSGS is a heterogeneous group of conditions, and those with familial or sporadic forms associated with mutation of slit-diaphragm proteins such as podocin do not recur, although rare cases of post-transplant nephrotic syndrome caused by the development of antibodies directed against the “neoantigen” within the donor kidney have been reported. FSGS secondary to vascular disease or reflux nephropathy, and those with a very slow rate of progression are at very low risk for recurrence. In contrast, patients with primary FSGS and in particular those with an aggressive initial course (heavy proteinuria and renal failure within 3 years of onset), age younger than 15 years, mesangial hypercellularity on biopsy, or with recurrence in a previous graft are at greatest risk.[31,32] The rate of recurrence is higher than 75% in subsequent grafts when the first graft was lost because of recurrence.[33] Living related donor transplantation has previously been implicated as a risk factor for recurrence; however, a major analysis of U.S. registry data (USRDS) refutes this notion.[16]

Recurrence may occur early (typically within the first month post-transplantation) and manifests initially with heavy proteinuria, followed by hypertension and graft dysfunction. Patients with recurrent disease appear more susceptible to acute rejection and acute kidney injury,[34] as well as graft loss. Recurrence has been associated with early graft loss in up to 50% of patients[32]; however, treatment with plasma exchange appears to have delayed graft loss in many patients and decreased the incidence of overall graft failure[3] (see Fig. 108.2).

Primary FSGS appears to be caused by a circulating factor that targets podocytes, although the specific factor(s) involved remain unknown. Soluble urokinase plasminogen activator receptor (suPAR)

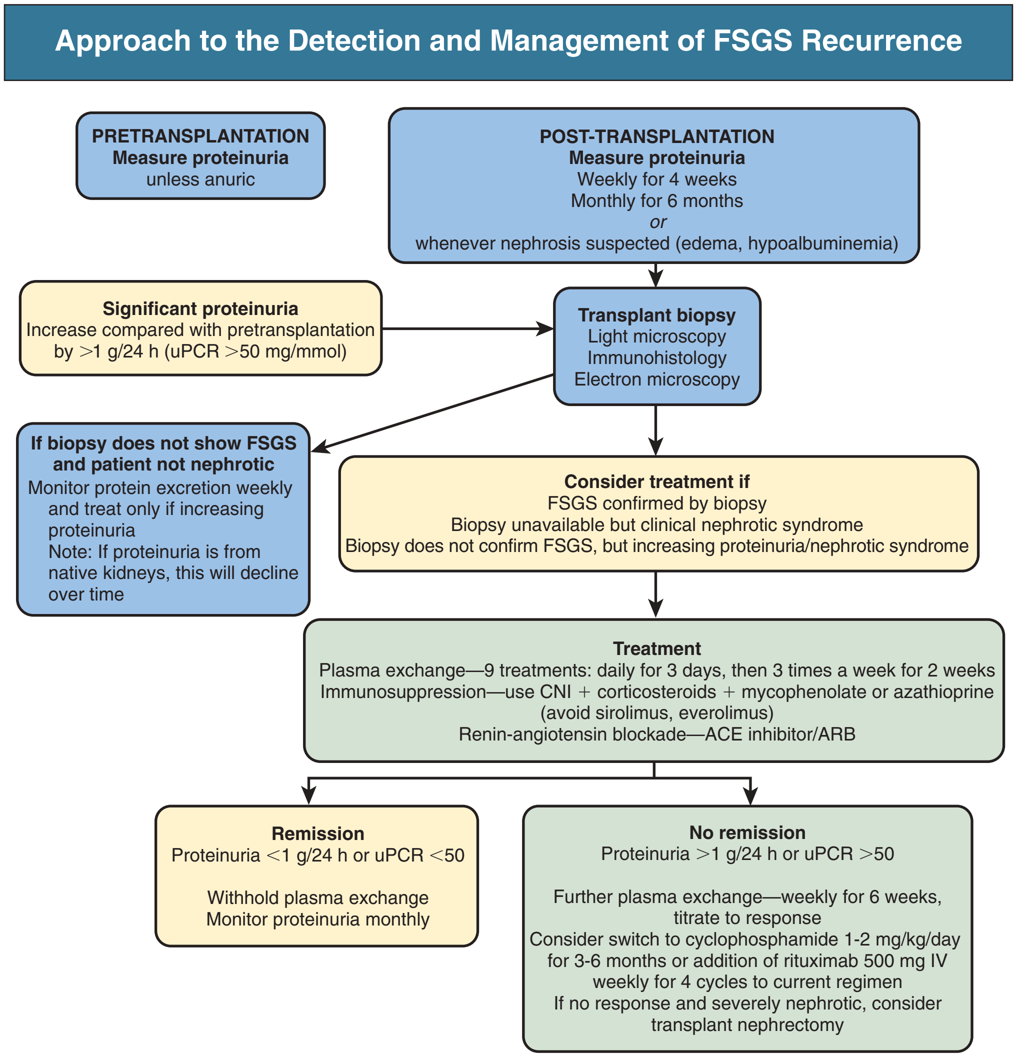
Approach to the Detection and Management of FSGS Recurrence
PRETRANSPLANTATION
Measure proteinuria
unless anuric
POST-TRANSPLANTATION
Measure proteinuria
Weekly for 4 weeks
Monthly for 6 months
or
whenever nephrosis suspected (edema, hypoalbuminemia)
Significant proteinuria
Increase compared with pretransplantation by >1 g/24 h (uPCR >50 mg/mmol)
Transplant biopsy
Light microscopy
Immunohistology
Electron microscopy
If biopsy does not show FSGS and patient not nephrotic
Monitor protein excretion weekly and treat only if increasing proteinuria
Note: If proteinuria is from native kidneys, this will decline over time
Consider treatment if
FSGS confirmed by biopsy
Biopsy unavailable but clinical nephrotic syndrome
Biopsy does not confirm FSGS, but increasing proteinuria/nephrotic syndrome
Treatment
Plasma exchange—9 treatments: daily for 3 days, then 3 times a week for 2 weeks
Immunosuppression—use CNI + corticosteroids + mycophenolate or azathioprine (avoid sirolimus, everolimus)
Renin-angiotensin blockade—ACE inhibitor/ARB
Remission
Proteinuria <1 g/24 h or uPCR <50
Withhold plasma exchange
Monitor proteinuria monthly
No remission
Proteinuria >1 g/24 h or uPCR >50
Further plasma exchange—weekly for 6 weeks, titrate to response
Consider switch to cyclophosphamide 1-2 mg/kg/day for 3-6 months or addition of rituximab 500 mg IV weekly for 4 cycles to current regimen
If no response and severely nephrotic, consider transplant nephrectomy

Fig. 108.4 Approach to the detection and management of focal segmental glomerulosclerosis (FSGS) recurrence. Authors' recommendation based on Davenport.[30] *ACE,* Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CNI,* calcineurin inhibitor; *uPCR,* urine protein-to-creatinine ratio, mg/mmol.

and the costimulatory protein B7-1 (CD80) have been proposed to mediate recurrence; however, reports have been anecdotal and subsequent studies have failed to prove the role of either molecule or consistently demonstrate success with therapies targeting them.[35-39]

Plasma exchange or immunoadsorption with either a protein A or anti-IgG column is effective for some patients who develop recurrent FSGS, presumably because it removes the circulating permeability factor.[40,41] Although not studied in a randomized controlled trial (RCT), several series have reported disease remission in the majority of patients who receive treatment within 2 weeks of recurrence.[32,41] The potential for positive publication bias and the absence of RCT evidence make prognostic information speculative; however, response rates appear likely to exceed 50% when therapy is commenced within 2 weeks of clinical recurrence, with lower response rates anticipated when therapy is delayed. Given that graft survival appears to be significantly prolonged in patients who respond to therapy, a course of plasma exchange is warranted in all patients without contraindications (see Chapter 99). Immunosuppression should include a CNI, and addition of an angiotensin-converting enzyme (ACE) inhibitor should be considered. A minority of patients with an incomplete response or relapse after cessation of initial therapy will require repeated or long-term plasma exchange[42] or concurrent treatment with secondary agents such as rituximab or cyclophosphamide.[41-44] For such patients we recommend a course of rituximab 500 mg weekly for 4 weeks, in addition to existing immunosuppression and weekly plasma exchange. Pretransplantation plasma exchange has not been shown to be beneficial for preventing recurrence. See Fig. 108.4 for an approach to the management of recurrent FSGS.

Minimal change disease is a far less frequent cause of ESRD. Recurrence of disease after transplantation has been reported; however, it is difficult to be sure that the underlying disease was not FSGS.

Membranoproliferative Glomerulonephritis

Recurrent MPGN bears major clinical and histologic similarities with the subgroup of patients with CR who have transplant glomerulopathy, and comprehensive assessment of transplant biopsy specimens (see Fig. 108.3 and compare Figs. 107.4 and 107.5), as well as accurate diagnosis of the native kidney disease, is crucial in making this distinction (see Table 108.1). MPGN type I, rather than transplant glomerulopathy, is suggested by the presence of crescents on light microscopy, stronger staining for C3 and weaker staining for IgM on immunohistologic examination, and subendothelial electron-dense deposits on electron microscopy.[17] This distinction has important clinical implications, particularly because a recurrence carries a higher risk for subsequent recurrence should retransplantation be considered. A retrospective analysis of renal biopsies that included 70 patients with MPGN suggests that the severity of histologic lesions is predictive of recurrence.[45]

Membranoproliferative Glomerulonephritis Type I

MPGN type I appears to be mediated by glomerular deposition of immune complexes, triggered by exposure to endogenous or exogenous (e.g., hepatitis C virus [HCV]) antigens). Because the antigens are not necessarily removed by transplantation, recurrence of disease is possible and is seen in 20% to 33% of graft recipients.[46] Graft loss has been reported in up to 40% of those with recurrence, and the risk for recurrence in subsequent grafts approaches 80%.[47] Significant geographical diversity in the risk for recurrence is evident, with much higher rates of graft loss resulting from recurrence in areas where the majority of patients with MPGN are HCV positive, such as Spain,[46] compared with low-HCV prevalence areas, such as Australia.[3]

No form of treatment for recurrent MPGN has been proven, and the underlying cause of MPGN should be considered in each patient. In HCV-associated MPGN, direct-acting antiviral therapy is effective for virus elimination and should provide substantial protection from HCV viremia and MPGN recurrence after transplantation. Other forms of MPGN type I have been successfully treated with immunosuppression or plasma exchange.

C3 Glomerulopathy

C3 glomerulopathy is a disease process secondary to abnormal complement activation (see Chapter 22). One form of C3 glomerulopathy is dense deposit disease, which also has clinical and histologic similarities to transplant glomerulopathy. Dense deposit disease is suggested by granular staining for C3 on capillary loops without immunoglobulin deposits, and the characteristic ribbon-like intramembranous dense deposits on electron microscopy (see Fig. 22.2).[17] Dense deposit disease has been found to recur in 50% to 80% of grafts, typically manifesting with proteinuria, hematuria, and slowly progressive loss of kidney function.[48] The disease course tends to be slow, and whereas graft loss caused by recurrence is ultimately seen in the majority of patients, this generally occurs beyond the first 10 years after transplantation.[3,48] Graft loss has been associated with male gender, crescents on biopsy, and heavy proteinuria.[48] No effective therapy is known, and although plasma exchange and immunosuppression have been described, these are not supported by good evidence, and control of blood pressure and proteinuria with renin-angiotensin blockade is the preferred therapy. Given the role of alternate complement pathway mutations in Dense deposit disease (see Chapter 22), plasma infusion or administration of complement antagonists may be beneficial but remain unproven.

Membranoproliferative Glomerulonephritis Type III

Recurrence of MPGN type III, a rare disease, has been reported and has resulted in graft loss in the longer term.[49]

Congenital Nephrotic Syndrome

Congenital nephritic syndrome of the Finnish type has been reported to recur after transplantation and cause graft loss; however, the mechanism of kidney damage is likely different between primary and recurrent disease. The primary disorder in some cases is caused by a mutation of the *NPHS1* gene that results in complete absence of nephrin, and therefore transplantation causes de novo exposure to nephrin in the transplanted kidney. Neoantigen exposure may cause antibody development and deposition that damages the slit diaphragm and produces a type of MN with podocyte fusion on electron microscopy and a clinical picture of heavy proteinuria and ultimately graft failure. Cyclophosphamide-based rescue therapy may be successful.[50]

Antineutrophil Cytoplasmic Antibody–Associated Pauci-immune Vasculitis

A pooled analysis of reported case series examining recurrence of ANCA-associated vasculitis, incorporating 127 patients,[51] showed that recurrence was detected in 17% of patients after 4 to 89 months of follow-up, with renal involvement demonstrated in approximately 60% and graft losses reported in 25% of these. Clinical parameters were not useful in predicting those patients likely to relapse. Pretransplantation disease course, duration of dialysis, ANCA titers at time of transplantation and during follow-up, cytoplasmic ANCA (c-ANCA) or perinuclear ANCA (p-ANCA) pattern, antibody specificity to PR3 or MPO, disease subtype (granulomatous polyangiitis [Wegener granulomatosis], microscopic polyangiitis, or renal-limited vasculitis), and donor source had no significant impact on recurrence rate.[51]

The prevention and management of relapse has not been prospectively examined. In most reports, patients did not receive a transplant until they were in clinical remission; however, successful transplantation in the face of persisting ANCA positivity is well recognized. In the absence of firm evidence, we recommend that clinical remission be maintained for at least 6 months before transplantation to reduce the risk for recurrence and also to avoid risks associated with performing transplantation in a debilitated patient, especially if ESRD has occurred soon after presentation with systemic vasculitis. Monitoring ANCA to indicate ANCA-associated vasculitis (AAV) recurrence is commonly performed; however, the test performance characteristics in this context have not been reported. Patients with renal relapses have generally been managed with cyclophosphamide-based regimens, as used for renal vasculitis in native kidneys, reported to be successful in inducing a remission in 11 of 16 (69%) cases.[51] Any negative impact of use of cyclophosphamide to treat relapse has not been reported, but cumulative dose, if it had also been used pretransplant, would significantly increase in the risk for bladder cancer.

Kidney transplantation for AAV is associated with a reduction in the frequency of disease relapse by approximately 50% compared with patients remaining on dialysis, and patient and graft survival posttransplantation is similar to that in other transplant recipients.[51]

Anti–Glomerular Basement Membrane Disease

Histologic recurrence of anti-GBM disease (Goodpasture disease) is seen in 50% of patients who receive a transplant while circulating anti-GBM antibodies persist, but rarely when patients undergo transplantation 6 months or more after the disappearance of anti-GBM antibodies. With delayed transplantation, the rate of clinical recurrence is very low, and since the implementation of this practice in Australia, no grafts were lost after transplantation in 47 patients followed for up to 10 years.[3] Rare episodes of recurrence should be treated as for native kidney disease with corticosteroids, cyclophosphamide, and aggressive plasma exchange (see Chapter 24).

Recurrent anti-GBM disease is distinct from de novo anti-GBM disease, which is seen in up to 15% of transplant recipients with Alport syndrome who develop anti-GBM antibodies in response to neoantigen exposure (α chain of type IV collagen) via the transplant.[52] This is discussed further in Chapter 24.

Lupus Nephritis

The reported recurrence rate of LN has varied from 2% to 54% depending on the diagnostic criteria used.[53,54] Recurrence has been reported early (days) and late (years) after transplantation, with a median time to recurrence of approximately 4 years.[53,54] The clinical and histologic pattern of recurrence is variable but is typically more benign in histology and clinical expression than the patient's original disease. Whereas the majority of patients with ESRD caused by lupus have had diffuse proliferative (class III or IV) LN, mesangial proliferative (class II) LN is the most commonly described lesion after transplantation, followed by class III and membranous LN (class V).[54] Duration of dialysis and serologic activity before transplantation do not predict recurrence, and antinuclear antibody titer and complement levels are unreliable markers of disease recurrence. There is no consistent relationship between recurrence of nephritis and activity of extrarenal lupus after transplantation.

The long-term outcome for lupus patients after transplantation is controversial but appears similar to that of the general post-transplantation population.[53,55] Although recurrence is an uncommon cause of graft loss within the first 10 years after transplantation, with no cases of graft loss reported from 86 recipients in one registry analysis,[3] late graft losses do occur. It is clear that lupus patients, particularly those with a lupus anticoagulant, are at increased risk for thrombotic events after transplantation, including graft thrombosis.[56]

Management of recurrent LN has not been systematically studied; corticosteroids, cyclophosphamide, MMF, and plasma exchange have been used, with variable results reported. Anticoagulation during the perioperative and early post-transplantation phases should be considered for those with a history of thrombosis or lupus anticoagulant positivity. Successful retransplantation has been reported after graft loss caused by recurrence.[56]

Thrombotic Microangiopathy and Hemolytic Uremic Syndrome

Recurrence risk is clearly associated with the underlying cause of thrombotic microangiopathy (TMA). Typical childhood Shiga toxin–associated HUS seldom recurs, whereas recurrence of atypical HUS is frequent and, particularly in hereditary forms associated with mutation of complement components or complement regulatory factors, occurs in up to 80% of patients.[57] The diagnosis of recurrent TMA, including HUS, is complicated by the fact that de novo TMA is seen in 1% to 5% of kidney transplant recipients, most commonly associated with the use of CNIs (both tacrolimus and cyclosporine carry a similar risk), sirolimus, or OKT3 or with acute vascular rejection. Drug-induced de novo TMA is generally observed within 14 days of drug commencement.

A meta-analysis that examined 10 reports covering 159 grafts in 127 patients reported recurrence in 28% of grafts, and this was strongly associated with a poor outcome: 1-year graft survival was 33% for those with recurrence versus 77% in those free from recurrence (P >.001).[58]

The risk for atypical HUS recurrence and its impact on graft survival are dependent on the complement pathway mutation responsible. Mutations in factors H and I are associated with a recurrence risk of approximately 75%, and more than 90% of those with recurrence incur graft failure, typically within the first year.[59] In contrast, mutations of membrane cofactor protein are associated with a recurrence rate of only 20% and substantially better survival rates than in patients with factor H or I mutations.[60] Given these variations in risk for recurrence, genotypic evaluation of the recipient and any potential living donors before transplantation is advisable for all patients with ESRD caused by atypical HUS.[61] Combined liver-kidney transplantation may be considered in selected candidates with defined mutations.[62] Recurrence is also associated with an older age at onset, rapid progression of the original disease, earlier transplantation, living-related transplantation, and the use of CNIs.[57] Recurrence is generally within the first 6 months after transplantation; however, late recurrences have been reported.[57] The clinical presentation may be gradual or abrupt, with thrombocytopenia, hemolysis, and progressive renal dysfunction.

Whereas de novo disease may respond to withdrawal of the inciting agent, management of recurrent disease is uncertain. We recommend withdrawal of any potential causative agent such as CNIs, and if this is not effective after 48 hours, a trial of plasma exchange should be initiated with three half-plasma volume exchanges performed on 3 consecutive days with fresh-frozen plasma used for replacement. Because an increased incidence of acute rejection has been reported in patients with recurrence,[58] inadequate immunosuppression after CNI withdrawal should be prevented with a temporary increase in the dose of corticosteroids. In patients with life-threatening thrombocytopenia or hemolysis, hematologic stability may be restored by transplant nephrectomy. Eculizumab, a humanized monoclonal antibody targeting C5 of the complement membrane attack complex, is emerging as an effective therapy in the treatment of atypical HUS. In case reports, eculizumab has been reported to be successful in both the treatment of recurrence and prophylaxis pretransplantation. Multicenter phase II trials are currently under way to evaluate its efficacy. Plasma exchange may be effective in patients with mutations in factors H or I, as well as those who have autoantibodies directed against factor H. However, it may be less effective in patients with mutations of membrane cofactor protein or thrombomodulin, in which the protein is membrane bound. The prognosis with recurrent disease is poor. More than 50% of grafts are lost within the first year, and graft survival beyond 5 years is quite uncommon.[58] There is no evidence that CNI avoidance is useful in preventing recurrence.

Scleroderma

Few patients with scleroderma undergo renal transplantation. An analysis of 86 patients reported to the UNOS registry demonstrated graft survival of 62% at 1 year and 47% at 5 years after transplantation; 24% of recipients died during the 10-year observation period.[63] The recurrence rate could not be accurately determined; however, recurrence was responsible for graft loss in 21% of patients in whom the cause was identified, which is consistent with previously accepted recurrence rates. A recent review of the literature suggests that rapid loss of renal function after diagnosis may predict recurrence in the graft.[64] The effect of transplantation on the extrarenal manifestations of scleroderma has not been well documented. The management of scleroderma after transplantation is unstudied; however, the use of RAS blockade after transplantation to treat hypertension would seem appropriate. Overall, renal transplantation appears to be an appropriate treatment for those with scleroderma and ESRD.

AMYLOID, LIGHT-CHAIN DISEASE, AND FIBRILLARY AND IMMUNOTACTOID GLOMERULOPATHIES

Amyloidosis

The risk and impact of recurrence for patients who undergo transplantation because of systemic amyloidosis are dependent on its cause. Management of AL amyloid is primarily directed at treating the underlying plasma cell dyscrasia, most commonly by high-dose chemotherapy and autologous stem cell or allogeneic bone marrow transplantation. Recurrence after transplantation is likely if the malignancy is not fully controlled but may be susceptible to further chemotherapy. The largest reported series includes 25 patients who received a kidney transplant for AL amyloid–induced renal failure, of whom 22 had received chemotherapy, which placed 3 patients in complete remission and 13 patients in partial remission at the time of the kidney transplant.[65] Graft survival rates at 5 and 10 years were 74% and 25%, respectively. Recurrence in the graft was documented by iodine-123 (^{123}I)-labeled serum amyloid

P component scintigraphy in 28% at a median of 5 years after transplant, although no grafts were lost through recurrence. Myeloma recurred in 5 patients (28%), of whom 3 achieved complete remission with further chemotherapy. The major cause of graft failure was death, in 13 patients (52%), most commonly caused by sepsis. Cardiac involvement on echocardiogram was noted in 5 patients before transplantation, and 1 died of cardiac failure after transplant. Thus transplantation appears to be a viable option for patients with ESRD caused by AL amyloidosis, provided they have achieved at least a partial remission after chemotherapy and have little or no cardiac involvement.

Secondary (AA) amyloidosis is typically a more insidious disease; renal failure is a relatively frequent complication, and renal transplantation is frequently effective.[65] The risk for recurrence of AA amyloid depends on the ability to eradicate the underlying cause of chronic inflammation. In AA amyloid, recurrence as a result of chronic infection is unlikely if the infection can be eradicated pretransplantation, whereas conditions such as rheumatoid arthritis may persist after transplantation and lead to recurrent amyloid in the graft. Less than 5% of patients with AA amyloid associated with familial Mediterranean fever (which can be managed with colchicine after transplantation) have recurrence at 10 years after transplantation.[66] A Norwegian series of 62 transplants in patients with AA amyloid, mostly secondary to rheumatic diseases, demonstrated a recurrence rate of 10% at an average of 5 years of follow-up, with recurrence causing graft loss in two patients only. Overall, patient and graft survival rates were 65% and 62%, respectively, at 5 years, with most losses resulting from infection.[67]

Light-Chain Nephropathy

Patients with light-chain nephropathy have occasionally received transplants, and recurrence is common; one case series reported recurrence in five of seven patients at a range of 2 to 45 months after transplantation. Those with recurrence developed proteinuria, hypertension, and progressive graft dysfunction. One of seven has had long-term graft function, and one died soon after transplantation because of myeloma.[68] Kidney transplantation is therefore generally inadvisable for patients with this disease, unless performed in conjunction with bone marrow transplantation as a means of curing the underlying disease. Rituximab and bortezomib have been used with success in patients with light-chain nephropathy recurrence in the graft, but insufficient evidence exists to recommend either agent as a standard of care.

Fibrillary and Immunotactoid Glomerulopathies

Fibrillary and immunotactoid glomerulopathies are known to recur in approximately 50% of those undergoing transplantation for these diseases, and although early graft loss as a result of recurrence has been reported, decline in graft function is most commonly slow and does not appear to have an impact on 5-year graft survival rates.[69]

RECURRENCE OF METABOLIC DISEASES AFFECTING THE KIDNEY TRANSPLANT

Diabetes Mellitus

Diabetes mellitus is the most common cause of ESRD in most parts of the world. However, these patients undergo transplantation less commonly than those with GN because of a higher prevalence and severity of cardiovascular comorbidity.[70] Recurrence of diabetic nephropathy affects at least 25% of recipients at an average follow-up of 6 years and with some patients diagnosed within 3 years of transplantation.[71] Histologic and clinical features are similar to those of native kidney diabetic nephropathy. The risk for graft loss from recurrence has not been well documented but appears to be significantly less than with GN, probably because of the competing risk for death from cardiovascular disease. NODAT is also common and has been reported to cause nephropathy in the graft, also manifesting within 5 years of transplantation in a small proportion of cases. The extent to which this contributes to graft loss also awaits clarification, although a registry analysis suggests that the impact on graft failure is insignificant in comparison with the impact on premature death with a functioning graft.[5]

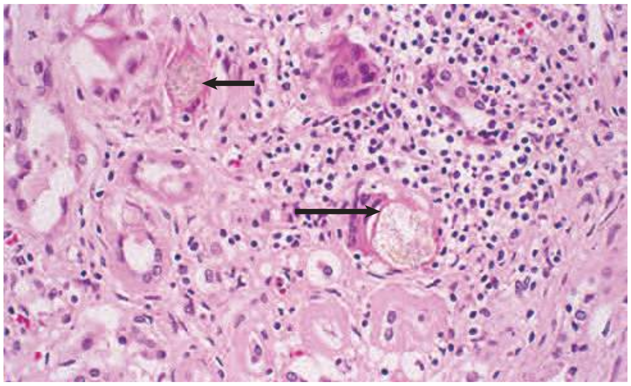

Fig. 108.5 Recurrent primary hyperoxaluria. Light microscopy demonstrates oxalate crystals within the tubular lumen *(arrows)* with a secondary interstitial inflammatory infiltrate.

Primary Hyperoxaluria

Primary hyperoxaluria (see Chapter 57) is a rare autosomal recessive disease caused by defective or absent hepatic production of alanine glyoxylate aminotransferase, resulting in systemic accumulation of calcium oxalate (oxalosis). Kidneys and blood vessels in particular are affected. Kidney transplantation alone is frequently complicated by hyperoxaluria and consequent recurrence in the graft and ultimately graft loss (Fig. 108.5). By contrast, combined liver-kidney transplantation corrects the underlying metabolic deficit and permits long-term kidney graft survival, provided the total body burden of oxalate present at the time of transplantation can be managed. In an analysis of the USRDS that included 190 adults with oxalosis who went on to undergo renal transplantation, 134 patients who received a kidney transplant alone experienced 48% 8-year death-censored graft survival. This was inferior to 56 patients who also received a liver (76%) and inferior to a control group with a primary diagnosis of GN (61%).[72] Aggressive removal of residual oxalate before transplantation by dialysis and after transplantation by maintenance of high urine volumes, urinary alkalinization, and pyridoxine supplementation for pyridoxine-sensitive patients also may decrease the risk for graft damage.

Fabry Disease

Fabry disease results from a defect in the lysosomal α-galactosidase A enzyme, which results in tissue accumulation of trihexosylceramide, eventually causing ESRD (see Chapter 46). Recurrent Fabry disease has been documented within the graft; however, graft survival does not appear to be affected. Treatment with recombinant α-galactosidase A, should this become widely available, is likely to reduce the risk for ESRD and also for recurrence.

RECURRENCE OF VIRUS-ASSOCIATED NEPHROPATHIES AND TUMORS IN THE TRANSPLANTED KIDNEY

Virus-associated kidney diseases may recur after transplantation. Hepatitis B and C virus–associated MPGN and MN are known to recur;

however, the risk for this can be substantially decreased by successful antiviral therapy before transplantation (see Chapter 55).

Retransplantation has been reported in patients experiencing graft loss because of BK virus nephropathy. In the largest series, recurrence was documented in 1 of 10 transplant recipients at an average follow-up of 3 years.[73] Measures to decrease the risk for recurrence included delay in retransplantation by an average of 13 months and transplant nephrectomy in 7 patients. CNI-based triple immunosuppressive therapy was used in all patients, and the 1 patient with recurrence experienced stabilization of graft function after a reduction in immunosuppression.[73] Thus retransplantation, ideally delayed until BK virus is not detectable in serum by polymerase chain reaction, appears to be safe and effective.

Patients with post-transplantation lymphoproliferative disease who incur graft loss secondary to direct infiltration or rejection after the withdrawal of immunosuppression may safely and successfully undergo retransplantation after they recover. There was no evidence of recurrence reported in one series of five cases.[74]

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SELF-ASSESSMENT QUESTIONS

1. Risk for graft loss because of recurrent disease is highest for kidney transplant recipients whose kidney failure was caused by:
   - **A.** Immunoglobulin A nephropathy (IgAN)
   - **B.** Familial focal segmental glomerulosclerosis (FSGS)
   - **C.** Type 1 diabetes
   - **D.** Lupus nephritis
   - **E** Reflux nephropathy
2. A diagnosis of recurrent disease affecting the allograft requires which of the following pieces of information?
   - **A.** Allograft biopsy confirming the disease
   - **B.** Biopsy diagnosis of the native kidney disease
   - **C.** Clinical features of the original kidney disease recurring after transplant
   - **D.** Allograft failure caused by the disease
   - **E.** Both A and B
3. Regarding management of recurrent FSGS:
   - **A.** First-line therapy includes a 3-day course of daily intravenous pulses of methylprednisolone.
   - **B.** Cyclophosphamide should be commenced once recurrence is confirmed.
   - **C.** In a patient who develops nephrotic-range proteinuria 2 weeks after transplant, a biopsy specimen that is normal on light microscopy excludes the diagnosis of recurrent FSGS.
   - **D.** Plasma exchange should be commenced once a diagnosis of recurrent FSGS is made, with a plan to complete approximately nine cycles of therapy.

109

Outcomes of Renal Transplantation

Jeremy R. Chapman

Improving the outcome for patients with end-stage renal disease (ESRD) is the only justification for renal transplantation. If there were not objective and relevant data on outcomes that are meaningful to the patient, few would trust the benefits of the procedure, which has the risk for multiple adverse events. The first patients in the 1950s were comparing the potential benefits of transplantation with certain death as a result of ESRD in the absence of dialysis therapy,[1] and this is still the stark choice offered in far too many countries today[2]; some chance of life is better than no chance. In the developed world, patients face a more complex decision, with excellent and available dialysis treatment, that must be compared with their risks and benefits of renal transplantation.

The field of renal transplantation is rich with data, and increasingly sophisticated outcome measures and analyses are available to inform patient decisions. Nevertheless, when a patient is faced with a clinical problem, the evidence base is often insufficient to inform a specific decision. Transplantation guidelines that have been created by several societies[3] and by Kidney Disease: Improving Global Outcomes (KDIGO)[4] demonstrate through the grading of evidence, that many decisions can be informed only by consensus opinion. At the very least, this emphasizes that there is often no right answer but also provides a challenge to prove more about the assumptions that are made in clinical practice every day.

This chapter reviews the techniques and factors that deliver the outcome measures available today to inform patients' decision making about renal transplantation.

METHODS OF MEASUREMENT AND ANALYSIS

Types of Outcome Analyses

Survival Analyses

If the outcomes of people transplanted at different times and in different places are measured, some will inevitably die over the following years. They may die because of the transplant, or they may have an accident or some other intervention that leads to death. How can this be related to the success or failure of the transplant? Table 109.1 provides a comparison of the commonly used analytic methods in transplantation. The most conventional method is to use a Kaplan-Meier plot that yields an actuarial estimate of outcome, as opposed to an actual measure.[5,6] Events—deaths in this case—are recorded, and the time to that event from the transplant then measured. The Kaplan-Meier method uses the time of follow-up for each individual to contribute to the analysis, providing a better estimate of what will happen to the entire group of patients and not just the small group who have reached a particular time point. An example of such an analysis is shown in Fig. 109.1 from the Collaborative Transplant Study.[7] When one is comparing two groups of individuals there may be issues that should be considered, such as age. For example, if one group had an average age of 30 years and the other 60 years, differing death rates would be predicted. Thus it may be important to show results adjusted for example for age and gender, to get appropriate comparisons between the results in different transplant programs. A multivariate analysis will provide the opportunity to adjust the results for all of the factors that, on their own, appear to have an impact on the outcome. It may be that there are statistically significant differences in death rates if the group is divided, based on age, the presence or absence of diabetes, gender, or the center where they were transplanted.[8,9] Using a multivariate analysis it is then possible to see which of these outcomes is influenced by the particular distribution of the others. It may be that one transplant center that appears to have worse results transplants mostly older patients and those with diabetes, whereas another with excellent results selects only young nondiabetic recipients for transplantation. The multivariate analysis may indicate that both centers would likely achieve the same results if they transplanted similar patients.

Half-Life Analysis

Half-life analysis is the second type of analysis used to extrapolate results beyond where the data stop. It may be that no one has passed the 10-year mark in a particular center, yet patients seek an estimate of how long their kidney may last. Actuarial analysis may indicate an 80% chance of a transplant lasting 10 years, but does not provide information about what happens after 10 years. A half-life analysis allows extrapolation from the known data. There are two different half-life calculations in the literature: the median survival, which is the time that the middle patient in the series survives, and the conditioned half-life, which is the median survival of only the patients who have survived 1 year or more. Fig. 109.2 provides an example of the use of half-life calculations to demonstrate the difference in outcomes related to human leukocyte antigen (HLA) matching between donor and recipient.[10]

Graft Survival

Graft survival is subject to two different presentations, each valid in its own right, but yielding quite different answers. One of the problems in the field is that many graft survival analyses do not make clear which is being used. It is possible to understand the problem with an example. Assume that 1000 patients were transplanted and 100 died with their transplant still functioning at the time of death, whereas 80 lost their grafts from rejection and other causes and returned to dialysis. If one counts death as a cause of graft loss, 180 of the 1000 patients lost their grafts; if one ignores death as a cause, only 80 of the surviving patients lost their grafts. The latter calculation is best described as "death-censored

TABLE 109.1 Analytic Methodologies in Transplantation

Outcome Analyses	Pros	Cons
Actuarial	Captures all data	Provides estimates
Actual	Considers only part of the data	Limits information potentially available
Univariate	Considers one factor	May miss relevant factors
	Multivariate Hard to power with sufficient numbers	Considers all factors
Half-life	Provides understandable outcome analyses	Artificially hides early loses
Study Types		
Randomized controlled trials	Hypothesis driven	Not easy to power
Cohort studies	Subject to bias	May be only approach
Meta-analyses	Collects all data	Bad data cannot be made good by aggregation
Case reports	Unique examples	May never happen again
Guidelines	Careful consideration of all data	Often unable to answer critical questions
Qualitative studies	Describe ranges of answers	Provide more questions than answers
Economic analyses	Provides economic answers	Useless if hard to cost/value

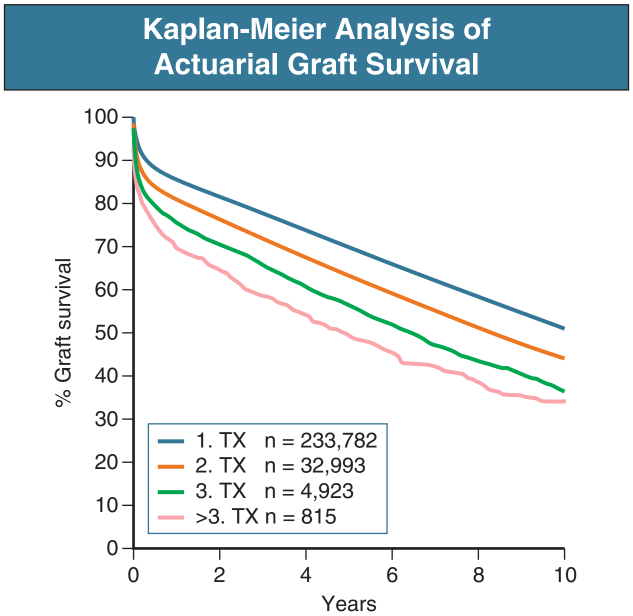
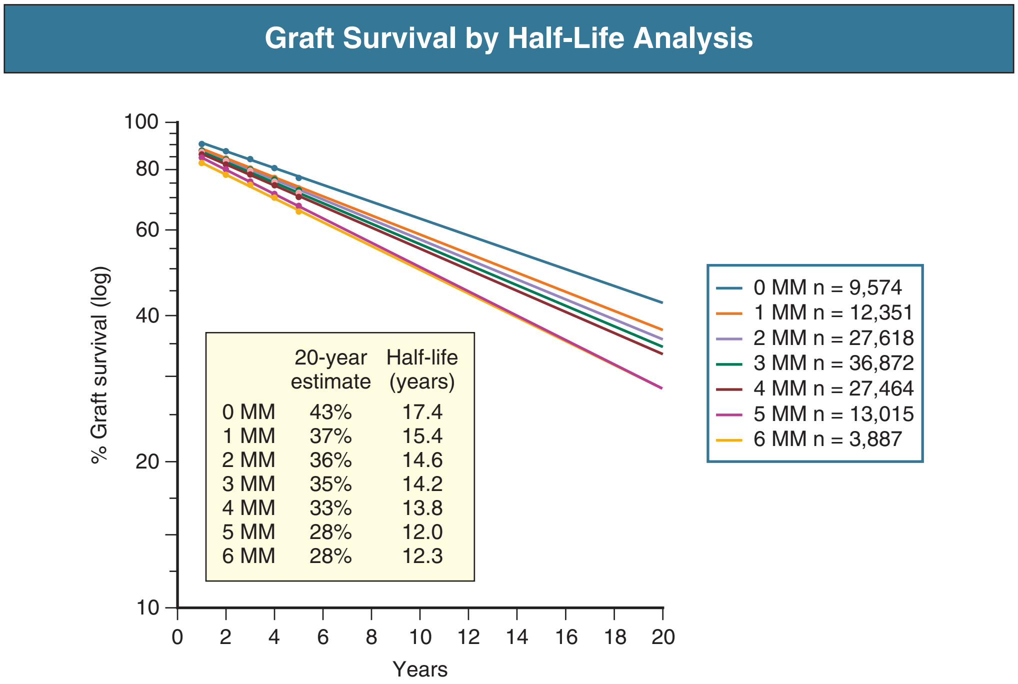

Kaplan-Meier Analysis of Actuarial Graft Survival

Fig. 109.1 **Kaplan-Meier analysis of actuarial graft survival.** Collaborative Transplant Study analysis of actuarial survival of deceased donor renal transplants by recipient graft number (1st, 2nd, 3rd, and >3rd). (Data available at www.ctstransplant.org/public/graphics.shtml. Accessed January 12, 2016.)


Graft Survival by Half-Life Analysis

	20-year estimate	Half-life (years)
0 MM	43%	17.4
1 MM	37%	15.4
2 MM	36%	14.6
3 MM	35%	14.2
4 MM	33%	13.8
5 MM	28%	12.0
6 MM	28%	12.3

Fig. 109.2 **Graft survival by half-life analysis.** Collaborative Transplant Study analysis of survival of first deceased donor renal transplants performed between 1985 and 2011 by human leukocyte antigen (HLA) mismatch *(MM)* showing the half-life calculation and 20 year estimates of survival. (Data available at www.ctstransplant.org/public/graphics.shtml Accessed January 12, 2016.)

graft survival," whereas the inclusive analysis is described as "patient and graft survival." When the analysis is not specified, the findings can be misleading and may make no sense. Both approaches are of course relevant to different situations: on the one hand to understand what causes kidneys to fail and separately to understand what causes patients to die.

Randomized Controlled Trials

Randomized controlled trials (RCTs) are a conventional way of determining difference between two or more therapies and have been used extensively in transplantation to evaluate new pharmaceutical products. Most RCTs compare two drug regimens—one with and one without the new agent. Two critical problems account for the value of RCTs in renal transplantation; first, the relatively small number of transplants performed in any one center means that it is hard to mount studies with sufficient power to detect significant differences, and, second, the lack of good early surrogate markers for long-term outcomes. In cardiovascular studies, in contrast, it is often possible to randomize many thousands of patients and detect differences in meaningful outcomes other than death. However, in cancer studies it is possible to use short-term evidence of tumor response as a surrogate for longer term outcomes. In an earlier era of renal transplantation, relatively small studies could be highly informative. An example of an RCT from the 1980s is the Oxford Cyclosporine trial,[11] in which azathioprine and prednisolone were compared with cyclosporine with sufficient power to detect a difference with fewer than 100 patients randomized to each group. This was because the survival rates in the control arm were susceptible to large improvements, and 5-year graft and patient survival improved by 20% from a baseline around 47% to 67% with the addition of cyclosporine. Today the results of standard of care therapy are so high that recruitment of sufficient patients to detect either graft or patient survival differences at 1 or 2 years is not only extremely expensive but, unless the trials are very large, likely to founder on small random variations.

In the 1990s the introduction of a composite end-point controlled the required size of RCTs. The composite end-point became an acceptable indicator of benefit for the U.S. Food and Drug Administration (FDA) and other regulatory authorities to register a drug for therapeutic use. The composite end-point includes patient death, graft loss, acute rejection episodes, and lost to follow-up. (Inclusion of the latter measure thus conservatively defaults the patients who are lost to follow-up as failing the therapy.) Analysis is by "intention to treat"; in other words for outcome analysis the patient is assigned as randomized, regardless of whether the patient ever received the assigned treatment. Three key studies confirming the benefit of mycophenolate mofetil (MMF) were conducted using this approach, and each recruited around 500 patients allocated randomly into three study arms.[12,13]

Moving forward another 10 years, the largest transplant RCT undertaken to date (the Symphony Trial)[14] required randomization of more than 1500 patients and even then was only powered for a surrogate marker of long-term outcome—notably differences in renal function. It is now accepted wisdom that transplant RCTs cannot be sufficiently powered to detect differences in the hard end-points of patient and graft survival and must all be powered for a composite end-point and surrogates of long-term outcomes. Which short-term surrogates provide good predictors of long-term outcomes has yet to be determined. Acute cellular rejection was, in the 1990s, a short-term measure of importance for long-term results, but perhaps that is no longer true when using current immunosuppressive regimens.[15]

There has been a dramatic influx into the literature of new potential biomarkers of immune responses and allograft damage.[16] The gold standards in use today include serum creatinine and renal histology, which were both introduced without the rigor required in today's regulated environment. Novel biomarkers range from gene sets to predict graft fibrosis[17,18] to marketed functional assays such as ImmunKnow (Cylex, Columbia, Md).[16] The next few years will test the ability of validation and clinical utility of these biomarkers to improve the outcomes of transplantation.

Cohort Studies

Some clinical issues are not susceptible to testing by RCT. For example, an RCT design will never be able to test whether a particular cancer is more prevalent in patients on dialysis compared with patients after transplantation, first because randomization to dialysis or transplantation is ethically unachievable, and second because the numbers required to power such a study would exceed global transplant capacity. However, it is still important to understand if the risks change between dialysis and transplantation and thus to understand if there is any action that can increase or decrease death from cancer after transplantation. An example of an analysis addressing these questions is the Australian cancer study in which data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry on a cohort of patients who were first treated for ESRD between 1982 and 2003 was linked to data from the national cancer registries.[19] It is critical to ensure the selection of the cohort is appropriate to the question being asked. All too often a cohort study is selected from a convenience sample and thus has critical systemic flaws. A typical convenience sample is all patients being followed by a particular transplant unit. The analysis becomes an assessment only of patients still alive and still coming to the transplant unit for follow-up. The cohort has been distorted by lack of the patients crucial to the analysis.

Meta-Analyses

Some areas of transplantation are rich in both RCTs and nonrandomized studies of a particular intervention, for example, interleukin-2 receptor blockade for induction in renal transplantation. Because the studies have produced variable results, which one should be believed? This issue is approached by meta-analyses and exemplified by the International Cochrane Study.[20] An example of a Cochrane review is demonstrated in Fig. 109.3.[21] These types of analyses combine the results from patients who have undergone the same interventions from all similar studies, which thus gives much greater statistical power than each study alone can provide. The methodology requires searching for all studies of the question and especially capturing unpublished studies. The problem of publication bias plagues the field, with studies with a positive finding for the intervention more likely to be published than negative studies. The compulsory preregistration of all trials of a drug by commercial entities in a public database such as www.clintrials.gov is designed to avoid this publication bias, and it is now widely accepted that nondisclosure of data by commercial sponsors of clinical trials is neither scientifically acceptable nor tolerated by the regulators.

Case Reports

Can a case report provide valuable information about outcomes after transplantation? There are some instances of rare events in which the knowledge from a case report has proved important. One example is the early anecdotal reports of hepatitis B (HBV) transmission from HBV surface antigen (HBsAg)-negative donors to recipients of their livers.[22] A few case reports led to a cohort analysis, which in turn led to an understanding that HBV can be transmitted from a donor who tests negative for HbSAg but positive for HBV core antibody. The surveillance and vigilance strategy for the safety of cells, tissues, and organs of human origin is based on this concept—identifying and publicizing

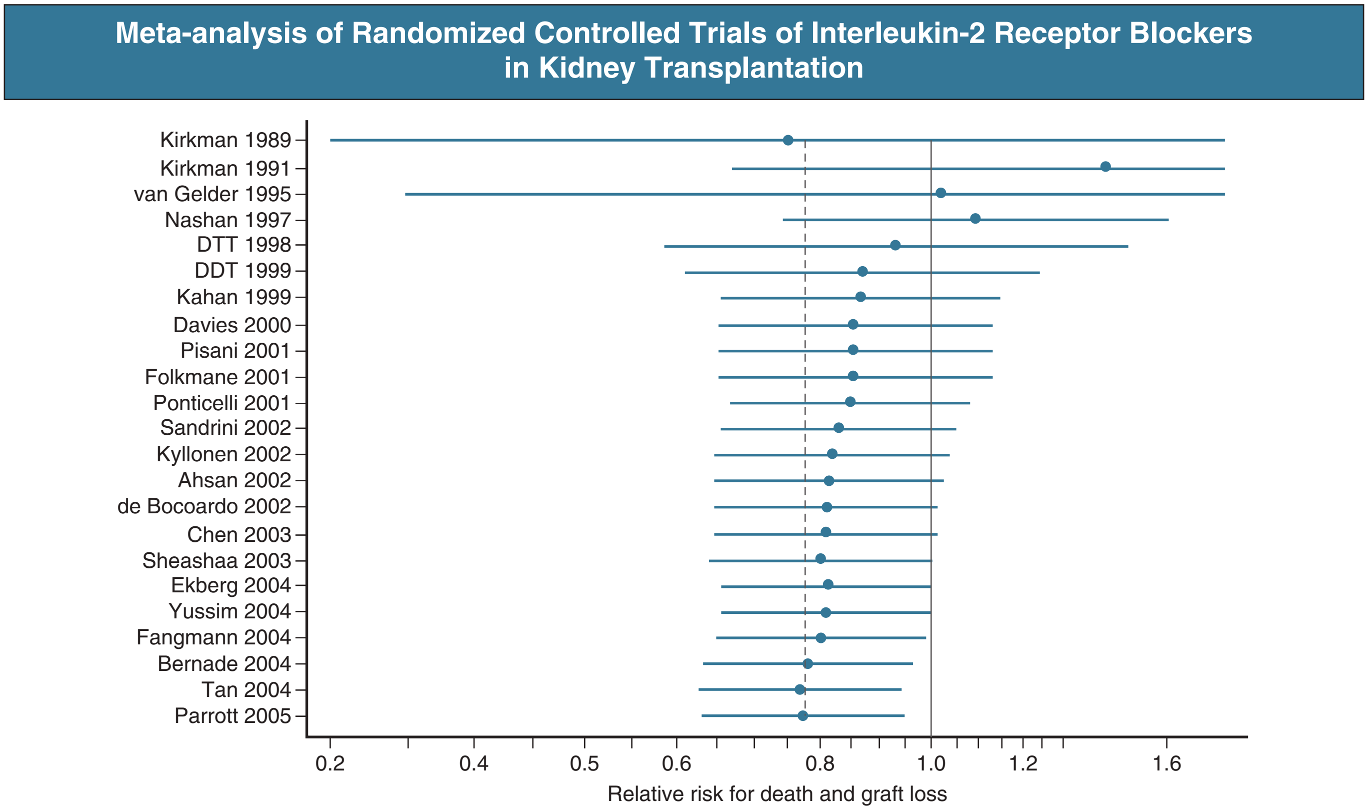


Fig. 109.3 **Meta-analysis.** A cumulative meta-analysis showing the effect of increasing numbers of trial on the confidence intervals of the outcome of death and graft loss in patients receiving interleukin-2 receptor blockers compared with placebo in all randomized controlled trials published between 1985 and 2005. *DDT,* Deceased donor transplants. (Data reproduced with permission, courtesy A. Webster; presented at the World Transplant Congress, Boston, Md, 2006.)

the rare cases so the problems can be recognized (see www.notifylibrary.org). Unfortunately, publication bias ensures that once a case is reported it becomes unique because the journal editor asked to publish the second and subsequent cases will usually decline to.

Expert Opinion Guidelines

Pervasive in the transplantation literature is citing of “expert opinion” leading to clinical practice guidelines. Only the major questions have answers in RCTs, meta-analyses, or cohort studies. The clinician is repeatedly faced with unanswered questions in day-to-day clinical decision making. Guidelines rate the available evidence on particular questions from good to nonexistent. An example of a widely disseminated set of guidelines is the KDIGO guidelines on the care of a transplant recipient,[4] which clearly set out the limits of knowledge in the area. Much of the guidance provided on how to maximize outcomes for particular patients is based on the combined wisdom and experience of clinical practitioners and not on RCT or other data analyses. However, we should beware of expert opinion because it can provide a rich tapestry of self-sustaining false wisdom.

Qualitative Studies

Some questions are not amenable to quantitative data collection yet are of great importance to the field. What causes potential living donors to decide to donate? What do physicians consider most important in assessment of living donors? Why does a particular community not donate organs after death? These questions are amenable to qualitative research and can be assessed and measured, not to produce proof related to a particular question, but to generate testable hypotheses. Qualitative studies create insights into behaviors and attitudes and do not assume that there is a single reality to be discovered. People have different views on organ donation, and using any system of measurement that expects everyone to be driven by the same perspectives is going to be a disappointment. A guide to the approach of qualitative studies in transplantation has been published to assist scientists familiar mostly with quantitative studies.[23]

Economic Analysis

Health funders and government policy makers rely on multiple inputs to make investment decisions; principal among these inputs is health economic analysis, which can be the dominant policy driver in high-cost areas of medicine. Transplantation has perhaps been slow to embrace these techniques that sometimes yield counterintuitive results when comparing the high cost of keeping a patient alive and well with a transplant to an inexpensive death.[24]

Types of Data Collection

All analyses of data depend on the methodology of data collection and completeness of the data. Clearly if the data entered into an analysis are flawed in some way, the analysis will simply embed those flaws and provide spurious confidence in the outcomes of the analysis. Once the flaws of data collection are hidden by an analysis, they usually are never again identified and clinical practice is influenced based on a false assumption. It is thus essential that the reader of any analysis verifies that the data are collected in a manner that is trustworthy and relevant to the question. There are many ways to collect data, all of which have their utility when used in the right way.

Registries

The methodology of registry data collection varies from voluntary to compulsory and from automated to manual. The completeness of data is related to the amount collected, the frequency with which it is updated, and the methods used. National transplantation registries are often voluntary, such as the ANZDATA Registry in Australia and New Zealand[25] or the similar Malaysian Dialysis and Transplant Registry. Some, such as the North American United Network for Organ Sharing (UNOS) database are mandatory in that financial penalties are threatened for failure to fill in critical data elements.[26] The largest international registry is the Collaborative Transplant Study run from Heidelberg, Germany, which uses voluntary data collection on the repeatedly stressed basis that all sequential transplants from contributing units are entered and followed.[7] Donor registries tend to be complete because they capture all data at the time of organ donation as a part of the process of donation.[27] Registries that collect data in a manner that is integrated into the process they are measuring, such as taking data directly from the patients' medical records (e.g., Hong Kong), tend to have the most reliable data. In the United States the Scientific Registry of Transplant Recipients (SRTR) could use data linkage between databases to increase its accuracy.[28] Data available to SRTR include deaths in the United States and Medicare billing data to cross-check whether a transplant recipient is being billed for dialysis, both useful pieces of information to construct an accurate view of survival of either the patient or the graft.

Incompleteness of follow-up data is a weakness of many transplant registries and depends on the ability of transplant programs to follow their patients and report outcomes. Regrettably, outcomes can be artificially inflated by assuming patients are alive and well. Bad data thus produce apparently good results.

Registries usually seek at least one data point annually that confirms the patient has been seen alive and the graft is still functioning and, otherwise, define the patient as lost to follow-up at the point of last contact. This technique yields the most benefit from the data that is known about any one individual and does not allow uncertain data to contribute to analyses.

International Statistical Collections

The most useful international statistics collections are perhaps those conducted by the World Health Organization and published on the Global Observatory for Donation and Transplantation (GODT) website (www.transplant-observatory.org). These data are contributed by all national governments and probably represent the best estimates of global transplantation activity, but little or nothing is available from that source on outcomes. The GODT does allow relationships to be analyzed between donation and transplantation indices on the one hand and national health and financial statistics on the other, as in Fig. 109.4.

Randomized Controlled Trials: Data Collection

The techniques of data management of commercially sponsored clinical research probably make these the most robust data available, because the primary data source is the patients' medical records, which are used to collect specific items of carefully predefined data and, most crucially, are audited for accuracy. These three elements—primary data source, predefined information, and auditing—deliver the most trustworthy data. There is, however, one major drawback: the predefined duration of the studies ensures that long-term outcomes are almost always missing. The longest clinical trial data collections are usually for only 5 years unless data are accrued from a different source, such as through a registry.[29,30]

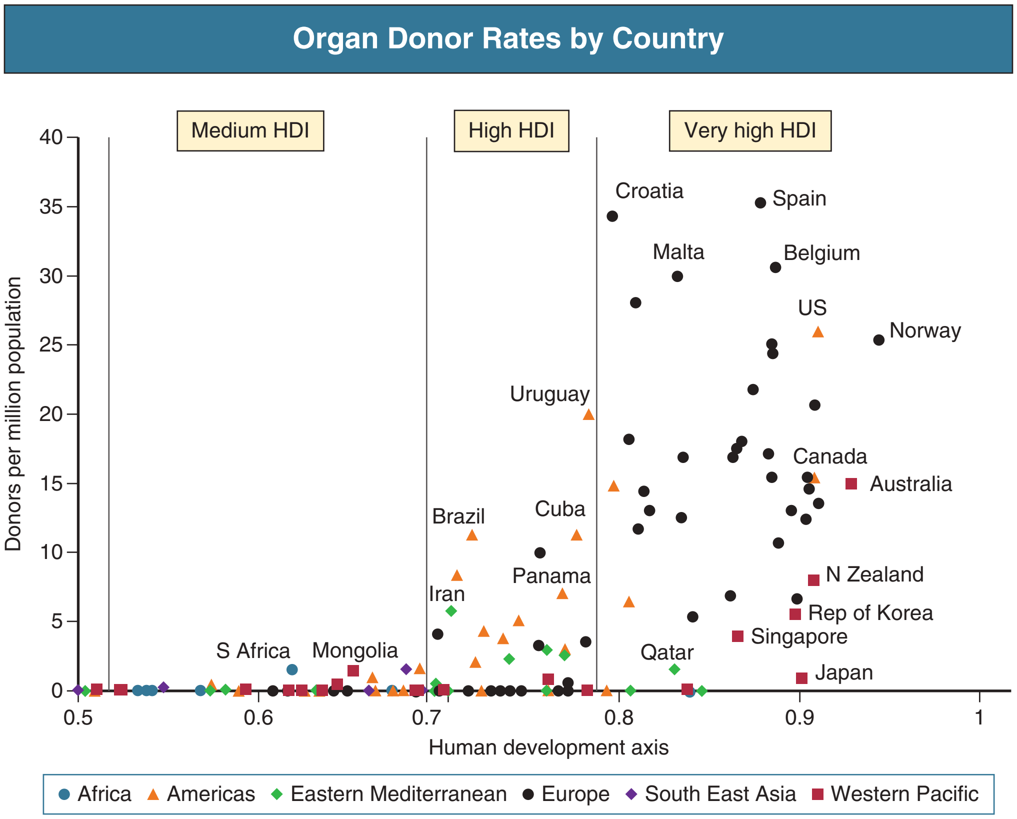


Fig. 109.4 Organ donor rates by country. World Health Organization data analysis of the number of organ donors plotted against the Human Development Index *(HDI)* by member state. (Data reproduced with permission. Global Observatory on Donation and Transplantation.)

Structured Reviews

Structured literature reviews are derived from medical reference literature search engines such as PubMed and EMbase. There are also two transplantation-specific databases of published clinical trials in the Cochrane Collaboration[20] and the Transplantation Library.[31] These databases contribute most information for the structured literature reviews needed for meta-analyses and guideline development, but searching of conference proceedings and abstracts are also needed to ensure complete data identification. The final source of data that must be included on registered therapeutic products is the manufacturing pharmaceutical company, which may hold critical unpublished data.

VARIABLES AFFECTING THE OUTCOMES OF TRANSPLANTATION

Deceased Donor Variables

The best transplant outcomes have been assumed to come from transplantation of kidneys from young adult male donors with simple head trauma as the cause of brain death and with no other medical conditions. These were the donors with which most transplant programs commenced and have become increasingly rare as road safety, accident retrieval, and neurosurgical interventions have all improved. The older recipient with previous medical conditions who finally dies from a cerebrovascular accident after many years of uncontrolled hypertension has been transplanted warily and somewhat reluctantly, usually into an older recipient. An analysis in the United States demonstrated that these extremes yield a twofold difference in graft survival.[32] Four donor factors provide the clearest distinction of outcome: donor age, cerebrovascular cause of death, history of hypertension, and renal function at the time of donation. These criteria provided a matrix of relative risk for graft failure that ranges from 1.00 for a 10- to 35-year-old donor with no adverse features to nearly a threefold increased risk for failure (2.69) for a donor over 60 years with a cerebrovascular accident, history of hypertension, and terminal serum creatinine over 1.5 mg/dl. These criteria were grouped to simplify the definition of a donor kidney likely to be associated with worse graft outcomes as the expanded criteria donor (ECD) using a cut-off of 1.7-fold worse outcome, with all other donors being classified as standard criteria donors (SCDs) (Table 109.2).

TABLE 109.2 **Expanded Criteria Donor Relative Risk for Graft Failure in the United States: 1999 to 2000**

				Donor Age 50-59 yr	Donor Age >60 yr
No comorbidity	—	—	—	1.41	1.90
1 Comorbidity	CVA	—	—	1.61	2.17
	—	HTN	—	1.60	2.16
		—	Creat	1.53	2.04
2 Comorbidities	CVA	HTN	—	1.83	2.47
	CVA	—	Creat	1.75	2.37
	—	HTN	Creat	1.75	2.37
3 Comorbidities	CVA	HTN	Creat	1.99	2.69

Compared with donor 10 to 39 yr with no adverse factors: Relative risk = 1.00.
Relative risk increases with increasing donor age, and presence of one or more of the following three comorbidities:
CVA = Death resulting from a cerebrovascular accident.
HTN = Donor history of hypertension.
Creat = Terminal predonation serum creatinine >1.5 mg/dl.
Definition of expanded donor criteria based on relative risk >1.70

The survival of recipients who received ECD grafts was 91% at 1 year compared with 95% for SCD, but because these kidneys had been allocated to older recipients the results were not directly comparable. However, by comparing within age cohorts it can be seen that there was a reduced patient survival after transplantation of a kidney from an ECD (Table 109.3). In a separate analysis it has been shown that the mean creatinine clearance 6 months after transplantation declines from around 65 ml/min if the donor was 20 to 25 years to only 35 ml/min with donors over 70 years.[33] The approach to allocation of such ECD kidneys varies around the world, for example, with the Eurotransplant policy to allocate older donors to older recipients.[34]

Further development of donor/recipient risk evaluation was undertaken using the U.S. donation and transplantation data. A more comprehensive Kidney Donor Risk Index (KDRI) was developed, tested, and implemented as an allocation tool.[35] The power of this index for estimating post-transplant survival has been tested on data from other countries and found to be robust, with a 40% to 50% difference in 10-year survival between the best and worst quintiles of KDRI.[36] This has allowed the KDRI to be used more widely to assist individuals' clinical decision making around every deceased donor offer.

The 10 factors of the KDRI are those that are most influential on long-term graft and patient survival and are worthy of analysis in all outcomes studies because of the impact they can have on the recipient results.[37] Donor age is perhaps the most obvious factor that, along with donor comorbidities identified by hypertension or death from cerebrovascular disease, predicts lower baseline donor renal function or nephron mass. In development of the KDRI, Rao and colleagues[38] added donor height, weight, ethnicity, history of diabetes, serum creatinine, and hepatitis C (HCV) infection status, as well as the mode of death after circulatory arrest rather than brain death. The numerical profile of donor quality thus can be used to provide rapid estimates of recipient outcome from transplantation with each kidney, the lowest numbers denoting the highest quality organs and best outcomes, with nearly a doubling of 5-year graft survival from 40% for the worst to 80% for the best KDRI in the United States.[38] Other countries and regions have adapted the KDRI for local use by testing the highest indicators of graft loss locally and transposing ethnicity based on North American Black populations with the equivalent high-risk local ethnic groups.

Donation after circulatory arrest (donation after cardiac death [DCD]) rather than after a diagnosis of brain death (donation after brain death [DBD]) now accounts for up to 20% of kidney donations in some countries. It has thus become important to determine the impact of DCD on short-term and long-term outcomes. The data are reassuring, in that although DCD kidneys more often have delayed graft function, graft survival, patient survival, and long-term renal function are not different from those in transplantation of DCD kidneys under the age of 45 years compared with DBD kidneys.[39] Markov modeling has

TABLE 109.3 **Patient Survival (Percent) After Receiving an Expanded Criteria Donor Kidney Versus a Standard Criteria Donor Kidney in the United States: 1999 to 2000**

Recipient Age	ECD 1 yr	ECD 5 yr	SCD 1 yr	SCD 5 yr
35-49	96	78	97	85
50-64	89	63	92	75
65+	86	55	89	59

Data from reference 32.

TABLE 109.4 Graft Survival After Transplantation Between 1985 and 1989 Percentage of Actuarial Nondeath Censored Graft Survival

Years	1	5	10	15	20
Living donor	91	75	61	45	35
Deceased donor	81	66	47	33	21

Reproduced with permission. From reference 25.

demonstrated that the combination of DBD and DCD donation is economically superior to a simpler strategy that focuses only on the use of DBD kidneys.[40]

Living Donor Variables

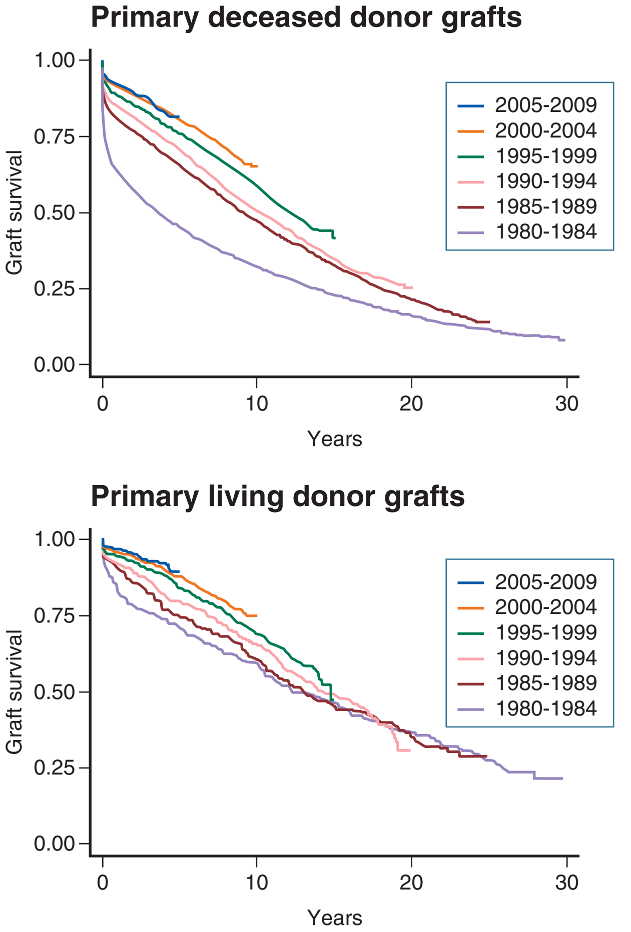
The assessment of the living donor is primarily directed at donor safety to ensure risk to the donor is minimized as far as possible. The secondary assessment is of factors that may affect the recipients' chances of a successful outcome. Impaired renal function or significant donor hypertension or diabetes are, for example, usually exclusion criteria based on donor safety rather than recipient outcomes.[41] Assessment of the living donor is further discussed in Chapter 102. The cumulative data from almost all studies show that transplantation of a living donor kidney offers superior outcomes to deceased donation, though the precise reason for this is probably a mixture of recipient and donor factors, including the ability to perform preemptive transplants with living donors. A long-term analysis performed by ANZDATA (shown in Table 109.4 and Fig. 109.5[25]) shows there was a 10% advantage to living donation at 1 year stretching to a 14% advantage by 20 years after transplantation.

A North American study of living kidney donors and recipients used a half-life calculation based on survivors at 1 year after transplant.[42] They demonstrated that the half-life—that is, the time at which 50% of grafts were still functioning and the patients were alive—was between 10 and 16 years when the donors were under 60 year of age and the recipients were under 60 years, but the results fell to between 7 and 10 years if either the donor or the recipient were over 60.

Other Donor Variables

Additional donor-related factors are known to affect both long-term and short-term graft and patient outcomes, such as those leading to initial nonfunction, and determine whether the recipient will need dialysis postoperatively (Box 109.1). These factors can be used in modeling outcomes, as recently undertaken to provide a decision aid for recipients offered one or more organs.[43] The models need to be adjusted for transplant year, cause of ESRD, panel-reactive antibody to HLA at transplant, previous transplant, years on dialysis, HCV serologic status, insurance status, recipient and donor race and ethnicity, and donor history of cigarette use. In addition to simple donor factors, such models need also to consider combined donor-recipient factors including age, sex, body mass index (BMI) of 30 or less, weight ratio, height ratio, HLA mismatch, and ABO compatibility, because it is the interaction of the donor and recipient characteristics that creates the risk.

Comparison of the Long-Term Outcomes of Transplantation by Era in Australia and New Zealand After Living and Deceased Donation



Primary deceased donor grafts

Primary living donor grafts

Fig. 109.5 Comparison of the long-term outcomes of transplantation by era in Australia and New Zealand after living and deceased donation. (Reproduced with permission. From reference 25.)

Recipient Variables

Many factors affect both patient and graft outcomes that relate directly to the recipient, some of which may be modifiable and some of which are intrinsic. Perhaps the most modifiable factor in theory would be when to perform a transplant: before the need for dialysis (preemptive transplantation) or after dialysis has commenced. The analysis of the benefit of preemptive transplantation is complex because the comparison cannot be between people receiving preemptive transplants and those who are transplanted after dialysis, as the delayed patients must survive long enough to be offered a transplant. Despite these complexities of lag time in analysis, there is both an economic argument (it is cheaper to avoid dialysis) and a survival advantage (patients with preemptive transplants have 5% to 10% better 5-year post-transplant survival). Fig. 109.6 shows the Australian experience with access to a living donor transplant showing that people in the top two socioeconomic demographics have greater chance of a preemptive transplant and greater total access to living donor transplants.

The various modifiable and unmodifiable factors influencing graft outcomes are shown in Table 109.5, and BMI is illustrated in Fig. 109.7.[44] In assessment of individual outcomes there are unfortunately no simple tables of risk analogous to cardiovascular risk profiles for the general population, but the dominant features affecting outcomes remain recipient age and cardiovascular comorbidities.

The two recipient diseases that have undergone the most significant transformations in the past few years are HIV and HCV infections. HIV-infected recipients are not only stabilized and living much more normal life expectancies today with antiretroviral therapy, but it is possible to transplant them successfully with minimal immunosuppression dose adjusted for drug interactions.[45] HCV infection is now a fully treatable disease with high rates of sustained virologic responses using current direct-acting antiviral agents such as a combination of sofosbuvir and ledipasvir.[46] The option to treat patients either before or after transplantation and to accept treated HCV-positive donors routinely for all recipients are now being tested. Again, the interaction of the new agents with renal function and immunosuppressant drugs needs to be considered.

BOX 109.1 Donor Factors Known to Worsen Graft and or Patient Outcomes After Transplantation of the Kidney

- Deceased versus living donor
- Donation after circulatory arrest compared with donation after brain death
- Increasing donor age
- Donor history of hypertension or diabetes
- Cause of donor death: Cerebrovascular disease or prolonged anoxia/drowning
- Worse terminal renal function
- Use of inotropes before donation
- Duration of final intensive care admission
- Female gender compared with male
- Nephron mass (donor/recipient weight ratio)
- Histology (percent of sclerosed glomeruli)
- Ex-vivo perfusion not used
- Transmissible disease (infection/malignancy)

Effects of Immunosuppression on Transplant Outcome

There are many examples of the use of outcome analysis to determine alternatives for immunosuppressive therapy after renal transplantation.[11-14] The proliferation of alternative immunosuppressive therapeutic regimens has yet to be resolved in the way that cancer chemotherapeutic regimens have specific strategies for specific indications. The standard therapy against which comparisons now must be made includes a calcineurin inhibitor, generally assumed to be tacrolimus despite some reluctance by the FDA to accept it over cyclosporine, MMF or mycophenolate sodium, and corticosteroids. The choice of immunosuppressive regimens is discussed further in Chapter 104.

The adverse outcomes of immunosuppression such as excess cancer risk[19] and observations of reduced cancer risk with inhibitors of the target of rapamycin (mTOR)[47] have, for example, led to the individualization of therapy for those with a high risk for skin cancer.[48] This is discussed further in Chapter 105.

Transplant Center Variables

The outcome of transplantation in different transplant centers is largely, but not entirely, driven by case selection. In the United States a center-based report card has been used to identify low-performing centers (which have statistically significant worse outcomes than predicted from their case mix) that remain low performing and do fewer transplants after a low performance report, suggesting that the information about poor outcomes assists both patients and administrations identify

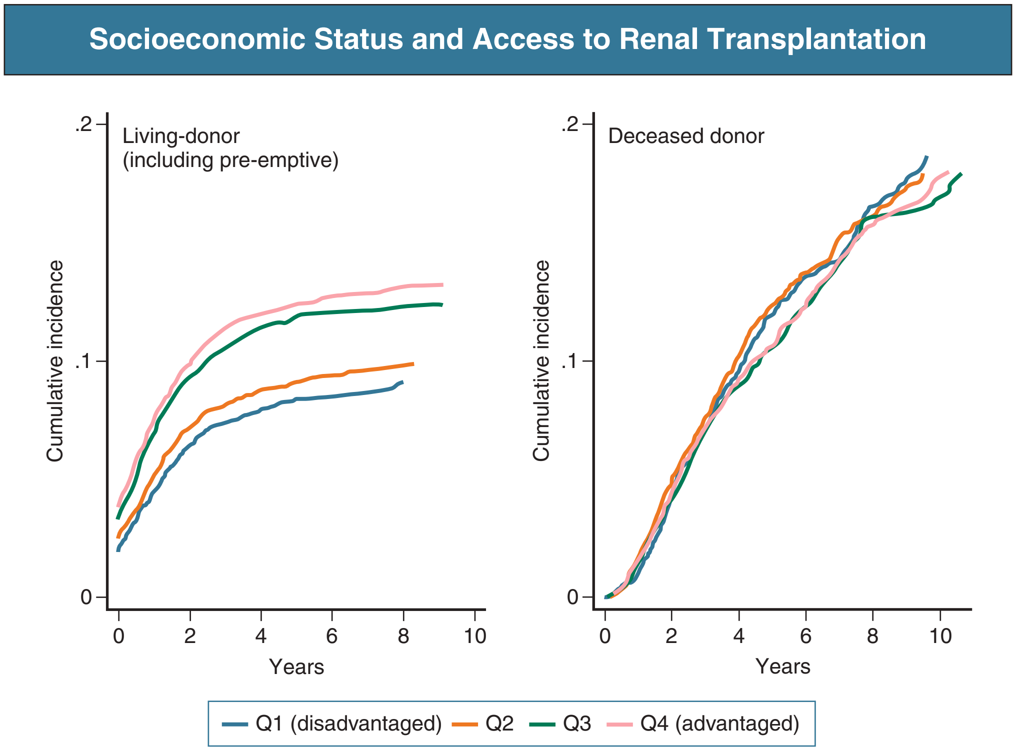
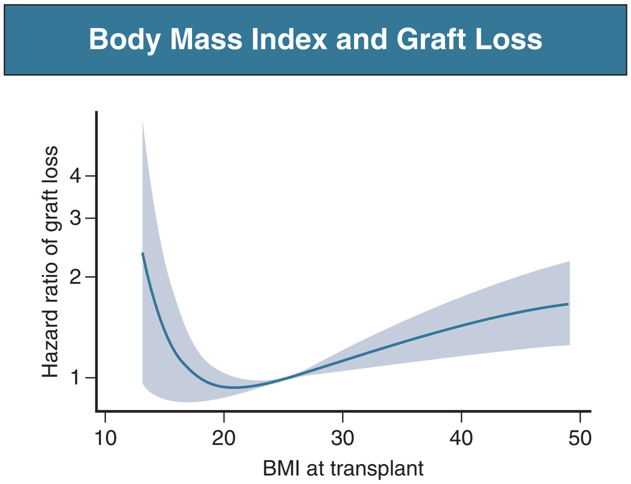


Fig. 109.6 **Socioeconomic status and access to renal transplantation.** Access to transplantation in Australia and New Zealand 2000 to 2010 by socioeconomic status of postcode of residence, demonstrating the cumulative incidence of transplantation by time from commencement of dialysis. There were no preemptive deceased donor transplants and no effect of socioeconomic status, but living donor transplants were accessed more frequently and sooner by the top two socioeconomic groups with an approximately 25% of living donor grafts being preemptive. (Data courtesy ANZDATA. From reference 25.)

TABLE 109.5 Recipient Factors Affecting Graft and Patient Survival After Renal Transplantation*

Patient-Related Factors	
Age	*Adults:* Outcome worse with increasing age. *Children:* Outcome worse <7 kg.
Gender	Better outcomes from male donor to female recipient presumed to be based on nephron mass.
Race	Worse outcomes compared with White in United States for African Americans, but better for Asians. Variable effects in other countries but generally worse for indigenous races.
Anti-human leukocyte antigen (HLA) antibodies	Worse with increasing sensitization as a result of previous blood transfusions, pregnancies, grafts.
Previous transplants	Worse outcomes with second and subsequent grafts.
Primary renal disease	Specific risks for recurrent disease by type of primary disease.
Comorbidities	Worse outcome with cardiovascular disease, chronic respiratory disease, diabetes mellitus, hepatitis B or C infection.
Body mass index (BMI)	Worse outcomes at extremes of BMI: <20 and >35 (see Fig. 109.7).
Medication and clinical follow-up adherence	Worse outcome with poor adherence to follow-up and medication protocol.
Transplantation-Related Factors	
Surgical experience	Worse outcomes with inexperienced surgeon.
Graft and patient vascular anatomy	Worse outcomes with multiple arteries and veins.
Warm ischemia time	Worse outcome with prolonged time.
Cold ischemia time	Worse outcome with prolonged time.
Transplant center experience and results	Center effects are usually not significant and are related more to patient and donor selection criteria than center expertise. However, some centers in some countries have been shown to produce worse outcomes based on multivariate analysis of all relevant factors, leaving center expertise the most likely remaining outcome variable.
HLA matching	Worse outcome with poor matching (see Fig. 109.2).
Donor-specific antibodies	Easily detected high titer anti-HLA class I and II antibodies detected by cytotoxicity crossmatch tests are associated with hyperacute, accelerated, and acute rejection. Anti-HLA antibodies detected only by solid-phase assay depending on their titer are associated with worse long-term outcomes (see reference 42).

*There is significant variation in some of these factors in different countries.



Body Mass Index and Graft Loss

Fig. 109.7 **Body mass index *(BMI)* and graft loss.** Univariate analysis of graft loss by BMI in 5684 patients in ANZDATA from 1991 to 2004. Obesity was not associated with cardiovascular disease (CVD)-related mortality and was associated with age, males, smoking, diabetes, CVD, long-term dialysis *P* <.001. (From reference 44.)

problems and avoid transplantation at those centers, but sadly not that the report leads to changes in low-performing centers and turns them into high-performing centers.[9,49]

Transplantation Matching Variables

HLA matching is perhaps the most dominant feature of individual patient outcome, with 15% 5-year differences in graft survival quite common across different analyses (see Fig. 109.2).[10,50] The advent of specific definition of anti-HLA antibodies through solid-phase assays, especially those using beads read by dual-laser flow cytometry,[51] has increased the precision of HLA typing and matching. However, a critical question remains that has not yet been amenable to long-term outcome analysis: at what sensitivity level and against which HLA antigens should an anti-HLA antibody be avoided? A recent consensus meeting has helped define the knowns and unknowns, but has not yet led to a conformity of HLA matching and crossmatching criteria.[52] Desensitization of patients with anti-HLA antibodies has been shown to be a successful way of transplanting patients who would otherwise not be transplantable.[53]

The blood group barrier, once thought immutable, is like the HLA antibody barrier, amenable to intervention providing the titer of anti-ABO antibody is known and reduced by physical removal to a low level at the time of transplantation.[54] The data support the view that antibodies to both HLA and blood group substances may be tolerated once the graft is in situ and it is only the critical early post-transplant days and weeks that cannot be accommodated. Understanding of the mechanism of accommodation has yet to be achieved, because continued activation of complement is seen in ABO-incompatible grafts but without obvious pathologic graft damage.[55]

OUTCOMES INFORM THE RECIPIENT DECISION

Patients with progressive end-stage chronic kidney disease must decide whether they wish to commence dialysis, receive a transplant, or elect not to be treated. The outcomes of the alternatives are obviously critical to that decision, and thus it is the responsibility of the treating physician and team to ensure each patient is properly informed to make that choice. The components of that decision extend beyond the medical facts and in many countries involve financial and other social factors, such as availability of therapy. The medical decision for each individual revolves around prognosis related to comorbidities, organ availability (of both living and deceased donor kidneys), and alternative dialysis therapies. The advantages are not all exactly as might be predicted. For example, a 25- to 35-year-old adult with no comorbidities can be predicted to do well after transplantation with either a living or deceased donor, but such an individual will also do well on dialysis, so the life year gain from transplantation may not be as much as expected.[56] On the other hand, a 55-year-old diabetic patient may have a poor prognosis with a transplant but will do even worse on dialysis and thus may wish to seek the added life years from transplantation.

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SELF-ASSESSMENT QUESTIONS

1. Actuarial survival is a:
   - **A.** Method of calculating how long a patient will live after kidney transplant failure
   - **B.** Statistical method of maximizing the information available for analysis of outcome from a group of patients and events
   - **C.** Way of making "actual results" seem more plausible
   - **D.** Statistical method to estimate the outcomes of patients who are lost to follow-up
2. The composite end-point accepted by the U.S. Food and Drug Administration for immunosuppressive drug trials in transplantation includes:
   - **A.** Graft failure and patient death
   - **B.** Graft failure, chronic rejection, and lost to follow-up
   - **C.** Acute rejection, graft failure, lost to follow-up, and patient death
   - **D.** Biopsy-proven acute cellular and acute antibody-mediated rejection
3. Meta-analysis is a:
   - **A.** Way of deciding which of several randomized trials is correct
   - **B.** Statistical software package
   - **C.** Method of combining the results from all similar trials to gain statistical power
   - **D.** Trial design used in large studies to decide which factor is most important in determining an outcome.

110

Pancreas and Islet Transplantation

Jonathan S. Fisher, Christopher L. Marsh

Pancreas transplants are performed to treat insulin-requiring diabetes. Initially, pancreas transplants were performed only in those diabetic patients with chronic kidney disease who needed kidney transplants; these patients underwent simultaneous pancreas-kidney transplantation (SPK). Today, pancreas transplantation alone (PTA) or pancreas transplantation after living or cadaveric renal transplantation (PAK) is increasingly common. SPK accounted for 72% of all pancreas transplants in 2010 (Fig. 110.1). There were approximately 2800 people in the United States waiting for pancreas transplants in 2016.[1] The 2014 Annual Report of the Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR) reveals that the number of new registrations as well as of pancreata recovered and transplanted in the United States steadily increased from 1997 to 2004, but there has been some decline since then.[2] Although data are less complete for pancreas transplants outside the United States, the trends are similar with a decline in non-U.S. transplants performed since 2007. Several factors are thought to play a role. New insulin formulations and delivery systems in the form of insulin pumps have reduced the need for transplant in some patients. Selection criteria for potential recipients have become increasingly stringent as the average age of recipients has increased as well as the number of transplants being done in patients with type 2 diabetes. Simultaneously, there has been a trend over time toward tighter donor criteria as transplant centers strive to ensure excellent outcomes. Last, there have been recent downward trends in numbers of patients registered for pancreas transplants. New SPK registrations in the United States rose from 1412 in 1997 to a high of 2007 in 2000 and declined to 1264 in 2015. Some of this reduction may be due to an increase in the number of patients receiving islet cell transplants.

PATIENT SELECTION CRITERIA FOR PANCREAS OR ISLET TRANSPLANTATION

Indications for Transplantation

Indications for pancreas or islet transplantation include insulin-dependent diabetes with associated diabetic complications (nephropathy, neuropathy, and retinopathy) and diabetes with episodes of hypoglycemic unawareness.

The relative roles of pancreas and islet cell transplantation remain controversial, but several factors influence the choice between these two approaches in clinical practice. Because the quantity of islets that are available for transplantation remains a limiting factor, islet transplants are more appropriate for patients with smaller insulin requirements, typically slender women. Larger patients (usually with higher insulin requirements) are more reliably served with whole-organ pancreas transplants. Islet transplantation is performed by a radiographic procedure and therefore is better suited for patients who cannot tolerate the surgical stress of whole-organ transplantation, such as older patients with severe coronary heart disease.

Pancreas or islet transplantations have not routinely been performed for type 2 diabetes mellitus because the primary defect in type 2 diabetes is insulin resistance, not insulin deficiency. There may be a role for pancreas transplantation in patients with type 2 diabetes who develop islet failure after years of insulin resistance or those who have deficiencies in beta cell function such as maturity onset diabetes of the young types 1-6. A review of the United Network for Organ Sharing (UNOS) registry from 2000 to 2007 revealed that after adjusting for a variety of factors (e.g., age, race, weight, time on dialysis, cardiovascular disease) there were no differences in risk for death or kidney or pancreas failure according to diabetes classification.[3] The analysis suggested that insulin-requiring patients who have type 2 diabetes, are younger than 50 years, and have body mass index (BMI) less than 30 kg/m^2 will become insulin independent with a pancreas transplant.[4] The proportion of pancreas transplants performed in people with type 2 diabetes has increased from 2% in 1995% to 9% in 2014.[5]

Should living kidney donor recipients be offered a PAK transplant? An analysis of UNOS data revealed no difference in survival of SPK recipients and living kidney donor recipients at up to 8 years of follow-up.[6] However, a European study showed an improved 10-year patient survival (83% in SPK vs. 70% in kidney transplants alone) and noted a significantly lower progression of macrovascular disease (cerebrovascular, coronary, and peripheral vascular) with SPK transplants.[7] Kidney graft ultrastructure and function are better preserved comparing SPK with LKD transplantation alone.[8] A review of the UNOS registry 1997 to 2007 divided those recipients with type 1 diabetes who received a living donor kidney transplant into two groups: those who subsequently received a PAK within a year of the kidney transplant (n = 1026) and those who did not (n = 3528). At the end of the eighth year, the patients who subsequently received a PAK had superior patient (85% vs. 75%) and kidney graft survival (75% vs. 62%).[9] Therefore the two-stage approach of PAK after a living donor kidney transplant should be considered for patients who have a living kidney donor and in whom the cardiovascular risk for the extended procedure required for SPK is considered too great.

The role of PTA transplants in those with preserved renal function remains unclear. A single-center study of 131 PTA recipients revealed that PTA is an independent risk factor for the development of kidney failure, presumably because of the nephrotoxicity of long-term immunosuppression.[10] Analyses of the UNOS database have shown conflicting results with respect to survival for those with diabetes and preserved kidney function receiving a PTA than for those who remained on the waiting list and received conventional therapy.[11,12] Further study is warranted, keeping in mind that a prospective, randomized trial of pancreas transplantation versus conservative therapy is not practical.

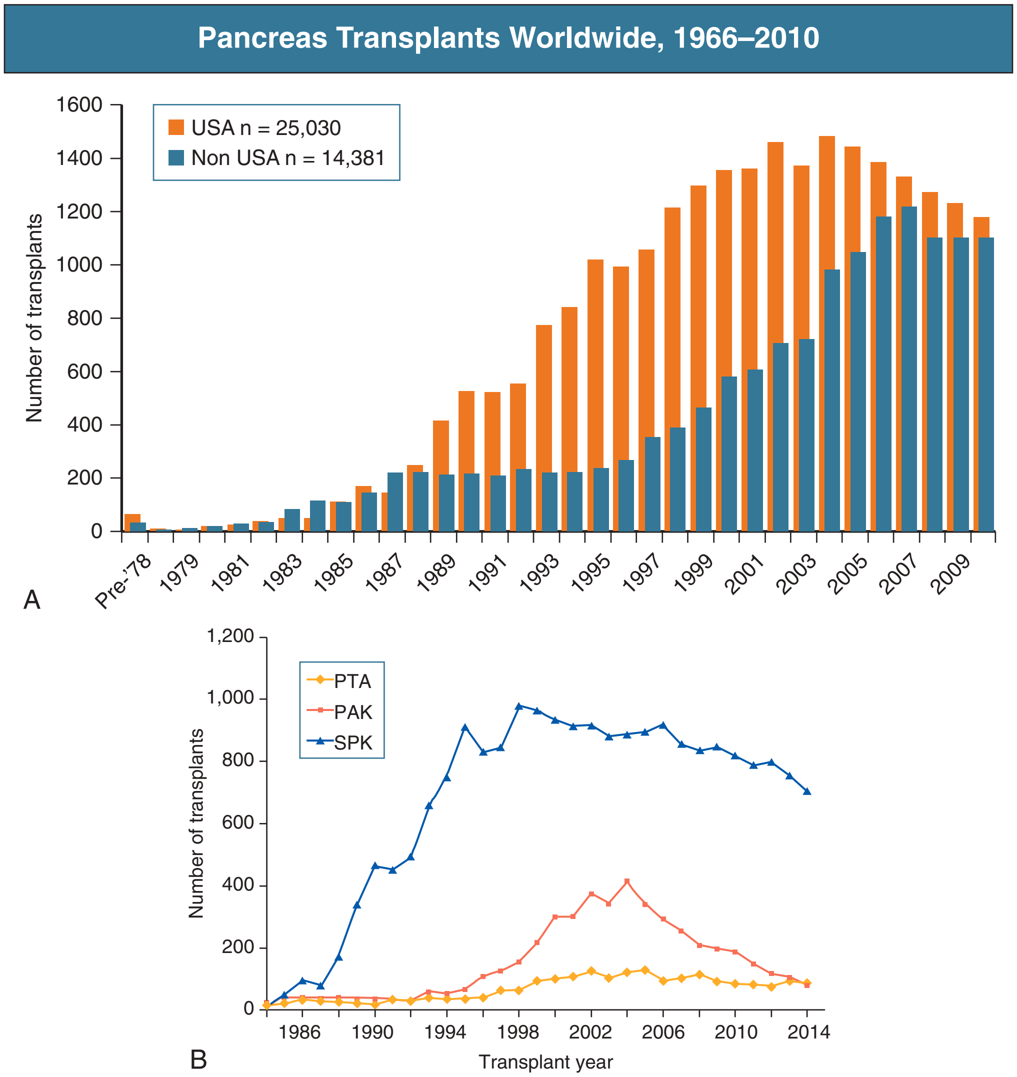


Fig. 110.1 Pancreas transplantation. (A) Number of pancreas transplants worldwide, 1966-2010. (B) Pancreas transplants in the United States by type, 1988 to 2011. *PAK,* Pancreas transplantation after living related or unrelated kidney transplantation; *PTA,* pancreas transplantation alone; *SPK,* simultaneous pancreas-kidney transplantation. (A, From reference 4; B, From American Journal of Transplantation Volume 16, Issue 9, pages 2556-2562, 8 JUL 2016.)

MEDICAL EVALUATION

The medical evaluation for the prospective pancreas transplant candidate is similar to that of the kidney-only recipient (see Chapter 102), although the cardiac workup is more extensive. The best candidates for transplantation are younger than 50 years and have a limited number of major complications of diabetes, such as hypoglycemic unawareness or diabetic neuropathy. Additional complications, such as vascular disease, orthostatic hypotension, and severe gastroparesis, put patients at higher risk for post-transplantation complications, but none of these factors by themselves exclude a patient from transplantation. It has been argued that chronologic age alone should not exclude a patient from pancreas transplant candidacy. Patient and graft survival has been shown to be comparable between younger patients and carefully selected older patients; however, there is a higher incidence of cardiac events in the older population.[13] Thus cardiovascular status is the primary deciding factor for transplantation eligibility because the surgery, infections, risk for thrombotic complications, and, until recently, rejection are more severe in the pancreas transplant recipient, demanding that the cardiovascular system be able to withstand multiple prolonged, hemodynamically stressful events. Cardiovascular or cerebrovascular problems (31%) and infections (21%) remain the leading causes of recipient death.[14] All patients require noninvasive cardiac stress evaluation because of the limited exercise capabilities of many patients. Cardiac catheterization is performed based on the results of noninvasive testing or is performed first for high-risk status (age older than 45 years, those with diabetes duration of more than 25 years, smokers of more than 5 pack-years, and those with an abnormal electrocardiogram). Peripheral vascular disease is evaluated by clinical examination and by arterial duplex ultrasound. Patients with limb-threatening ischemia are typically poor pancreas transplant candidates. The medical evaluation for islet transplantation is similar to that for pancreas transplantation, but exclusion criteria are fewer because of lower surgical and inflammatory risks.

The last criteria for transplantation are that the donor and recipient match for ABO blood group and that the recipient sera are crossmatch

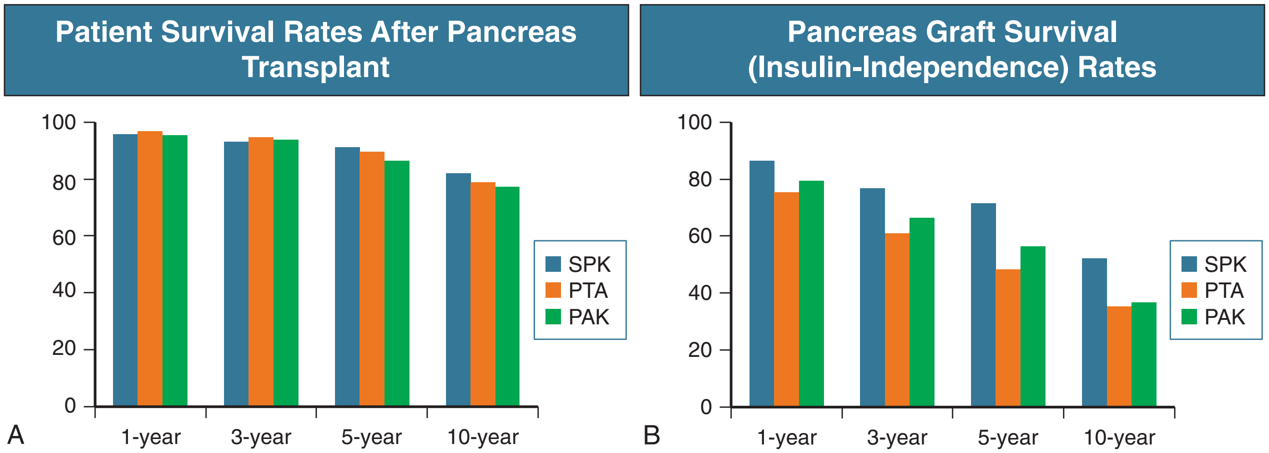


Fig. 110.2 Patient and graft survival after pancreas transplantation. Unadjusted pancreas patient and graft survival by type. (A) Patient survival rates. (B) Pancreas graft functional survival (insulin-independence) rates. *PAK,* Pancreas transplantation after living related or unrelated kidney transplantation; *PTA,* pancreas transplantation alone; *SPK,* simultaneous pancreas-kidney transplantation. (*A,* Modified from reference 2. *B,* From reference 1.)

negative against donor T cells by either the standard antiglobulin or flow cytometry crossmatch.

PANCREAS TRANSPLANTATION

Patient and Graft Survival

The reported 1-, 5-, and 10-year patient survival rates show a marked improvement from 1991 to 1995 to 2012 to 2013.[2] Pancreas graft survival rates have shown similar improvements (Fig. 110.2). Better outcomes are due to changes in surgical techniques, donor selection criteria, and improvement in the composition of the preservation fluid, as well as more effective immunosuppressive regimens, despite an increasing proportion of high-risk patients.

There has been a trend toward tighter donor selection criteria. The ideal donor is between 10 and 40 years of age, with a BMI less than 27.5 kg/m^2 and a cause of brain death other than cerebrovascular disease.[15] The UNOS database demonstrates that over the past 5 years more than 60% of such donors have had a cold ischemic time of less than 12 hours.[2]

Most organs are stored in the University of Wisconsin (UW) solution, which has increased early pancreas graft function and reduced the occurrence of preservation pancreatitis. A second cold storage solution, histidine-tryptophan-ketoglutarate (HTK), offers better tissue perfusion because of lower viscosity, less reperfusion hyperkalemia, and significantly lower cost. However, studies have suggested a higher incidence of graft pancreatitis and an increased rate of graft loss with HTK, particularly with longer cold ischemia times.[16,17] Approaches using either a two-layer storage method with UW or an HTK solution and a second layer of highly oxygenated perfluorocarbon or the attachment of the pancreas to a low-pressure pulsatile perfusion system are being investigated.

The current gold standard immunosuppression for pancreas transplants is antibody induction therapy, tacrolimus, mycophenolate mofetil (MMF), and corticosteroids; this has led to a 40% decrease in incidence of rejection and an increase in 1-year graft survival to more than 90%. Graft survival is not directly impacted by human leukocyte antigen (HLA) matching, though rejection, particularly for solitary pancreas transplants, has been correlated with the number of mismatches with a roughly twofold increase in the risk for rejection with four or more mismatches or with mismatching at the HLA-B or HLA-DR loci.[18] Moreover, rejection during the first year after transplant is the most critical factor in predicting whether the patient would reach 5 years with a functioning pancreas.[19] The same analysis suggested that either positive donor or positive recipient cytomegalovirus (CMV) status significantly decreases the likelihood of long-term graft function.

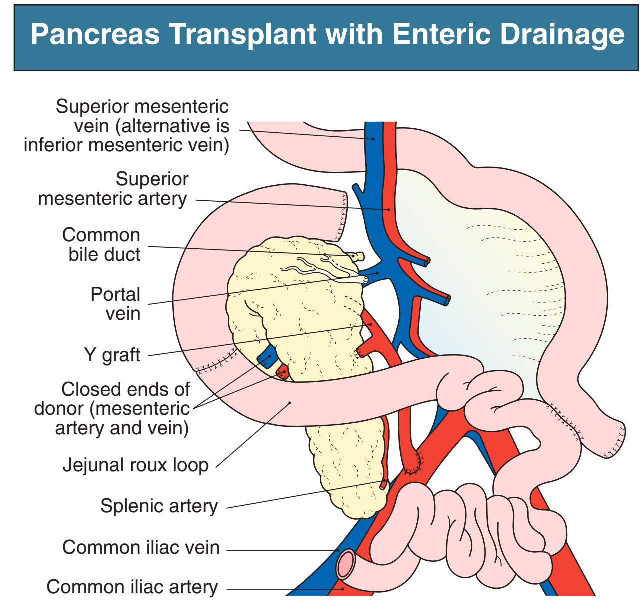

Pancreas Transplant with Enteric Drainage
Superior mesenteric vein (alternative is inferior mesenteric vein)
Superior mesenteric artery
Common bile duct
Portal vein
Y graft
Closed ends of donor (mesenteric artery and vein)
Jejunal roux loop
Splenic artery
Common iliac vein
Common iliac artery

Fig. 110.3 Pancreas transplant with enteric (portal) drainage.

Surgical Procedure

Current practice is to transplant the whole pancreas with a cuff of duodenum, which preserves the blood supply of the head of the pancreas and provides a means to drain exocrine secretions into either the small bowel (enteric drainage) or the bladder (Figs. 110.3 and 110.4).[1] A growing majority of the pancreas transplants in the United States are now enterically drained (Fig. 110.5).[1] The graft may be placed in the right iliac fossa like a kidney, intraperitoneally, and vascularized from the common iliac vessels so that the secreted insulin enters the systemic circulation. However, an alternative is to construct the venous anastomosis to the superior mesenteric vein, allowing more physiologic insulin output through the portal circulation. Currently, 15% to 20% of

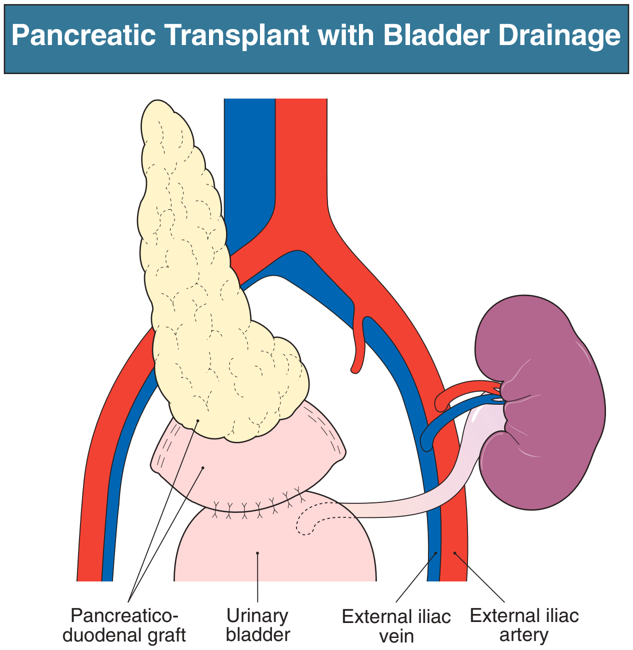

Pancreatic Transplant with Bladder Drainage
Pancreatico-duodenal graft
Urinary bladder
External iliac vein
External iliac artery

Fig. 110.4 **Pancreas transplant with bladder drainage.** The pancreas may be placed in either the intraperitoneal or extraperitoneal position.

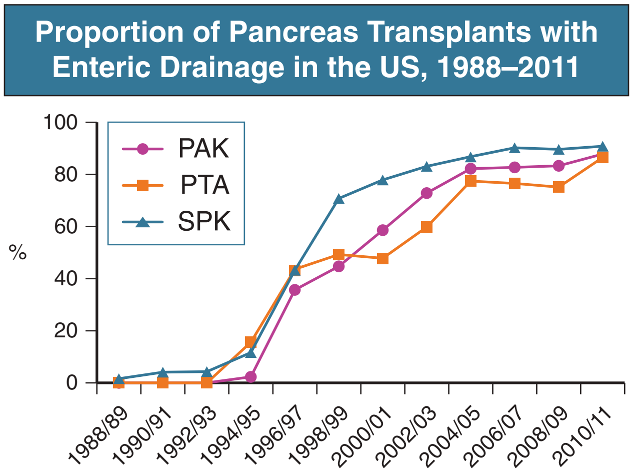


Fig. 110.5 **Pancreas transplant technique.** Proportion of U.S. primary pancreas transplantations using enteric drainage, by recipient category and era, 1988 to 2008. There has been a shift toward enterically drained compared with bladder-drained pancreas transplantation. *PAK,* Pancreas transplantation after living related or unrelated kidney transplantation; *PTA,* pancreas transplantation alone; *SPK,* simultaneous pancreas-kidney transplantation. (Modified from reference 4.)

enterically drained transplants use portal drainage. In either approach, an interposition graft from the donor (typically a Y graft containing common iliac artery with external and internal branches) is used to provide inflow from the recipient common iliac artery to the graft superior mesenteric and splenic arteries. Some surgeons have advocated reconnection of the graft gastroduodenal artery if the pancreaticoduodenal arcades are not intact.

BOX 110.1 Causes of Pancreas Graft Dysfunction

- Ductal obstruction
- Vascular: arterial or venous thrombosis (partial or complete), arteriovenous fistula
- Volume depletion
- High calcineurin inhibitor levels
- Graft pancreatitis (preservation, viral, bacterial, or fungal)
- Exocrine secretion anastomotic leak
- In cases of bladder drainage
  - Reflux pancreatitis
  - Urinary tract infection
  - Bladder outflow obstruction
- In cases of enteric drainage
  - Bowel obstruction

Bladder drainage allows monitoring for rejection by measurement of urinary amylase and avoids enterotomy-associated risks for infection and leak. The disadvantages of bladder drainage include susceptibility to dehydration, metabolic acidosis, and frequent urologic complications. Primary enteric drainage avoids these complications and is more physiologic but does not allow urinary amylase monitoring. With improved surgical techniques, increased use of real-time ultrasound, and percutaneous needle biopsy, the outcomes of enteric drainage now match those of bladder drainage. Bladder drainage is still appropriate when there is a history of major abdominal surgery, in the presence of Crohn's disease or other small bowel disease, and for older patients with less cardiovascular reserve, in whom a laparotomy may be avoided through a smaller lower quadrant retroperitoneal incision similar to that for a kidney transplant. Pancreas transplants with venous outflow to the superior mesenteric vein can be placed either anterior to the small bowel mesentery or in a retroperitoneal position behind the ascending colon, where the superior mesenteric vein is reached from the side. Surgical outcomes do not differ whether the venous drainage is systemic or portal. Although portal drainage is considered more physiologic and avoids hyperinsulinemia, these benefits are not well characterized.

Immunosuppression

Most centers use antibody induction therapy during the first 1 to 2 weeks after transplantation, mostly antithymocyte globulin (ATG).[20] Other centers use an interleukin-2 (IL-2) receptor antagonist (basiliximab) or, most recently, an anti-CD25 antibody (alemtuzumab).[21,22] Antibody-mediated rejection may be more common than acute cellular rejection in patients receiving alemtuzumab.[23] Most centers employ triple-drug maintenance immunosuppression with tacrolimus (or less commonly cyclosporine), MMF (or rarely azathioprine), and corticosteroids. There is increasing evidence of equivalent success with rapid corticosteroid elimination or corticosteroid avoidance protocols. Some centers replace the calcineurin inhibitor (CNI) or MMF with sirolimus typically after at least 1 month after surgery (after primary wound healing). With the more profound immunosuppressive induction produced by the newer antibodies (particularly alemtuzumab), there have been reports of immunosuppression protocols limited to a depleting antibody and a single additional agent.[22,24] Fortunately, CMV infection rates appear to be lower in corticosteroid-free regimens,[22] although there has been some increase in CMV infection in those receiving depleting antibody therapies.[21]

Graft Monitoring

The causes of pancreas graft dysfunction and the evaluation process are shown in Fig. 110.6, Box 110.1, and Table 110.1.

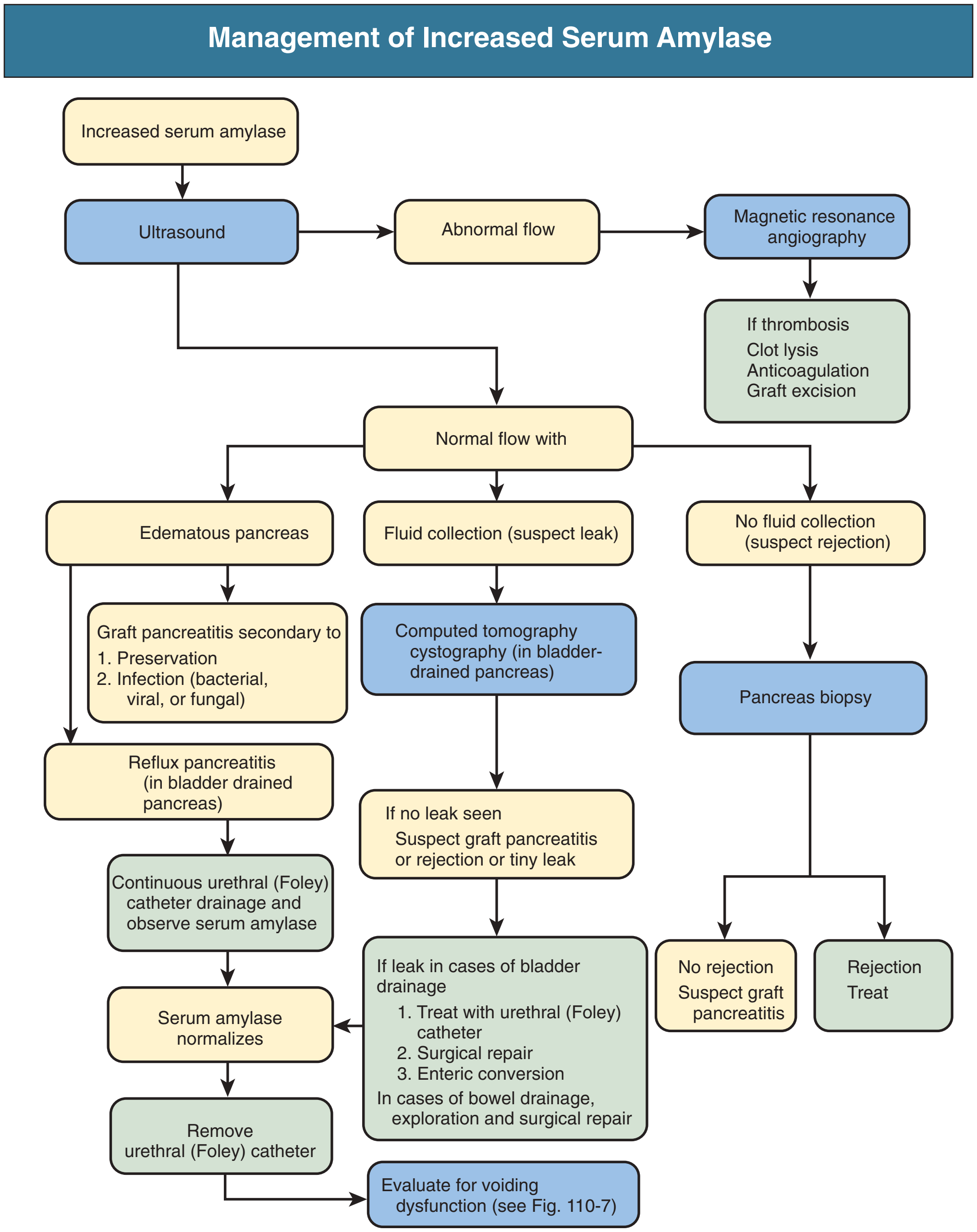

Management of Increased Serum Amylase
Increased serum amylase
Ultrasound
Abnormal flow
Magnetic resonance angiography
If thrombosis
Clot lysis
Anticoagulation
Graft excision
Normal flow with
Edematous pancreas
Fluid collection (suspect leak)
No fluid collection (suspect rejection)
Graft pancreatitis secondary to
1. Preservation
2. Infection (bacterial, viral, or fungal)
Computed tomography cystography (in bladder-drained pancreas)
Pancreas biopsy
Reflux pancreatitis (in bladder drained pancreas)
If no leak seen
Suspect graft pancreatitis or rejection or tiny leak
Continuous urethral (Foley) catheter drainage and observe serum amylase
If leak in cases of bladder drainage
1. Treat with urethral (Foley) catheter
2. Surgical repair
3. Enteric conversion
In cases of bowel drainage, exploration and surgical repair
No rejection
Suspect graft pancreatitis
Rejection
Treat
Serum amylase normalizes
Remove urethral (Foley) catheter
Evaluate for voiding dysfunction (see Fig. 110-7)

Fig. 110.6 Management of increased serum amylase after pancreas transplantation.

During the immediate perioperative phase, intravenous insulin is used to maintain serum glucose concentration around 100 to 120 mg/dl (5.5 to 6.6 mmol/l). Serum glucose values are not an early marker of pancreas dysfunction; elevations are observed only after significant parenchymal pancreatic damage has occurred. During the first 1 to 2 weeks after transplantation, serum amylase may be elevated as a result of pancreatic preservation injury. Trends are followed rather than absolute values, taking into consideration factors such as length of cold ischemic time and degree of gland edema. Stable serum levels are usually attained within 2 weeks after transplantation. Rising serum amylase or lipase concentration (typically by more than 20% of baseline) indicate possible graft injury requiring evaluation. Elevated serum amylase and serum lipase concentrations are moderately sensitive markers of pancreas rejection. However, other conventional causes of pancreatitis can still occur. Elevated fasting glucose and 2-hour postprandial glucose levels are relatively late indicators and only indicate dysfunction, without revealing cause.

With bladder drainage, urinary amylase excretion serves as an additional indicator and can be measured in 12-hour collections and reported as units per hour. In contrast to serum amylase, urinary amylase decreases with organ dysfunction. Like serum amylase, trends are followed rather than absolute levels, stable levels are usually achieved with 2 weeks of transplant, and other causes of pancreatitis may alter levels.

Ultrasound examination of the pancreas transplant is performed frequently in the early post-transplantation period to rule out vascular thrombosis. If the pancreas cannot be well visualized by ultrasound scan, magnetic resonance imaging and angiography may be informative. Any inflammatory state also can yield images of an edematous gland; however, other than for vascular thrombosis, imaging generally cannot reveal the cause of the dysfunction.

TABLE 110.1 **Evaluation of Pancreas Graft Dysfunction**

Assessment	Tests
Laboratory tests	Serum amylase, blood glucose, human anodal trypsinogen, cyclosporine or tacrolimus levels, C peptide In bladder-drained cases, urinary amylase and urine culture
Doppler ultrasound	Pancreatic blood flow, peripancreatic fluid collection, pancreatic ductal dilation In bladder-drained cases, evidence of bladder outlet obstruction
Computed tomography with or without cystography	Looking for leak and collections; this is performed by cystography in bladder-drained cases

Biopsy of the pancreas transplant remains the gold standard for diagnosis of acute or chronic rejection. A biopsy may be performed in apparently well-functioning grafts by protocol or at times of clinically suspected graft dysfunction to identify rejection or other causes of pancreatic injury before irreversible tissue damage has occurred. The easiest approach is a percutaneous biopsy with ultrasound or computed tomography guidance. Cystoscopic biopsy through the duodenal cuff is used in bladder-drained transplants if the percutaneous technique is not possible because of difficult visualization or overlying bowel. The most frequent complication of percutaneous biopsy is a perigraft hematoma or transient hematuria, but rarely seen are pancreatitis, arteriovenous fistula, abdominal hemorrhage, bowel perforation requiring exploration, and even graft loss. Because of the risks associated with biopsy, if the clinical picture is consistent with a mild case of rejection, patients may be treated without biopsy confirmation.

Treatment of pancreas rejection is similar to that of kidney rejection and generally involves pulse intravenous corticosteroids or antilymphocyte antibodies (see Chapter 104).

Treatment response is monitored by following the return of serum amylase and lipase or urinary amylase to baseline values. Imaging can be used to show resolution of edema and inflammation. Repeated biopsy, usually at a 2-week interval, is required to show resolution of more moderate or severe rejections and to look for histologic signs of the development of chronic rejection.

Patients with isolated pancreas rejection have an increased risk for kidney graft loss, supporting the concordance of acute rejection in the majority of patients.[25] In SPK or PAK patients, when biopsy of the pancreas cannot be performed safely, a kidney transplant biopsy may be used as a surrogate indicator. This must be done, however, in conjunction with serum and urine tests because synchronous rejection occurs only 70% to 80% of the time.[26]

Antimicrobial Prophylaxis

Antimicrobial prophylaxis is much like that for a kidney transplant alone. Trimethoprim-sulfamethoxazole is prescribed for the prevention of urinary tract infections (UTIs) and *Pneumocystis* infection. Oral clotrimazole or nystatin is used for the prevention of oral candidiasis; some centers use fluconazole for prophylaxis of *Candida* UTIs and intraabdominal fungal or yeast infections. Oral acyclovir is given to patients with a history of herpes simplex infection and to patients who are CMV negative and receive CMV-negative donor organs. Otherwise, valganciclovir or ganciclovir is given for 3 months after transplantation to all patients who are CMV positive. Patients who are CMV negative who receive CMV-positive organs are often treated for 6 months. Patients treated for rejection are typically returned to any discontinued antiinfectious prophylaxis for 1 to 3 months after rejection therapy.

Metabolic Monitoring

In addition to monitoring of the serum and urinary concentrations of amylase and the serum concentration of lipase, serum creatinine, potassium, magnesium, and bicarbonate levels must be monitored. Magnesium wasting is common with CNIs and frequently requires oral supplementation. With bladder drainage, there is high urinary loss of bicarbonate in pancreatic exocrine secretions, which may require as much as 130 mmol/day of replacement. Without replacement, patients develop metabolic acidosis with nausea and vomiting, which may lead to volume depletion, hypotension (exacerbated by underlying autonomic neuropathy), and graft thrombosis. Oral sodium bicarbonate, typically 2 g four times daily, is needed. Fluid intake should be 2.5 to 3 l/day to accommodate pancreatic and renal fluid outputs. This intake may be difficult to achieve because abdominal bloating from diabetic gastroparesis is exacerbated by the large fluid intake and the gas released from sodium bicarbonate tablets. Patients who are unable to maintain adequate oral intake may require intravenous fluids, including sodium bicarbonate. In patients who require intravenous repletion for longer than 1 month, consideration should be given to placement of a tunneled venous catheter or a buried central venous port for fluid administration.

Surgical Complications

Surgical complications of pancreas transplantation are shown in Table 110.2. Superficial infections and deep-seated abscesses are commonly fungal. The source of fungal contamination is thought to be the duodenal segment. Therefore topical antibiotic and antifungal solutions are used to irrigate the donor duodenum during procurement and implantation. Patients commonly receive 24 to 48 hours of postoperative antibiotics and fluconazole.

The causes of wound drainage are seroma, lymphocele, pancreatic fistula from either the tail or the anastomosis to the bladder or bowel, wound dehiscence, and preservation pancreatitis. Preservation pancreatitis is a complication of cold storage and may lead to wound drainage of whitish yellow, thick, noninfectious material formed from the enzymatic digestion of tissue, leading to fat necrosis and saponification. Wound drainage is seen more often with the extraperitoneal placement of the pancreas and also occurs when a pancreas from an obese donor is used. It is also associated with a mild increase in serum amylase concentration, low urinary amylase excretion, and variable changes in the serum glucose concentration.

Vascular complications occur in about 5% of patients and include arteriovenous fistulas secondary to surgery or biopsy, venous and arterial thrombosis, and, rarely, mycotic aneurysms. Vascular thrombosis rates were previously as high as 10%, but current rates are below 5%. Means of reducing the rate of thrombosis include minimization of warm and cold ischemia, no-touch procurement procedures using the duodenum and spleen as handles, and postoperative treatment with aspirin. In cases with longer cold ischemia times, a more edematous graft, or concern about low inflow or outflow, intravenous heparin is sometimes used for the first few postoperative days. Partial thrombosis may resolve with thrombolytic therapy or anticoagulation. More extensive thrombosis requires urgent surgical intervention. Complete graft thrombosis, especially in the immediate postoperative period, mandates urgent graft removal to prevent sepsis or a diffuse hypercoagulable state that might precipitate complications such as myocardial infarction.

Nonsurgical Complications

Nausea and vomiting are common, and causes include gastroparesis, constipation, cholelithiasis or esophageal reflux developing from motility

TABLE 110.2 **Surgical Complications After Pancreas Transplantation**

Type of Complication	Presentation	Diagnostic Findings and Testing	Treatment Options
Abscess	Fever, erythema of wound, wound drainage	Elevated WBC count, fluid collection on CT scan, pus on aspiration	Open or percutaneous drainage
Graft pancreatitis	Pain over allograft, lower abdominal pain	Elevated serum amylase, enlarged pancreas allograft	Octreotide or somatostatin Urethral (Foley) catheter if bladder drained
Lymphocele	Mass on palpation, urgency if bladder compression	Fluid collection on CT scan, clear fluid on aspiration	Open or percutaneous drainage
Wound drainage	Pancreatic debris, no erythema	Culture, CT scan to rule out deep abscess	Local wound care
Dehiscence	Wound open		Wound care, surgical closure
Arteriovenous fistula	Hematuria, abdominal bleeding	Doppler ultrasound, angiography	Embolization, surgical repair
Graft thrombosis	Elevated blood glucose Bloody urine if bladder drained	Low serum and urine amylase, sepsis-like syndrome; ultrasound or magnetic resonance imaging	If partial, thrombolytic therapy or anticoagulation (high risk for bleeding), graft pancreatectomy
Pancreatic fistula or leak (bowel drained)	Pain over allograft, sepsis, peritonitis, fever	Elevated WBCs, fluid collection on CT scan	Surgical drainage and repair

CT, Computed tomography; WBC, white blood cell.

TABLE 110.3 **Urologic Complications of Bladder-Drained Pancreas Transplants**

Complication	Cause	Presentation	Evaluation	Treatment Options
UTI	Diabetic bladder dysfunction (DBD)	Asymptomatic, or dysuria, fever, sepsis	Urine culture; check postvoid residual, if elevated urodynamics	Culture-specified antibiotics, prophylactic antibiotics *Female:* Double and timed voiding, CIC *Male:* α-Adrenoceptor blockers to aid bladder emptying, CIC, bladder neck–prostate incision If treatment failure, enteric conversion: Foley catheter drainage
Reflux pancreatitis	DBD	Asymptomatic or pain over pancreas allograft, elevated serum amylase	Check serum amylase, CT cystogram to exclude leak or duct obstruction	*If DBD:* Double and timed voiding, CIC, α-blockers to aid bladder emptying *If multiple and symptomatic episodes:* Bladder neck–prostate incision or enteric diversion
Duodenal cystotomy leak	Ischemic injury to duodenal cuff, cytomegalovirus or other infection, rejection, DBD	Pain over allograft, or peritonitis, elevated serum amylase	Check serum amylase, elevated creatinine, leak on CT cystogram	Foley catheter drainage, if small If early, open surgical repair with resection and closure of layers, evaluate for DBD after recovery If late, consider enteric conversion
Urethritis or dysuria syndrome, occasional urethral disruption	UTI or DBD causing activation of pancreatic enzymes with digestion of urethral mucosa	Dysuria, urinary retention, hematuria	Check postvoid residual, low-grade UTI; after recovery, evaluate for DBD	Foley catheter, analgesics, empiric treatment of UTI *If multiple and symptomatic:* Enteric conversion

UIT, urinary tract infection; CIC, clean intermittent catheterization; CT, computed tomography.

problems, and esophagitis with or without CMV disease. Antiemetics plus histamine-2 (H_2) blockers or proton pump inhibitors are usually effective therapy and are given for 2 to 3 months after transplantation. Persistent symptoms may require prokinetic agents (metoclopramide or erythromycin). Diarrhea can be caused by immunosuppressive medications, intrinsic gut motility problems, food intolerance, or CMV or other infection. Constipation is treated with increased fluid intake, dietary modification, increased activity, and regular low-dose schedule of stool softeners or laxatives.

Orthostatic hypotension may worsen after transplantation because of prolonged bed rest in the presence of diabetic autonomic neuropathy. Treatment may include a high-sodium diet with a mineralocorticoid (fludrocortisone) or an α-adrenergic agonist (midodrine).

Urologic Complication

Urologic complications are common after bladder drainage (Table 110.3).[27] Pretransplantation bladder dysfunction secondary to diabetic autonomic neuropathy causes a large-capacity bladder, decreased bladder sensation, increased residual urine volume, and decreased urinary flow rates. Bladder function is worsened by the autoaugmentation of the bladder by the added duodenal segment. Preoperative urodynamics are abnormal in up to 43% of patients but do not predict post-transplantation urologic complications such as reflux pancreatitis or infections.[28]

Urinalysis is difficult to interpret with the bladder-drained pancreas. The urine contains white cells from duodenal mucosal sloughing and may be leukocyte esterase positive without bacteriuria. Urine protein excretion is elevated to 1 to 3 g/day in most patients, composed of pancreatic enzymes, immunoglobulins, other globulins, albumin, and digested fragments of these proteins. Urinary albumin, if it is measurable in the presence of enzymatic degradation, may come from the transplanted or native kidneys.

Macrohematuria occurs in up to 28% of bladder-drained pancreas recipients. Early hematuria is related to surgical trauma to the bladder or duodenal mucosa near the cystoduodenostomy site and usually clears with diuresis or bladder irrigation.[27] Continuous bladder irrigation requires caution because the cystoduodenostomy is vulnerable to rupture if the drainage catheter becomes obstructed. Late hematuria, beyond 2 to 4 weeks after transplantation, can arise from anastomotic bleeding, duodenal mucosal sloughing or ulceration, reflux pancreatitis, cystitis, graft thrombosis, rarely arteriovenous fistulas, and pseudoaneurysms. Evaluation should include ultrasound, urine culture, and cystoscopy. If the pancreas appears to be the source on cystoscopy, biopsy of the pancreas may be required to determine the exact cause.

Microhematuria should be evaluated. Evidence is sought for recurrent disease, new renal disease, or genitourinary malignant neoplasms.

Urinary Tract Infections

Risk factors for UTI after bladder-drained pancreas transplantation include large bladder capacity, incomplete bladder emptying, high bladder urine pH (as a result of pancreatic bicarbonate), bladder and urethral mucosal irritation from activated pancreatic enzymes with the loss of mucosal barrier, prolonged bladder catheterization, and immunosuppression.[28] Most centers administer oral antibacterial and antifungal prophylaxis for up to 6 to 12 months or indefinitely after transplantation.

Urinary reflux pancreatitis, which causes pancreas graft dysfunction, may be associated with perigraft abdominal pain and fever. It is often a result of poor bladder function and requires drainage with a bladder catheter for 5 to 7 days and assessment of bladder dysfunction (Fig. 110.7).

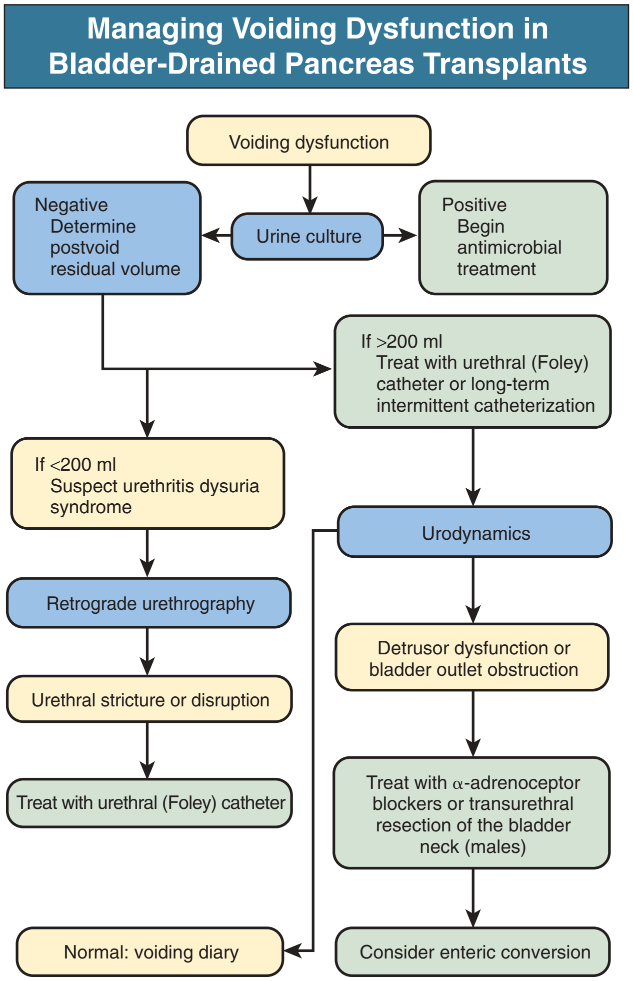

Managing Voiding Dysfunction in Bladder-Drained Pancreas Transplants
Voiding dysfunction
Urine culture
Negative Determine postvoid residual volume
Positive Begin antimicrobial treatment
If >200 ml Treat with urethral (Foley) catheter or long-term intermittent catheterization
If <200 ml Suspect urethritis dysuria syndrome
Urodynamics
Retrograde urethrography
Detrusor dysfunction or bladder outlet obstruction
Urethral stricture or disruption
Treat with urethral (Foley) catheter
Treat with α-adrenoceptor blockers or transurethral resection of the bladder neck (males)
Normal: voiding diary
Consider enteric conversion

Fig. 110.7 Management of post-transplantation voiding abnormalities. (From reference 27.)

A urethritis dysuria syndrome occurs in 2% to 8% of pancreas recipients with bladder drainage and is caused by uroepithelial exposure to the activated pancreatic proenzymes trypsinogen, chymotrypsinogen, and procarboxypeptidase. Pancreatic exocrine secretions consist of bicarbonate, amylase, lipase, and proenzymes, which are activated by the enterokinase in the graft duodenal brush border. Increased intravesical enzyme activation occurs with low-grade UTIs and urinary stasis, and patients will develop voiding pain or penile, glandular, meatal, or vulvar ulceration. Enzyme activation may be minimized by treatment of low-count bacteriuria, increase in fluid intake, and frequent voiding. If emptying does not improve with α-blockers, continuous Foley catheter drainage for 7 to 10 days is effective.[29]

Enteric Conversion

Enteric conversion is an option for most of the chronic urologic complications associated with bladder-drained pancreas transplantation. The indications are urethral disruption, recurrent urine leak, persistent bleeding, chronic UTI, dysuria, recurrent hypovolemia, and metabolic acidosis. The conversion rate varies from 8% to 14%. It is ideal to wait until 6 to 12 months after transplantation, when possible, to allow monitoring of urine amylase for early rejection episodes.

Late Complications

Late complications after pancreas transplantation typically fit into one of two patterns. There can be an acute presentation of graft rejection, not different from that seen in early graft dysfunction. The second pattern is more insidious; chronic inflammatory states from chronic rejection, ischemia, or infection may lead to gradual graft loss. Unfortunately, there is no practical test to measure small decrements in graft function in the way serum creatinine allows detection of kidney transplant dysfunction. Although its sensitivity is not optimal, patients are typically asked to measure 2-hour postprandial glucose levels (which are more sensitive than fasting blood glucose levels) weekly and to report trends or sudden increases to the physician.

IMPACT OF PANCREAS TRANSPLANTATION ON DIABETIC COMPLICATIONS

Pancreas transplantation is performed to eliminate the need for exogenous insulin and the risk for severe hypoglycemic episodes and to stop or to reverse the consequences of hyperglycemia. Well-functioning pancreas transplants result in normal fasting blood glucose concentrations, normal glycated hemoglobin levels, and only slightly abnormal oral glucose tolerance testing.[30]

Hypoglycemia

Although severe hypoglycemia is rare, mild hypoglycemia may develop in patients with a well-functioning pancreas graft once low baseline immunosuppression has been reached, especially in patients who have regained little weight after transplantation and who are physically active. Postprandial hypoglycemic episodes are not always symptomatic. They are associated with high-carbohydrate meals, excessive intake of caffeine or alcohol, excessive exercise, and, in some patients with hypoglycemia, circulating antiinsulin antibodies. This is not often a significant clinical problem and is usually resolved by avoidance of carbohydrate-rich meals.

A major benefit of pancreas transplantation is restoration of glucagon secretory responses to hypoglycemia. In patients with type 1 diabetes, the absence of functional beta cells within the islet eliminates the normal physiologic response by which intraislet insulin tonically dampens secretion of glucagon from alpha cells. Consequently, diabetic subjects are usually at risk for prolonged hypoglycemia secondary to injected insulin because there is failure of the normal counterregulatory action of glucagon on the liver to increase glycogenolysis. Despite the fact that the transplanted pancreas is placed ectopically and does not develop vagal control, the transplanted organ has normal glucagon responses to insulin-induced hypoglycemia and resultant counterregulation of hypoglycemia through increased hepatic glucose production. After pancreas transplantation, hypoglycemic awareness returns, as well as partial return of defective epinephrine secretion during insulin-induced hypoglycemia.

Hyperglycemia

Post-transplantation hyperglycemia may be caused by pancreas graft dysfunction, inadequate insulin release secondary to high tacrolimus or occasionally cyclosporine levels, resistance to insulin secondary to corticosteroids, weight gain, and inadequate physical activity. Although the use of tacrolimus has reduced pancreas graft rejection, it also decreases insulin gene transcription. If laboratory and imaging evaluations (see Table 110.1) are normal, hyperglycemia is the result of decreased insulin production or peripheral insulin resistance, which can be identified by measurement of glucose utilization rates and glucose/arginine-potentiated insulin secretion. In the absence of graft rejection, post-transplantation hyperglycemia should first be managed by dietary intervention and exercise. Insulin may be needed initially but often can be discontinued as oral hypoglycemic agents begin to take effect. Sulfonylureas are effective therapy. Hyperglycemia secondary to rejection is a late event and indicates irreversible graft damage. Because of the increased risk for rejection with manipulation of immunosuppression, minimizing the tacrolimus dose or changing to cyclosporine or sirolimus should not usually be considered until these measures have failed.

Microvascular Complications

Retinopathy

In a prospective fundoscopic study of patients with SPK over 45 months, there was a decreased need for post-transplantation laser therapy and the diabetic retinopathy showed stabilization in 62%, improvement in 21%, and progression in 17%.[31] In the postoperative period, patients may develop neoproliferation and retinal hemorrhages if preoperative blood glucose control is very poor and blood glucose normalizes rapidly after transplantation. Patients remain at risk for retinal detachment because of scarring secondary to previous retinal damage. Cataracts are more common after transplantation.

Neuropathy

Sensory and motor nerve conduction velocities improve rapidly after pancreas transplantation and then stabilize.[32] Greater recovery is seen in nonobese, younger, shorter patients; in those with better initial action potential amplitudes; in those not receiving renal replacement therapy; and possibly in those receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[33] The recovery of action potential amplitudes is gradual, continuing to improve up to 5 years beyond transplantation. Recovery is more complete in sensory than in motor nerves.

There is greater improvement in autonomic reactivity and gastric emptying in SPK recipients compared with diabetic kidney-only transplant recipients.[34] But if autonomic symptoms are severe at the time of pancreas transplantation, improvement is unlikely.

Nephropathy

Early diabetic nephropathy is characterized by increased glomerular basement membrane thickness and an increase in mesangial volume. Renal transplant biopsy specimens from diabetics with SPK and kidney-only transplants within 2.5 years of transplantation show glomerular basement membrane thickness within the normal range. After 2.5 years from transplantation, 92% of renal biopsy specimens from the kidney-pancreas recipients have a normal glomerular basement membrane thickness compared with only 35% of the biopsy samples from the kidney-only recipients; relative mesangial volume was normal in 82% of the biopsy specimens from kidney-pancreas recipients compared with only 12% in the kidney-only recipients.[35] Thus concurrent pancreas transplantation decreases the occurrence of the changes of diabetic nephropathy that may result in allograft loss.

Vascular Disease

Successful kidney-pancreas transplantation results in a significant improvement in the control of hypertension compared with kidney transplant alone in patients with type 1 diabetes.[36] Increase in peripheral vascular disease has been reported in kidney-pancreas transplant recipients compared with kidney-alone transplant recipients[37]; however, another study found the same prevalence of peripheral vascular disease after pancreas transplantation as occurred in diabetic kidney-only recipients who refused pancreas transplantation for nonmedical reasons and in nondiabetic kidney transplant recipients.[38] Encouragingly, one study showed that after a 10-year mean observation period, the progression of macrovascular diseases (cerebrovascular, coronary, and peripheral vascular) was significantly lower in recipients with a functioning SPK compared with a kidney transplant alone.[7]

A study using intravital microscopic evaluation of nail bed and conjunctival vasculature found improved vascularization (as assessed by a reduction in venular diameter, increased number of arterioles per unit area, and elevation of the perfusion capacity) only in kidney-pancreas recipients.[39]

Quality of Life and Social Issues

Pancreas transplantation is a very stressful event and can tax even the strongest of family relationships. Pretransplantation debilities (decreased vision, neuropathy, muscle weakness, orthostatic symptoms) can be exacerbated by the surgery and immunosuppressive medications. Patients who smoke or drink significant amounts of alcohol and are without family support have worse survival after transplantation than those who do not. However, kidney-pancreas transplant recipients with social support and well-functioning grafts report an increased global quality of life and frequently return to work, although the number returning to work is not much different from those receiving a kidney transplant alone.[40] In living donor simultaneous kidney-pancreas transplantation, preliminary results suggest that quality of life is stable for donors whereas recipients experience improvement.[41]

Pregnancy After Pancreas Transplantation

Within 1 year of transplantation, menstruation and ovulation return in most women of childbearing age. The U.S. National Transplantation Pregnancy Registry has reported 62 pregnancies in 40 SPK patients.[42] The outcomes were 50 live births, 3 therapeutic and 10 spontaneous abortions (1 twin reduction), and 1 ectopic twin pregnancy. The newborn outcomes were prematurity (39 of 50), low birth weight (32 of 50), other neonatal complications (28 of 50), and neonatal death (1 of 50). Ten patients had rejections that resulted in graft loss, and 58% of the patients required cesarean section. Hypertension, prematurity, preeclampsia, and growth restriction frequently complicated the pregnancies, even with good renal function. Gestational diabetes appeared in 3%.

All transplant recipient pregnancies require high-risk obstetric care. Consensus opinion is that pregnancy is safe by 1 year after transplantation under the following conditions: no rejection has occurred in the past year, graft function is stable, no active infections that could have a negative impact on the fetus (e.g., CMV infection) are present, and the patient is not taking any teratogenic medications.[43] MMF has been linked to structural malformations, and patients planning on conception should transition to another agent 6 weeks before trying to conceive.[44] Cyclosporine and tacrolimus levels often decline during pregnancy and require close monitoring to prevent rejection. Cesarean section is not mandatory, but vaginal deliveries must be observed for signs of allograft duodenal rupture. The average gestational period is 35 ± 2 weeks; the average birth weight is 2150 ± 680 g. There is no evidence that the children of transplant recipients are more likely to have abnormal development.

The management of other medical issues does not differ from that in kidney-only transplant recipients (see Chapters 105 and 106).

ISLET TRANSPLANTATION

Islet transplantation, with its reduced antigen load, technical simplicity, and low morbidity, has the potential to dramatically improve the quality of life of individuals with type 1 diabetes. The first series of islet allotransplantations in patients with type 1 diabetes were reported in 1977.[45] There were then sporadic reports in the 1990s of insulin independence for extended periods after islet allotransplantation.[46,47] Autotransplantation studies (free of any donor-recipient immunologic issues) then demonstrated that a critical mass of 300,000 islet equivalents (IE) could reestablish and maintain insulin independence beyond 2 years.[48] To date, the longest period of insulin independence after autotransplantation is more than 16 years.[49] The primary goal of islet transplantation remains optimal glycemic control without severe hypoglycemia rather than insulin independence.[50]

Preliminary work suggests that an artificial pancreas can improve average glycemic control and simultaneously reduce moderate hypoglycemia. Though untested, it should be able to prevent severe hypoglycemia. Technical problems remain, such as glucose sensor accuracy, network connectivity, and insulin pump reliability. Combining an artificial pancreas and an islet transplant may eventually allow the former to deliver a large fraction of the required insulin and the latter to provide fine tuning.[50]

Islet allotransplantation will never supply sufficient islets for the treatment of the millions with diabetes. Additional potential future sources of islets include xenogeneic islets (mostly from pigs), stem cells, or beta cell regeneration, though these remain in the preclinical realm.

Islet After Kidney Transplantation

The initial allogeneic islet transplants in patients with type 1 diabetes beginning in the late 1970s were in patients with end-stage renal disease as sequential islet after kidney (IAK) or simultaneous islet-kidney transplantation. Because the kidney transplant patients were already immunosuppressed, the IAK transplant procedure carried a minimal risk. However, there could be destabilization of the transplanted kidney and also islet dysfunction because most kidney transplant immunosuppression protocols included corticosteroids. Nevertheless, there were beneficial effects from improved glycemic control on both survival and function of transplanted kidneys.[51] Metabolic control (hemoglobin A_{1c} [HbA_{1c}] level and fasting glycemia) improved after IAK even in patients receiving low-dose corticosteroids. Adverse events included procedure-related pleural effusion and cholecystitis.[52]

Of the 237 well-documented allotransplants recorded in the Islet Transplant Registry from 1990 to 2000, less than 12% of recipients were insulin free at 1 year after transplantation. The reasons for this failure rate may include subtherapeutic islet implant mass, high rate of engraftment failure, islet damage in the liver (the site of implantation) by direct local toxic effects of the immunosuppressants, ineffective immunosuppression that fails to prevent rejection, recurrent autoimmune diabetes, and islet functional exhaustion. Four criteria were associated with insulin independence: (1) an islet implant mass of more than 6000 IE/kg, (2) a cold ischemia (preservation) time of less than 8 hours, (3) induction therapy with polyclonal antibodies such as antilymphocyte globulin or ATG, and (4) the liver as the favored implantation site. Early immunosuppressive regimens were relatively ineffective in preventing allograft rejection compared with their effect on vascularized pancreas grafts. Most if not all immunosuppressive agents were associated with impaired beta cell function and reduced graft revascularization.

As of the end of 2013, there were 1011 allogeneic islet transplant recipients, both islet transplant alone and islet after or simultaneous with kidney. Overall achievement of insulin independence was 65% in the first year after islet infusion (with or without reinfusion), and by year 2 this rate increased to 75%.

More success with insulin independence was reported in nonuremic patients with type 1 diabetes transplanted with an average of 800,000 islets by use of the Edmonton protocol, a corticosteroid-free immunosuppression regimen of daclizumab, sirolimus, and low-dose tacrolimus. Although follow-up of this cohort has since confirmed long-term C-peptide production with therapy that is safe and well tolerated, insulin independence is maintained in only a minority.[53] There has since been an exponential increase in clinical islet transplant activity; more patients with type 1 diabetes have now received islet transplants in the past 5 years than in the entire preceding 30-year history of islet transplantation.

Partial graft function, such as improvement of fasting C-peptide alone (to 0.3 to 0.5 ng/ml) combined with exogenous insulin, is sufficient to be associated with improved HbA_{1c}, glycemic control, and lower levels of severe hypoglycemia. The results are improved with higher fasting C-peptide level.

Technique of Islet Transplantation

The current technique of islet transplantation involves deceased donor pancreas procurement, organ preservation, enzymatic isolation of the islets, purification, and percutaneous injection of sterile islets into the liver through the portal vein by a catheter placed under radiographic guidance (Fig. 110.8).[54] Although accessing the portal vein percutaneously is relatively invasive, the entire procedure can be performed on outpatients. Effective mechanical and physical methods to seal the catheter track reduce the risk for postprocedural bleeding. Bleeding related to the procedure (23%), thrombus in segmental branches of the portal vein (8%), and punctured gallbladder (3%) are the most observed acute complications after islet transplantation.[54]

Medical Complications

There are also complications of islet transplantation that are not directly related to the procedure itself.[49] Changes consistent with fatty liver are reported in 22% of subjects who had magnetic resonance imaging after transplantation. Mouth ulcers occur in 90% of patients, usually

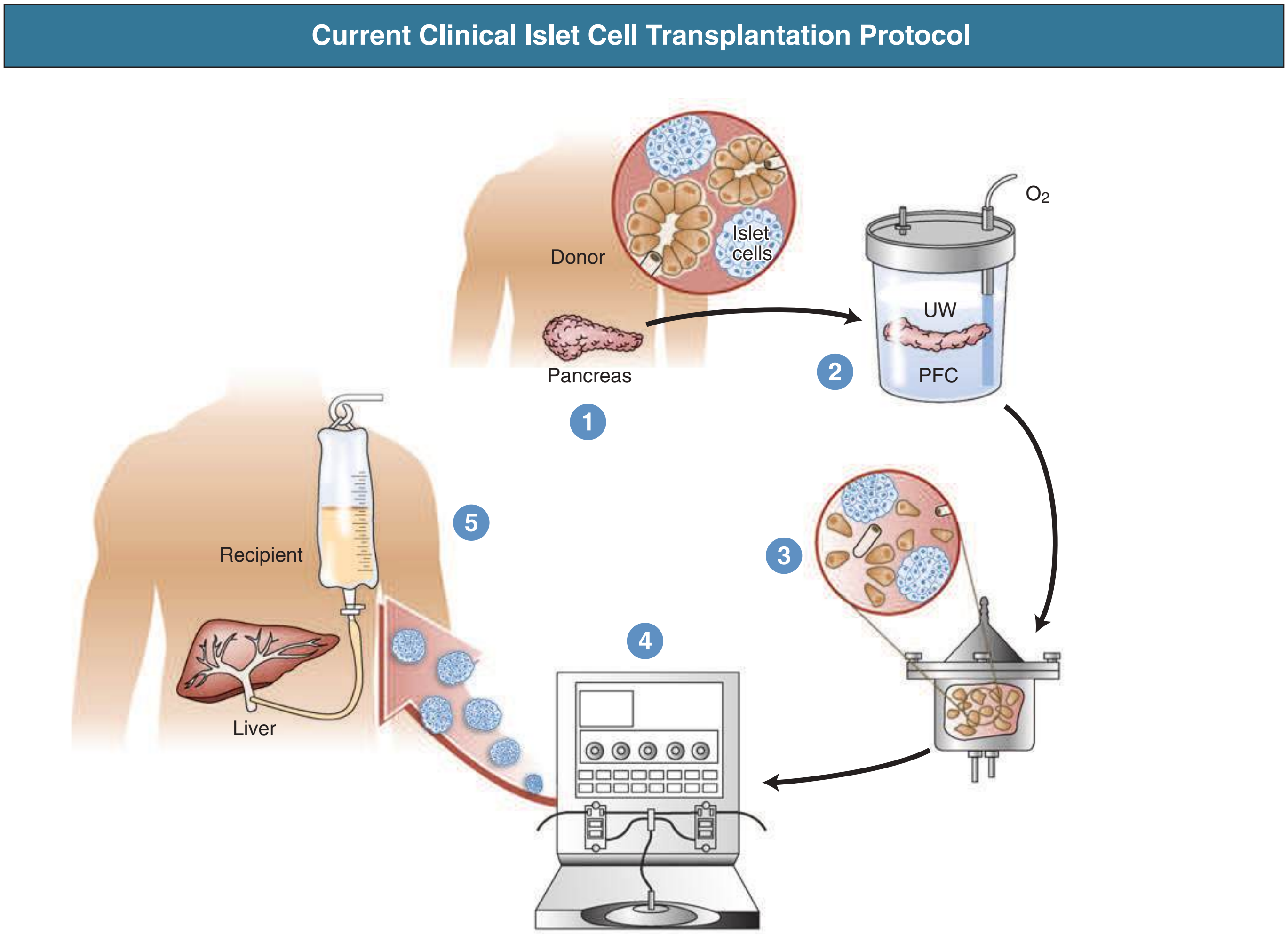


Fig. 110.8 **Clinical islet cell transplantation protocol.** The retrieved donor pancreas *(1)* is preserved *(2)* with a two-layer storage method using University of Wisconsin solution *(UW)* over a layer of highly oxygenated perfluorocarbon *(PFC)*. The pancreas is distended with collagenase and placed in a digestion chamber *(3)*. The disrupted exocrine and endocrine elements are purified by centrifugation *(4)*, and the islet preparation free from exocrine elements is transplanted by intrahepatic portal vein infusion *(5)*. (Modified from reference 53.)

responding to simple antiseptic measures or topical triamcinolone ointment together with a reduction in the dose of sirolimus. Diarrhea (60%) and acne (52%) are frequent. Forty-three percent of recipients reported edema, severe enough in 12% to necessitate a change in the immunosuppressive regimen. Weight loss is common.

In 27 of the 571 islet recipients in the Collaborative Islet Transplant Registry, 29 incidents of neoplasm were diagnosed. Of these incidents, 21 (72%) were benign and 6 were malignant.

Glycemic Control and Insulin Independence

Successful islet transplantation establishes normal HbA_{1c} levels, although the fasting glucose concentration tends to be slightly elevated and there is often impaired glucose tolerance. Another difference between successful pancreas and islet transplants is that placement of islets within the liver results in failure of the beta cell response to hypoglycemia, even though there is responsiveness to intravenous arginine. In a recent analysis, 82% of 118 islet recipients in three North American centers were insulin free at 1 year.[55] However, in a 5-year follow-up in Edmonton,[55] only 7.5% maintained insulin independence, although 82% had detectable C-peptide (Fig. 110.9). The median duration of insulin independence was 15 months.

Between 1997 to 2002, the prevalence of insulin independence at 1 year after islet transplant was 51%, decreasing to 18% by post-transplant 5 year. Improvements in islet isolation and transplant procedures has improved the prevalence of insulin independence to 66% by 1 year and 44% by 3 years after transplant for procedures performed in 2007 to 2010 (Fig. 110.10). Durability of islet graft function improved significantly when comparing islet transplants between 1999 to 2003 and 2004 to 2007, with 1- and 5-year fasting C-peptide of 0.3 ng/ml or greater of 74% and 35%, compared with 78% and 43%, respectively (see Fig. 110.10).[56]

Immunosuppressive Regimens

Tacrolimus, cyclosporine, and corticosteroids are diabetogenic through increased peripheral insulin resistance or direct islet cell toxicity. Oral administration increases portal venous drug concentrations and the

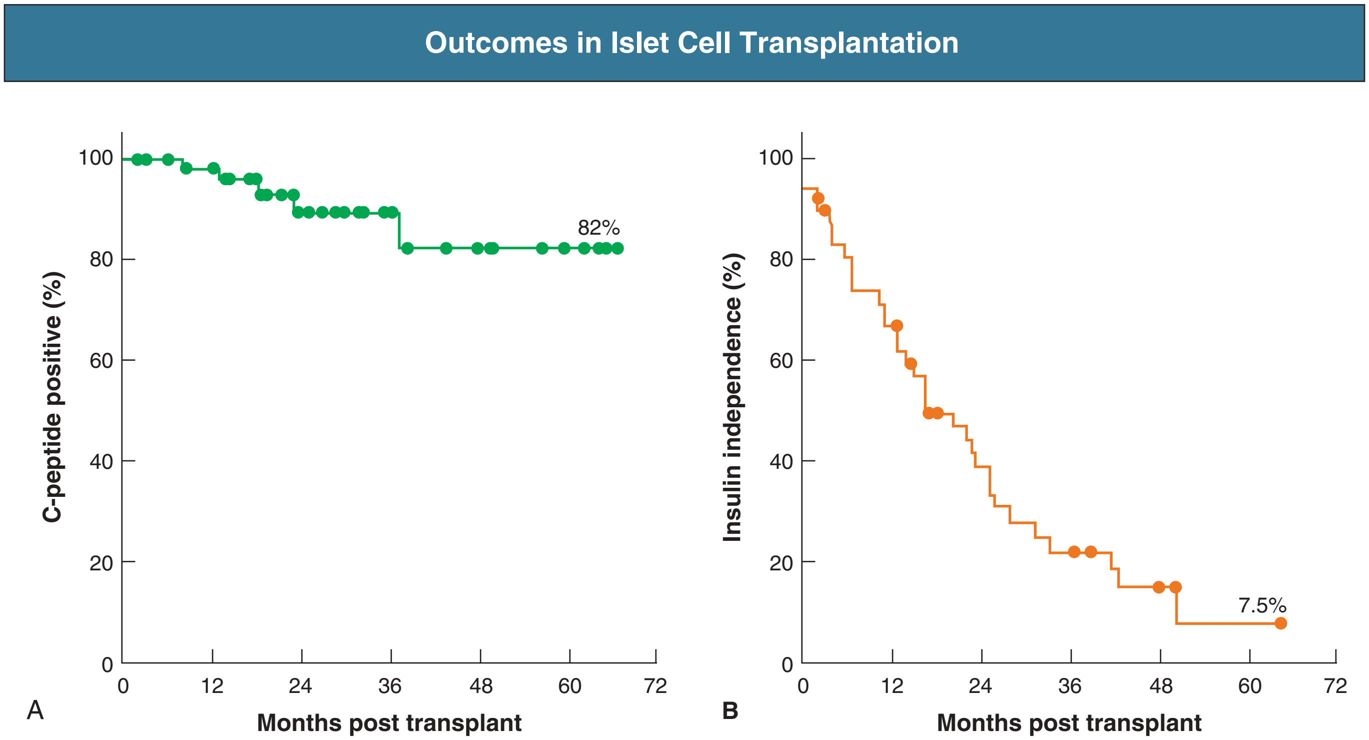
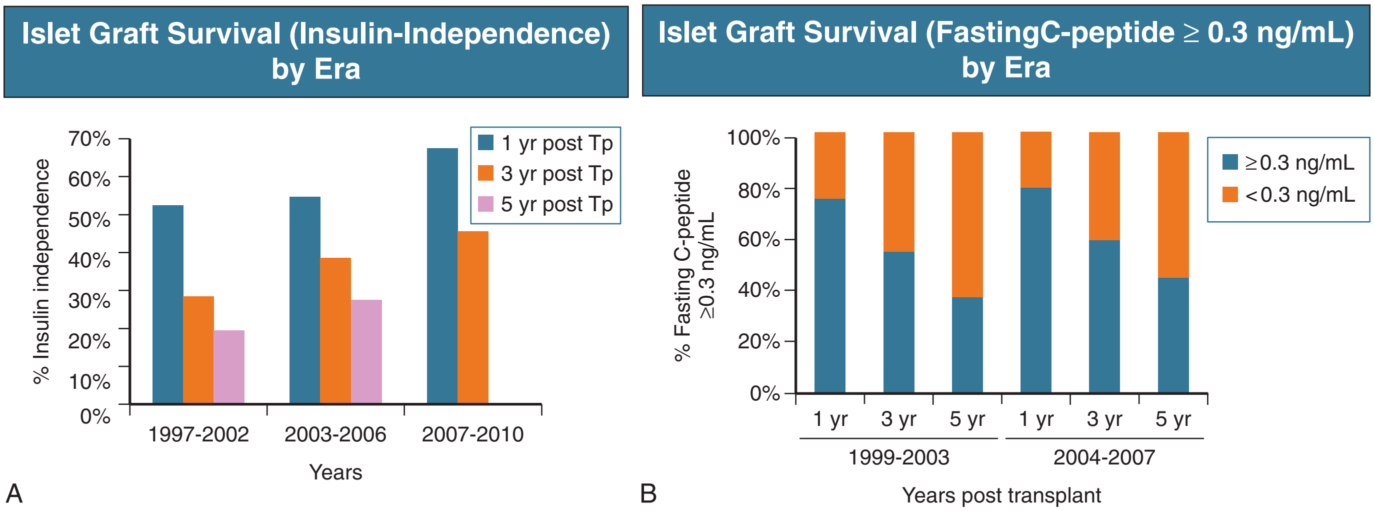

Outcomes in Islet Cell Transplantation

Fig. 110.9 **Outcomes in islet cell transplantation.** (A) Persistence of C-peptide secretion over time. The curves are dated from the time of the final transplant. (B) Persistence of insulin independence over time. (From reference 51.)


Islet Graft Survival (Insulin-Independence) by Era

Islet Graft Survival (FastingC-peptide ≥ 0.3 ng/mL) by Era

Fig. 110.10 **Islet graft survival.** (A) Insulin-independence rates by era. (B) Fasting C-peptide rate by era. *Tp,* Transplant. (From reference 58.)

possibility of significant injury to intrahepatic islet grafts. Most programs use corticosteroid-free and CNI-sparing protocols for islet or kidney recipients with different combinations of MMF and sirolimus. MMF reduces early pancreas rejection rates. Insulin independence has now been achieved with islet grafts derived from non–heart-beating donors and after sequential kidney-islet transplantations using sirolimus-based therapy. Islet engraftment also can be improved with use of a CNI-free regimen with profound T-cell depletion. Anti–T cell therapy using ATG may be associated with a cytokine storm, which is toxic to islets, and newer induction agents (anti–IL-2 receptor blockers) may be particularly useful to minimize cytokine release.

Several new immunosuppressive agents that offer the potential for more islet-friendly approaches are now entering clinical trials. These include combinations of biologic agents, such as ATG, rituximab, and alemtuzumab; novel anti–T cell biologic agents, some of which offer the prospect of inducing tolerance based on animal studies; and agents that produce costimulatory blockade.[57]

Based on Collaborative Islet Transplant Registry (CITR) data, the highest prevalence of insulin independence at 5 years after transplant (60% to 70%) was seen with a combination of T-cell depletion and tumor necrosis factor antagonists and a maintenance combination that included (calcineurin) CNI and MMF. This regimen was first used in the 2004 to 2006 era of islet transplantation, leading to improved likelihood of insulin independence at 1 and 3 years (see Fig. 110.10).[58] However, one recent study used CNI-free protocol arms based on belatacept (a costimulation blocker) or efalizumab (an antileukocyte functional antigen-1 antibody) and produced 3-year insulin independence as high as 70%.[59]

Preliminary data suggest there may be a role for the pancreas after failed islet and islet after failed pancreas transplants to help preserve renal function, be it from native kidneys or renal transplant if performed in a timely manner. The former has been more difficult due to increased antigen sensitization and thus longer waiting times. However, this may change as current islet induction and maintenance protocols are much less susceptible to recipient sensitization.[60]

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SELF-ASSESSMENT QUESTIONS

1. Transplant options for insulin-dependent diabetics with renal failure include which of the following:
   - **A.** Cadaveric renal transplant alone
   - **B.** Living donor kidney transplant alone
   - **C.** Simultaneous kidney-pancreas transplant
   - **D.** Kidney transplant followed by pancreas after kidney transplant
   - **E.** Kidney transplant followed by islet after kidney transplantation
   - **F.** All of the above.
2. Which of the following statements about pancreas transplantation is false?
   - **A.** It is a viable treatment option for both select type 1 and type 2 insulin-dependent diabetics.
   - **B.** Pancreas transplant recipients require the same amount of immunosuppression as kidney transplant recipients.
   - **C.** The beneficial effect of pancreas transplantation on long-term diabetic complications takes 8 to 10 years to be seen.
   - **D.** Hypoglycemic unawareness may be a sufficient indication for an insulin-dependent diabetic to receive a pancreas transplant.
   - **E.** Most pancreas transplants performed in 2013 had their exocrine secretions enterically drained.
3. Which of the following statements about islet transplantation is true?
   - **A.** Islets are infused in the portal vein and seed the liver.
   - **B.** Islet transplants are more successful in patients with lower body mass index (BMI).
   - **C.** The primary goal of islet transplantation remains optimal glycemic control without severe hypoglycemia rather than insulin independence.
   - **D.** An appropriate islet cell mass has been shown to be critical to produce insulin independence.
   - **E.** All of the above.

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Kidney Disease in Liver, Cardiac, Lung, and Hematopoietic Stem Cell Transplantation

Claire Kennedy, Colm C. Magee

It is now well recognized that kidney disease can complicate all forms of nonrenal solid organ transplantation (SOT) and is associated with longer hospitalization, higher morbidity, higher mortality, and greater expense.[1,2] Although there are organ-specific factors that can have an impact on the incidence and severity of kidney disease, some useful generalizations can be made.

GENERIC ISSUES OF KIDNEY DISEASE IN NONRENAL SOLID ORGAN TRANSPLANTATION

Use of Serum Creatinine and Derived Equations to Estimate Glomerular Filtration Rate

Transplant candidates and recipients often have low muscle mass and low creatinine generation. Hence, a mildly elevated serum creatinine concentration may represent severe kidney disease.[2,3] Such patients should have their glomerular filtration rate (GFR) estimated by 24-hour urinary creatinine clearance (which will tend to overestimate because of tubular secretion) or preferably by direct measurement of iothalamate clearance. Of the various serum creatinine–based equations to estimate GFR, the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations appear to correlate best with true post-transplantation GFR.[3]

Nephrotoxicity of Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) are the cornerstone of immunosuppression in SOT recipients, but there is little doubt that they contribute significantly to acute kidney injury (AKI) and chronic kidney disease (CKD) in this setting.[1] It is probable that CNI nephrotoxicity is more severe in nonrenal (than renal) transplantation because higher blood concentrations of CNIs may be recommended in nonrenal SOT recipients and the transplanted kidney is denervated, which may protect it from early sympathetic-mediated CNI injury. CNIs also exacerbate post-transplantation hypertension and diabetes mellitus, which cause renal damage in the long term.

Acute CNI nephrotoxicity is mainly a prerenal syndrome caused by vasoconstriction of the afferent glomerular arteriole (see Chapter 101); tubular damage and microvascular disease may occur in more severe cases. It may be difficult to quantify the contribution of CNI toxicity to post-transplant AKI, and thus in practice the CNI is often temporarily reduced. Acute CNI-induced thrombotic microangiopathy (TMA) is rare after SOT but is associated with a poor prognosis. In many cases there is a precipitant such as infection, rejection, or addition of a mammalian target of rapamycin (mTOR) inhibitor to CNI-based immunosuppression. Treatment usually involves discontinuation of the CNI (or mTOR inhibitor if triggered by its initiation).

Chronic CNI nephrotoxicity is probably a result of prolonged renal ischemia and other effects, such as direct stimulation of renal fibrogenesis. Typically the patient is hypertensive and there is a steady fall in GFR, most marked in the first 6 to 12 months after transplantation (Fig. 111.1).[4,5] Dipstick urinalysis usually shows minimal/no hematuria and minimal/mild proteinuria. Renal histologic examination shows striped interstitial fibrosis, arteriolar hyalinosis, arteriosclerosis, and secondary focal glomerulosclerosis.[4] There also may be features of chronic TMA.[4]

However, not all CKD in this setting is CNI related. Indeed, the typical histologic findings listed previously are nonspecific, making it difficult to estimate the actual true contribution of CNI toxicity to CKD. Biopsy series have reported a variety of histologic diagnoses in this context; in practice, renal biopsies are rarely performed unless there are clinical features suggestive of a renal disorder other than CNI toxicity.[6]

The presumed high prevalence of chronic CNI nephrotoxicity has generated interest in low-dose or even zero-dose CNI protocols.[1,2,4] Another strategy is to use tacrolimus as the de novo CNI or to switch from cyclosporine to tacrolimus if there is evidence of nephrotoxicity. The rationale here is that tacrolimus provides equivalent or even better immunosuppression at concentrations that are less nephrotoxic than cyclosporine. Furthermore, tacrolimus is associated with less hypertension and hyperlipidemia (which might exacerbate CKD) than cyclosporine. Conversely, tacrolimus is associated with more post-transplant diabetes mellitus. CNI-sparing strategies are discussed in more detail later.

The usefulness of dihydropyridine calcium channel blockers in ameliorating CNI nephrotoxicity in SOT remains controversial. Experimental studies suggest that agents that block the renin-angiotensin system (RAS) may provide protection against the arteriolar hyalinosis and tubulointerstitial injury associated with chronic CNI use. Control of hypertension per se is probably more important than use of any particular antihypertensive agent.

Acute Kidney Injury in the Immediate Pretransplant Period

AKI is common in the days to weeks immediately before liver, heart, or (less commonly) lung transplantation and is typically prerenal (e.g., renal hypoperfusion or hepatorenal syndrome), intrarenal (ischemic or toxic tubular injury), or a combination. A mildly elevated serum creatinine may mask a significant fall in GFR in malnourished patients with severe organ failure.[2]

Management of AKI focuses on treatment of the underlying cause and provision of dialytic support according to standard criteria. Because the patients are critically ill, continuous renal replacement therapy (CRRT) may be preferred to intermittent hemodialysis (HD), but there

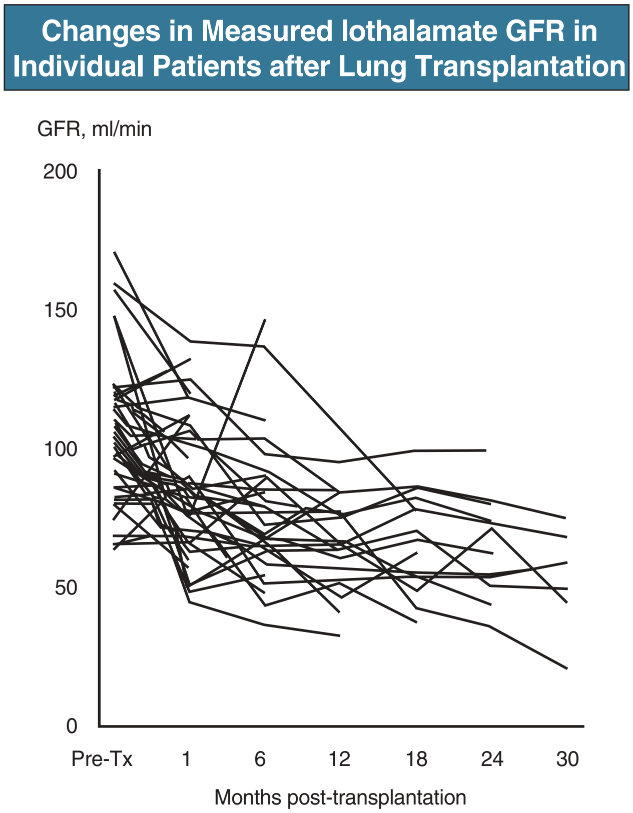

Fig. 111.1 Changes in measured iothalamate glomerular filtration rate *(GFR)* in individual patients after lung transplantation. Note the variation in GFR before transplant and the large fall in GFR in many patients within the first 6 months. *Tx,* Transplantation. (Modified from reference 5.)

are no randomized controlled trials (RCTs) showing improved outcomes with CRRT. There is a small evidence base advocating intraoperative CRRT in selected patients undergoing liver transplantation; typically those who have severe AKI preoperatively and are likely to tolerate the surgery poorly from a fluid/transfusion perspective.

When severe or prolonged AKI occurs before planned/anticipated transplantation, estimation of reversibility becomes very important, because presumed irreversible severe AKI is generally a contraindication to transplantation or shifts the management toward simultaneous dual-organ (e.g., liver plus kidney) transplantation. Kidney biopsy might be useful in determining the degree of reversibility, but in practice it is not commonly performed because of technical difficulties in critically ill—often coagulopathic—patients.

The advantages and disadvantages of simultaneous dual-organ transplantation are shown in Table 111.1. Concerns exist in the transplant community regarding current practice. Liver, lung, and heart allocation is based on medical urgency, whereas kidney allocation is generally based on waiting time and immunologic factors. As a result, multiorgan transplants assume the priority of the nonkidney organ and may therefore divert kidneys from those with "definite" end-stage renal disease (ESRD), who may wait a long time for a kidney-only transplant. Often standard criteria donor kidneys (rather than expanded criteria donor kidneys) are prioritized for this multiorgan transplant group, again diverting these kidneys from the kidney-only wait-list. Recent guidelines address some of these controversies.[7,8] Other specific issues are discussed in detail later.

TABLE 111.1 Advantages and Disadvantages of Simultaneous Renal and Nonrenal Transplantation

Advantages	Disadvantages
Potentially provides much better renal function over the short and long term	Surgery more technically complex and prolonged
Single donor—potential for lower cumulative dose of immunosuppression (as opposed to kidney transplantation later)	Deprives patients with "definite" end-stage renal disease of a kidney transplant
	Not needed when the acute kidney injury is reversible

BOX 111.1 Causes of Acute Kidney Injury After Solid Organ Transplantation

Prerenal
- Hypovolemic shock (e.g., aggressive diuresis)
- Cardiogenic shock (e.g., severe cardiac allograft dysfunction)
- Distributive shock (e.g., sepsis)
- Cyclosporine or tacrolimus

Intrarenal (Acute Tubular Injury)
- Prolonged shock
- Cyclosporine or tacrolimus
- Aminoglycosides, amphotericin
- Intravenous contrast
- Hydroxyethyl starch, intravenous immunoglobulin
- Massive hemolysis

Postrenal
- Rare

Acute Kidney Injury in the Early Post-Transplant Period

AKI is common in the days to weeks after transplant and is often multifactorial (Box 111.1). AKI is associated with higher mortality in the early postoperative period and, in those who survive, an increased risk for developing CKD.[9,10] Delayed introduction or reduced doses of CNIs are sometimes used, usually under the cover of induction antibody immunosuppression.[9]

Passenger lymphocyte syndrome can occur in the early weeks after transplant (usually liver, but also other SOT) in the setting of a minor ABO or other blood group system mismatch (e.g., blood group O donor for blood group A or B recipient). Donor lymphocytes—"passengers" with the transplant—produce anti–blood group antibodies, which causes hemolysis that, if severe, can lead to renal failure and other complications.

Acute Kidney Injury in the Late Post-Transplantation Period

Severe AKI occasionally occurs several months after transplantation. The major causes are shown in Box 111.1. Severe rhabdomyolysis has been reported; usually when statins are prescribed with cyclosporine and an inhibitor of the cytochrome P-450 system, such as diltiazem or azole-based antifungal agents.

Chronic Kidney Disease

With the growing number and longer survival of transplant recipients worldwide, the absolute number of recipients with CKD has increased.

In the most comprehensive study to date, the cumulative incidence of post-transplant CKD (defined as estimated GFR <30 ml/min/1.73 m^2) at 5 years varied according to organ transplanted, from 7% to 21% (Fig. 111.2).[10]

By multivariate analysis, the following pretransplant variables increased the risk for CKD: older age, female, white or black (as opposed to Asian) ethnicity, lower GFR, diabetes mellitus, hypertension, hepatitis C virus infection, and need for dialysis. Several post-transplant variables were also implicated: postoperative AKI and initial use of cyclosporine (as opposed to tacrolimus).[10] Minimizing post-transplantation AKI (see earlier) and controlling hypertension and diabetes are therefore likely to prevent or slow CKD. Safe and effective low-dose CNI protocols would be an important advance in preventing severe CKD, as discussed elsewhere.

Many studies have confirmed that CKD (particularly ESRD) after nonrenal transplantation portends a poor prognosis (Fig. 111.3), as well as increased hospitalization and infection rates.[10,11]

Although not well studied, the complications of CKD in this setting are likely exacerbated by other post-transplant factors. For example, antiproliferative immunosuppressant medications exacerbate anemia and corticosteroids exacerbate metabolic bone disease.

Cumulative Incidence of Stage 4 or 5 Chronic Kidney Disease in Nonrenal Organ Transplant Recipients

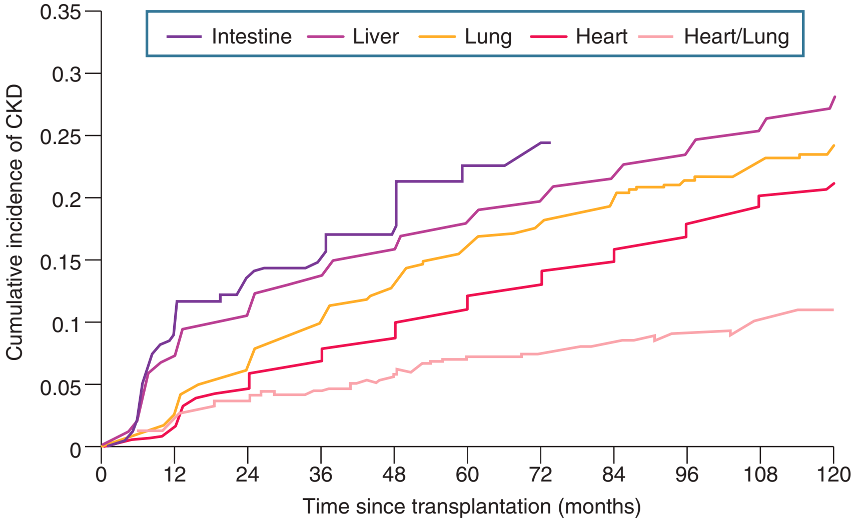

Fig. 111.2 Cumulative incidence of chronic kidney disease *(CKD)* (estimated GFR *[eGFR]* <30 ml/min/1.73 m^2) after transplantation of various solid organs. (Modified from reference 10.)

Mortality Associated with Chronic Kidney Disease in Organ Transplant Recipients

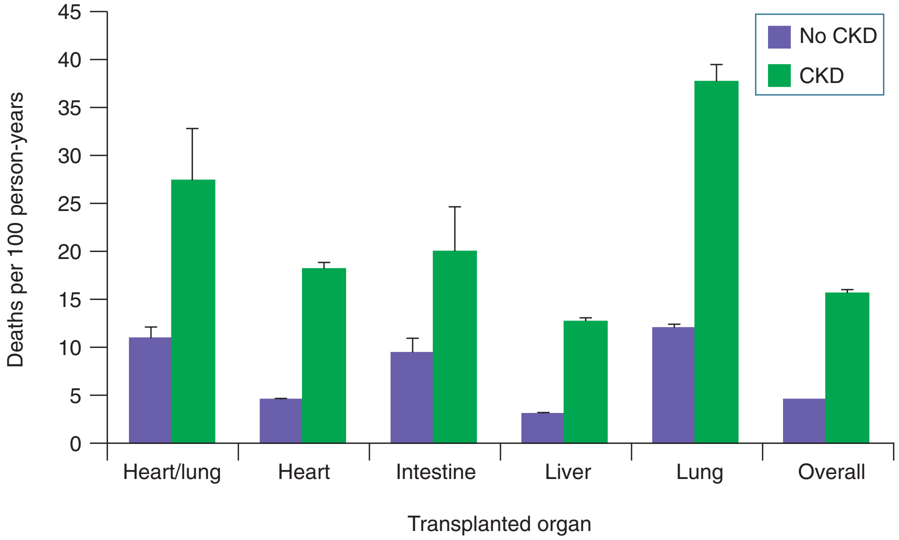

Fig. 111.3 Mortality associated with stage 4 and 5 chronic kidney disease *(CKD)* in organ transplant recipients. (Data from Scientific Registry of Transplant Recipients.)

Management of Chronic Kidney Disease

The CKD-EPI equation (despite its limitations) is useful in identifying CKD in this setting. Referral to a nephrologist should be considered in those with a falling eGFR. The initial evaluation should include thorough review of renal function in the peritransplantation period and exposure to nephrotoxins. If urinalysis shows moderate/severe proteinuria or hematuria or both, renal biopsy should be considered; it may identify pathologies other than CNI nephrotoxicity.[6]

Close consultation with the primary transplant team is important. When CNI toxicity is deemed the main cause of CKD (as it is in most patients), reduction in CNI dosage for patients at low immunologic risk should be considered. If the patient is receiving azathioprine, a change to mycophenolate mofetil (MMF) should be considered to maintain adequate immunosuppression; if the patient is already receiving MMF, the dose probably should be increased. An alternative strategy (one that we favor less) is to substitute an mTOR inhibitor for the CNI; this should not be done in the early post-transplant period because of the adverse effects of mTOR inhibitors on wound healing. Experimental models also demonstrate delayed recovery of renal function as a result of effects on tubular cell proliferation in sirolimus-treated animals with renal injury; mTOR inhibitors also potentiate the nephrotoxicity of cyclosporine and sometimes induce proteinuria. Finally, some have advocated switching cyclosporine to low-dose tacrolimus, although the supporting data are less compelling. It should be noted that most studies of CNI reduction or cessation in these settings are small and with limited follow-up. There is still understandable reluctance to pursue such protocols because CNIs are effective immunosuppressants and organ replacement therapy analogous to dialysis is not available for other SOT recipients if severe rejection occurs.

In the absence of specific studies, it seems reasonable to apply standard CKD guidelines for the management of hypertension, anemia, hyperparathyroidism, etc. Although there is experimental evidence that angiotensin-converting enzyme (ACE) inhibitors may have antifibrotic effects in nonrenal transplant CKD, there are no trials showing improved renal outcomes with ACE inhibitors or angiotensin receptor blockers compared with other antihypertensive agents.

In those with advanced CKD, there is little doubt that sequential renal transplantation is the best form of RRT in those fit enough for the procedure. The addition of the renal allograft does not require a huge increase in immunosuppression (typically this is increased in the perioperative period only). Where feasible, a preemptive living donor transplant is the best option. In the immediate post-transplant period, mortality is higher than remaining on the waiting list (reflecting the complications of surgery and more immunosuppression), but mortality in the medium to long term is much lower.[10] The number of patients with a nonrenal transplant subsequently wait-listed for a renal transplant in the United States has increased dramatically over the last 15 years.[12]

Patients who do not receive a preemptive kidney transplant are typically managed with HD rather than with peritoneal dialysis (PD), although the choice of modality should be dictated by patient-specific factors. With either modality, mortality is much higher compared with that in matched nontransplant controls.[12] Nevertheless, some have reported reasonable outcomes with home therapies (both HD and PD).[13]

BK Virus Nephropathy

BK viruria is occasionally noted after nonrenal transplantation, but the absolute risks for BK viremia and nephropathy remain low and routine screening is not recommended. This probably reflects the lack of a "second hit" to the native kidneys, such as human leukocyte antigen mismatching or inflammation. BK virus nephropathy should be considered in the differential diagnosis of unexplained renal dysfunction after SOT, especially because more intensive maintenance immunosuppressive protocols are being increasingly used.

KIDNEY DISEASE IN LIVER TRANSPLANTATION

AKI is common before liver transplantation. Indeed, use of the Model for End-Stage Liver Disease (MELD) scoring system (which measures severity of liver dysfunction based on international normalized ratio, serum creatinine and bilirubin, and predicts 90-day risk for death) to guide allocation of deceased donor liver allografts means that a raised serum creatinine concentration increases the chances of the patient being offered a liver transplant.[14] In the United States, the United Network for Organ Sharing (UNOS) updated policy on liver allocation (termed "Share 35") was implemented in 2013. This policy facilitates regional organ sharing to prioritize those with a MELD score of 35 or greater to reduce wait-list mortality.[15]

The most common causes of AKI before transplantation are hepatorenal syndrome (see Chapter 73), acute tubular necrosis (ATN), or both. Prolonged hepatorenal syndrome may cause ATN. Glomerulonephritis (GN) is relatively common (cirrhosis is associated with immunoglobulin A nephropathy and hepatitis C with membranoproliferative glomerulonephritis) but is rarely the cause of severe pretransplantation kidney disease. If RRT is required, CRRT is often preferred, in part because it is thought to have less effect than intermittent dialysis on intracranial pressure.

Post-transplantation AKI is also common and is usually multifactorial.[16] In one series, 37% of liver transplants were complicated by some degree of AKI, 19% requiring RRT.[16] Requirement for RRT was associated with higher 30-day and 1-year mortality rates. Pretransplant AKI associated with hepatorenal syndrome often (but not always) improves if the transplant is successful.

Although relatively low doses of CNIs are traditionally used in liver transplantation (because rejection is less of a concern than in other SOT), CKD remains common and is associated with higher mortality.[10] Thus, although CNIs are an important cause of CKD, other factors must play a role. These include the high prevalence of hepatitis B and C viral infections (which predispose to GN) and the high prevalence of diabetes mellitus.

Protocols involving reduction or cessation of CNIs have been studied with mixed results.[17,18] Delayed introduction of tacrolimus, with the cover of interleukin-2 (IL-2) receptor blockade, has been shown to better preserve renal function while maintaining excellent allograft and patient outcomes.[19] A phase II study evaluating belatacept (in CNI-free regimens) in de novo liver transplant recipients was terminated early because of safety concerns with belatacept despite a higher GFR.[11] De novo use of sirolimus is not recommended because there is concern that it may be associated with hepatic artery thrombosis.

The number and percentage of simultaneous liver-kidney transplants (SLK) have increased greatly in the United States since the 2002 allocation policy based on the MELD score was adopted. In 1998, for example, there were 98, and in 2015, there were 626 (~8.8% of total liver transplants).[20] This is likely to increase in the years following Share-35 implementation.

Although selected patients with severe pretransplant kidney disease benefit from SLK transplant, a critical issue is predicting which patients are likely to have meaningful renal recovery without kidney transplant. Duration of time on dialysis before the liver transplant is often used as a surrogate marker of renal recoverability, although the duration beyond which a recovery to independent renal function is unlikely is controversial.[21] In those not on dialysis, or on dialysis for a short period, prognostication is further complicated by the known poor accuracy of GFR estimations and concerns about the high risk for renal biopsy.

BOX 111.2 United Network for Organ Sharing and Organ Procurement and Transplantation Network Policy Regarding Candidacy for Simultaneous Liver-Kidney Transplant in Patients Listed for Liver Transplant

- CKD defined as GFR <60 ml/min/1.73 m^2 for >90 days and one of:
  - Dialysis dependence
  - GFR <35 ml/min/1.73 m^2 at transplant wait-listing
- AKI defined as ≥6 weeks of one or a combination of the following:
  - GFR <25 ml/min/1.73 m^2 at least once every 7 days
  - Dialysis at least once every 7 days
- Specific metabolic diseases
  - Hyperoxaluria
  - Atypical hemolytic uremic syndrome (from factor H or I deficiency)
  - Methylmalonic aciduria
  - Familial non-neuropathic systemic amyloidosis

Modified from reference 8.
AKI, Acute kidney injury; *CKD,* chronic kidney disease; *GFR,* glomerular filtration rate.

Single-center studies suggest that using a combination of clinical and histologic criteria allows effective prediction of which patients will benefit most from SLK transplantation.[22,23] Renal biopsy was performed by the percutaneous or transjugular method and had a moderate rate of complications.

In the United States the Organ Procurement and Transplantation Network (OPTN) policy has provided updated recommendations as to who should receive SLK transplants (Box 111.2).[8] Some think SLK does not represent good use of available kidneys because of a high rate of renal allograft failure in this population and argue that organ allocation should instead assign priority for delayed kidney transplant after recovery from liver transplant.[24] The Canadian forum guidelines suggest that patients are eligible for SLK if they are dialysis dependent for more than 3 months. They are “possibly eligible,” to be determined on a case-by-case basis, if they are on dialysis for a shorter time or if they have an estimated GFR (eGFR) less than 30 ml/min/1.73 m^2 for more than 1 month.[7]

There is single center experience of delayed (up to 3 days) deceased donor kidney transplant after liver transplant from the same donor. This ensures stabilization of the liver transplant recipient and potentially more effective kidney utilization. Good short to medium term results were reported.[25]

KIDNEY DISEASE BEFORE CARDIAC TRANSPLANTATION

Preoperative AKI is common. In the largest reported study, 1% of heart transplant recipients required RRT before transplantation.[10] The main cause of AKI is renal hypoperfusion from severe congestive heart failure. Ventricular assist devices are increasingly used as a bridge to cardiac transplantation and can improve renal function in this setting. Interestingly, emerging evidence suggests that venous congestion is independently associated with the presence of AKI; whether therapies directed at reduction of central venous pressure improve renal outcomes remains to be proven. In some patients there may also be a component of CKD caused by chronic hypoxia, renovascular disease, hypertension or atheroembolism.

Postoperative AKI is also common, with a strong association between the stage of AKI (as defined by Kidney Disease: Improving Global Outcomes [KDIGO] criteria) and both mortality and renal dysfunction at 1 year.[26] In addition to the causes shown in Box 111.1, risk factors after cardiac transplant surgery are prolonged aortic cross-clamping, large fluid volume shifts, prolonged cardiac allograft ventricular dysfunction, postoperative bleeding, and reexploration.

CKD is now well recognized as an important complication in the medium to long term (see Fig. 111.2). The cumulative incidence of stage 4 or stage 5 CKD in cardiac transplant recipients has been reported as 11% at 5 years, which is lower than in bowel, liver, or lung transplant recipients.[10] The principal cause of CKD after cardiac transplantation is CNI toxicity. Several studies have shown that early or late renal dysfunction is a risk factor for death after cardiac transplantation; furthermore, cardiac transplant recipients on dialysis have poorer survival than other ESRD patients.[27]

A number of studies have assessed the renal effects of CNI reduction after cardiac transplantation. The majority are small, single-center studies and have shown improvement in GFR with no adverse effects on the allograft.[28,29] However, these studies involve patients at low immunologic risk with short-term follow-up. CNI withdrawal, on the other hand, showed less favorable outcomes. One study showed high rates of rejection after patients were switched to a corticosteroid plus MMF protocol.[30] Another pilot study showed concerning outcomes with a de novo CNI-free protocol,[31] which cannot be recommended at present.

Low-dose everolimus (an mTOR inhibitor), in combination with low-dose cyclosporine, MMF, and steroids (compared with standard-dose cyclosporine, MMF, and steroids) was associated with improved renal function at 1 year, with less cardiac allograft vasculopathy and similar cardiac function (despite more episodes of asymptomatic biopsy proven acute rejection).[11] These results need validation in larger trials with longer follow-up.

The question of whether the patient is best served by heart-alone or simultaneous heart-kidney transplant sometimes arises. The absolute number of such dual transplants remains low but is steadily increasing in the United States (141 in 2015, equivalent to about 5% of total heart transplants).[20] Some single-center and registry reports document good results.[32,33] One recent UNOS registry analysis found that simultaneous heart plus kidney (as opposed to heart-alone) transplantation was associated with a long-term survival benefit in those patients requiring dialysis before cardiac transplant and in those with reduced eGFR (<60 ml/min/1.73 m^2) plus a high risk for post-transplant renal failure (based on several clinical factors).[34] Canadian guidelines are as outlined above in the SLK discussion.[7] At this time, it seems reasonable to limit the combined transplants to patients with at least a severity of kidney disease similar to that shown in Box 111.2

KIDNEY DISEASE IN LUNG TRANSPLANTATION

Preoperative AKI is less common in this group, with 0.1% of lung transplant recipients requiring dialysis before transplantation.[10] Postoperative AKI is common; in one series, 56% of patients had at least a doubling of serum creatinine in the first 2 weeks after transplantation.[35] CKD, although often underappreciated, is common in the first year after lung transplantation, and the incidence increases thereafter. UNOS data showed that 5.5% of patients required RRT after lung transplantation, with dramatically lower survival.[36]

AKI can occur for the usual reasons (see Box 111.1), but several factors specific to lung transplantation may be important. First, aggressive diuresis is often prescribed to minimize any pulmonary edema.[35] Second, nephrotoxic antimicrobial agents, such as aminoglycosides and amphotericin, are sometimes required to treat resistant or severe infections.[35,37] Acute oxalate nephropathy leading to irreversible renal failure has been described in lung transplant recipients. It is thought that enteric hyperoxaluria is caused by either prolonged antibiotic administration (which interferes with colonic flora, specifically *Oxalobacter formigenes*) and/or cystic fibrosis–related pancreatic exocrine insufficiency which leads to fatty acid malabsorption and increased oxalate bioavailability in the colon.[37] Although it is probably rare, this "new disease" emphasizes the importance of maintaining a broad differential diagnosis for any kidney disease occurring after SOT and the utility of renal biopsy when the clinical manifestation is unusual.

As with other forms of post-transplantation CKD, the most common cause is probably CNI toxicity.[37] CNI dosages tend to be higher because of the increased risk for rejection in lung transplantation. Although CNI withdrawal is poorly tolerated in this setting, a small number of studies have reported improvements in GFR when doses of CNIs were reduced. CNI reduction should be accompanied by addition/optimization of MMF. De novo use of mTOR inhibitors is not recommended because they may cause breakdown of the bronchial anastomosis; later use is associated with a risk for pneumonitis.

Patients with pulmonary hypertension appear to have a lower GFR immediately before transplant than those with other diagnoses but have a less severe fall in GFR after transplantation.[5] This probably reflects the adverse effects of pulmonary hypertension on renal perfusion and reversal of these effects after successful lung transplantation. Simultaneous lung-kidney transplantation is rarely performed.[20]

KIDNEY DISEASE IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

The goal of hematopoietic stem cell transplantation (HSCT) is to allow administration of otherwise lethal (and ideally curative) doses of chemoradiotherapy, followed by engraftment of stem or progenitor cells for marrow recovery.[38,39] HSCT is most commonly used to treat hematologic cancers, but other indications include certain nonhematologic cancers, severe genetic disorders (such as immunodeficiencies), and severe autoimmune diseases.[40] Stem and progenitor cells may be harvested from peripheral blood, bone marrow, or umbilical cord blood. Myeloablative HSCT uses intensive conditioning regimens involving high-dose chemo-radiotherapy; the hematopoietic system is then reconstituted by infusion and engraftment of stem cells. In *allogeneic* myeloablative HSCT, nonself stem cells are used; in *autologous* myeloablative HSCT, the patient's own cells are used. The toxicities of myeloablative regimens generally preclude older and sicker patients; nonmyeloablative or "reduced-conditioning" regimens have been developed to allow allogeneic HSCT in such patients. In both forms of allogeneic HSCT, acute and chronic graft-versus-host disease (GVHD) can be problematic; CNIs are prescribed to prevent and treat this complication. The main target organs of GVHD are the liver, gastrointestinal tract, and skin. AKI and CKD are common complications of HSCT and are associated with higher early and late mortality (Table 111.2).

Acute Kidney Injury After Hematopoietic Stem Cell Transplantation

AKI is common after HSCT, but its incidence and severity depend on the type of HSCT (and on the definition of AKI used). It is most common (over 70% of patients in some series) after myeloablative allogeneic HSCT, reflecting the propensity of this regimen to cause profound immunosuppression (with associated risk for sepsis) and liver damage (with associated risk for hepatorenal syndrome). Furthermore, CNIs are routinely prescribed for the first 100 days after transplantation.[39] Severe AKI is less common after nonmyeloablative HSCT (although patients are older and sometimes sicker), reflecting the shorter period of pancytopenia and rarity of hepatic sinusoidal obstructive syndrome (SOS). The principal cause of AKI in this setting is probably CNI toxicity; severe AKI necessitating dialysis is relatively rare.[39] Whatever the form of HSCT, if dialysis is required, the overall prognosis is usually very poor (early mortality >70%).[39] Fortunately, rates of AKI are decreasing; this is probably related to multiple improvements in peritransplant care.

It is helpful to consider the causes of AKI according to the period after HSCT (Box 111.3).[38] Nephrotoxic effects of the transplant itself include tumor lysis syndrome and marrow infusion toxicity. Marrow infusion toxicity occurs when autologous bone marrow transplant patients are exposed to cell lysis products (including hemoglobin and

TABLE 111.2 The Three Types of Hematopoietic Stem Cell Transplantation and Their Associated Renal Complications

	Myeloablative Allogeneic	Myeloablative Autologous	Nonmyeloablative Allogeneic
Diseases treated	Many leukemias, NHL, myelodysplastic syndromes	Lymphomas, multiple myeloma	As for myeloablative allogeneic type
Used in patients older than 60 years	Rarely	Sometimes	Common
Comorbidities permissible before HSCT	Minimal	Minimal	Some
Intensity of conditioning regimen	High	High	Low
GVHD after HSCT	Common	None	Common
CNIs used routinely	Yes	No	Yes
Incidence of AKI	Very common; sometimes severe	Common	Common; rarely severe
Causes of AKI	Hepatic sinusoidal obstruction syndrome, shock syndromes, nephrotoxic drugs, CNIs	Shock syndromes, nephrotoxic drugs; occasionally hepatic sinusoidal obstruction syndrome	CNIs
Incidence of CKD	Common	Common (but less severe than myeloablative allogeneic type)	Mild forms probably common
Causes of CKD	Irreversible AKI, renal TMA, CNIs, ? GVHD	Irreversible AKI	Pretransplant mild CKD, irreversible AKI, CNIs, ? GVHD

AKI, Acute kidney injury; *CKD,* chronic kidney disease; *CNIs,* calcineurin inhibitors; *GVHD,* graft-versus-host disease; *HSCT,* Hematopoietic Stem Cell Transplantation; *NHL,* non-Hodgkin lymphoma; *TMA,* thrombotic microangiopathy.

BOX 111.3 Causes of Kidney Disease According to Time After Hematopoietic Stem Cell Transplantation

Immediate (Very Rare)

- Tumor lysis syndrome
- Marrow or stem cell infusion toxicity

Early (Acute Kidney Injury in First 3 Months)

- Prerenal
  - Hypovolemia
  - Hepatorenal syndrome
  - CNI toxicity
- Intrarenal
  - Ischemic and/or toxic acute tubular necrosis (shock syndromes, aminoglycosides, amphotericin, etc.)
- Postrenal
  - Hemorrhagic cystitis

Later

- Thrombotic microangiopathy*
- Calcineurin inhibitor toxicity
- Irreversible acute kidney injury
- Membranous nephropathy or other glomerular diseases
- Recurrence of original disease, which then affects kidneys (e.g., myeloma)*
- ? Graft-versus-host disease

Modified from reference 41.
*Can cause late acute kidney injury.

myoglobin) released during cryopreservation. This can lead to pigment cast formation and/or toxic ATN. Within the first few weeks of myeloablative HSCT, when the conditioning regimen has caused pancytopenia, mucositis of the gastrointestinal tract, and liver damage, recipients are at high risk for many forms of AKI. These include prerenal syndromes caused by hepatorenal syndrome (see later) and hypovolemia (induced by vomiting and diarrhea or bleeding). Neutropenia predisposes to septic shock. Exposure to nephrotoxic agents, such as amphotericin, aminoglycosides, intravenous contrast agents, and CNIs, is relatively common and may also precipitate acute tubular injury. GVHD is associated (directly or indirectly) with various forms of intrarenal AKI (see later). Obstructive uropathy is much less common but can be caused by severe hemorrhagic cystitis or fungal infection of the collecting system. Causes of hemorrhagic cystitis include high-dose cyclophosphamide and viral infection (by adenovirus or BK virus). BK virus nephropathy and adenovirus nephropathy have been described but appear to be rare.

Hepatic Sinusoidal Obstructive Syndrome

Hepatic SOS, previously called venoocclusive disease of the liver, is one of the most common causes of severe AKI after myeloablative HSCT, particularly allogeneic myeloablative HSCT (see Table 111.2 and Box 111.3). The pathophysiology is thought to involve radiotherapy- and chemotherapy-induced damage to the endothelium of hepatic venules with subsequent venular thrombosis and sinusoidal and portal hypertension that in turn decreases renal perfusion. Risk factors include allogeneic HSCT, older age, female, hepatic irradiation, preexisting liver disease, use of cyclophosphamide or busulfan in the conditioning regimen, and exposure to methotrexate, progesterone, or antimicrobial drugs (i.e., infection).[41]

Clinically, SOS manifests as a form of hepatorenal syndrome during the first 30 days after HSCT. There is frequently a precipitating factor such as sepsis. The initial symptoms and signs are weight gain, edema, and ascites, followed by right upper quadrant abdominal pain and tenderness, jaundice, and abnormal liver function tests. Falling urine output, low urine sodium, and rising serum creatinine then follow.[41] In mild to moderate cases, sodium and fluid restriction, diuresis, and analgesia may suffice until liver function recovers. Severe SOS complicated by liver and renal failure (and frequently respiratory failure) carries a mortality approaching 100%. The differential diagnosis includes acute GVHD of the liver, sepsis, drug-induced cholestasis, gallstone disease, and hepatotoxic effects of parenteral nutrition. The diagnosis of SOS is usually based on the typical clinical and laboratory features. Liver biopsy is occasionally performed to confirm the diagnosis.

Current preventive strategies for SOS, although based on nonconclusive evidence, include avoidance of precipitating factors where possible and use of ursodeoxycholic acid (UDCA) or low-dose heparin.[42] UDCA alters the bile acid milieu, rendering bile less hydrophobic and toxic to parenchymal cells if cholestasis is present; it also exerts local cytokine-mediated immunomodulatory effects. Defibrotide, an oligonucleotide with antithrombotic and fibrinolytic effects on microvascular endothelium, but with apparently few systemic adverse effects, has demonstrated encouraging results both in preventing and treating SOS.[43]

Management of Acute Kidney Injury After Hematopoietic Stem Cell Transplantation

Evaluation of the patient should be as for any patient with hospital-acquired AKI but with particular focus on the possible contribution of hepatorenal syndrome to the clinical picture. The patient's cancer diagnosis, conditioning regimen, and type of HSCT are important factors. Where possible, further exposure to nephrotoxic drugs should be minimized (e.g., effective alternatives to amphotericin are now often available). If CNI trough concentrations are high, dose reduction should be considered.

No RCTs have compared intermittent HD with CRRT in this setting, and thus the decision is usually based on the hemodynamic stability and volume status of the patient. Whatever the modality used, the prognosis in those who develop severe AKI after HSCT is poor. In the setting of hepatorenal syndrome, there is some evidence that continuous therapies are associated with less increase in intracranial pressure than intermittent hemodialysis (see Chapter 73). In addition, the daily obligate fluid intake in these patients is frequently massive, and fluid balance is most easily controlled by a continuous technique. Vascular access can be problematic because of thrombocytopenia and neutropenia predisposing to bleeding and infection, respectively.

Chronic Kidney Disease After Hematopoietic Stem Cell Transplantation

CKD is an important long-term complication of HSCT, particularly allogeneic HSCT.[39] The reported cumulative incidence of CKD varies between 10% to 50%.[39] As recipients of HSCT are living longer, CKD may become more prevalent.

The role of GVHD in the development of AKI and CKD remains controversial. There is evidence from animal and human studies that GVHD or its accompanying inflammatory state can cause glomerular disease (see later); some think it also may play a role in the pathogenesis of CKD.[39] The causes of CKD are shown in Table 111.2.

Thrombotic Microangiopathy

Subacute or chronic renal TMA is probably the most common cause of CKD (particularly severe CKD) after HSCT.[44] It typically manifests 4 to 12 months after HSCT with slowly rising serum creatinine, hypertension, and disproportionate anemia (see Chapter 29), although some patients have a more fulminant presentation (e.g., severe nephritic syndrome). Dipstick urinalysis shows variable proteinuria and hematuria.

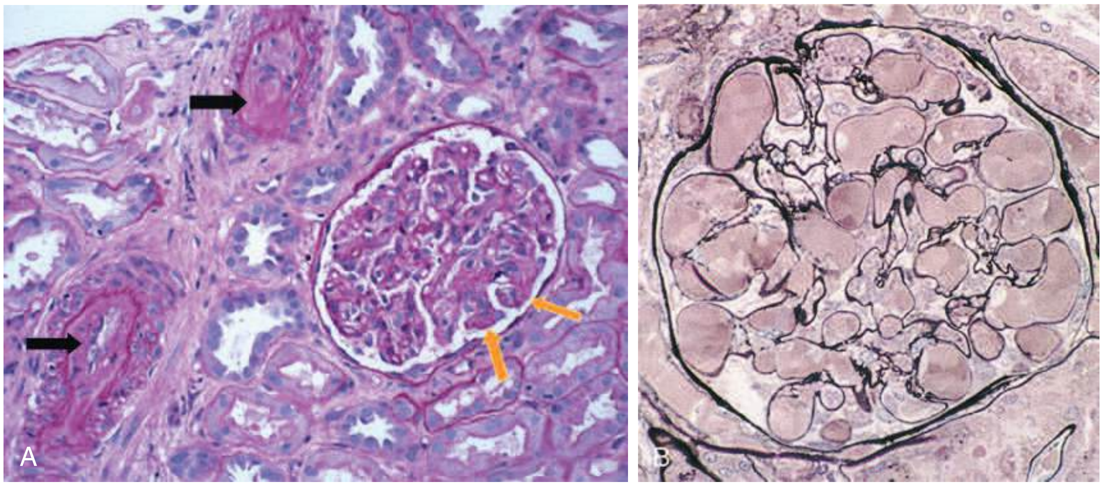

Fig. 111.4 **Thrombotic microangiopathy after allogeneic hematopoietic stem cell transplantation (HSCT).** (A) Renal biopsy specimen from a patient who had undergone allogeneic HSCT and developed subacute renal failure 12 months later. Periodic acid–Schiff (PAS) staining shows near occlusion of two small arteries by subintimal connective tissue and swollen endothelium *(black arrows)*. The glomerulus shows thickened capillary walls with "double contours" and segmental occlusion and collapse of capillaries *(orange arrows)*. (B) Severe mesangiolysis in a patient with thrombotic microangiopathy after HSCT. Note the aneurysmal capillary loops and the lack of mesangial cells or matrix. (*A* courtesy Dr. H. Rennke, Harvard Medical School, Boston, Massachusetts.)

Careful review of previous laboratory test results often will show evidence of an intermittent or persistent low-grade TMA, although the classic laboratory findings of TMA may not all be present. Diagnostic criteria (and their limitations) are summarized elsewhere.[44] Renal imaging is usually unremarkable. Kidney biopsy carries increased risks in patients with thrombocytopenia and is rarely required unless the presentation is atypical. Histopathology typically shows microthrombi in arterioles and glomerular capillaries, mesangiolysis, glomerular basement membrane duplication, and tubular injury with interstitial fibrosis (Fig. 111.4).[44] The main cause of TMA after HSCT is thought to be direct damage to the renal endothelium, and possibly the tubulointerstitium, by the chemoradiotherapy conditioning regimen (particularly the radiotherapy component).[44] Renal cells have a much slower mitotic rate than mucosal cells, and thus manifest chemoradiotherapy damage much later. Other factors such as infection, GVHD, CNIs, and activation of the RAS may play a facilitating role (Fig. 111.5).[38,44] Although deficiency of ADAMTS13 is thought not to be the primary cause in most patients, recent studies have suggested a role for complement factor H abnormalities and factor H autoantibodies.[44]

Treatment of renal TMA after HSCT is mainly supportive (see later). Prevention involves renal shielding (from irradiation damage) and avoidance of other nephrotoxic agents at the time of conditioning. Plasma exchange does not appear to be beneficial.[44] Given the complement pathway abnormalities described previously, there is recent interest in eculizumab. A series of 30 patients treated with eculizumab showed improved survival compared with standard therapy.[44]

Calcineurin Inhibitor and Sirolimus Nephrotoxicity

CNIs are routinely prescribed after allogeneic HSCT to prevent and to treat GVHD. Because CNIs are often stopped after 3 to 6 months (unless there is ongoing GVHD), their contribution to CKD is thought to be limited. The contribution of CNIs to chronic renal TMA is unclear. TMA can certainly occur in patients on non-CNI protocols.[45] There is a high incidence of TMA when sirolimus is added to CNI therapy (particularly if drug levels are high), but fortunately this is often reversible.[46]

Glomerular Disease

Nephrotic syndrome has been described after both allogeneic (particularly nonmyeloablative) and autologous HSCT. In allogeneic HSCT, it appears to be strongly associated with the presence of GVHD. Clinical response is usually seen with increased immunosuppression (typically corticosteroids and/or CNI; some reports of rituximab). De novo membranous nephropathy is the most common biopsy finding, and minimal change disease also has been reported.[47] The original hematologic disease (such as myeloma) may recur with renal involvement.

Management of Hematopoietic Stem Cell Transplantation–Related Chronic Kidney Disease

General treatment should be as recommended for any patient with CKD. Aggressive control of hypertension is warranted. There is limited evidence regarding the superiority of RAS blockade, but their use seems reasonable.[48] CNI doses should be minimized, if this is thought appropriate for the management of the HSCT. Alternatively, substitution of CNIs with IL-2 receptor blockers in the setting of GVHD and renal dysfunction might improve renal function but remains experimental at this time.[49]

Approximately 4% of patients will progress to ESRD, and overall these patients have worse survival on dialysis than non-HSCT controls.[44,45] Suitability for renal transplantation should be judged on a case-by-case basis. On occasion, the allogeneic stem cell donor can donate a kidney; the great benefit of this approach is that tolerance to the kidney allograft should exist, and hence minimal or no immunosuppression is required.[50] If this option is not available and the patient receives a conventional kidney transplant, low-dose immunosuppression should generally be prescribed because HSCT recipients may not have normal immunity and remain at higher risk for infection. Good outcomes after renal transplantation have been reported in carefully selected patients.[50,51]

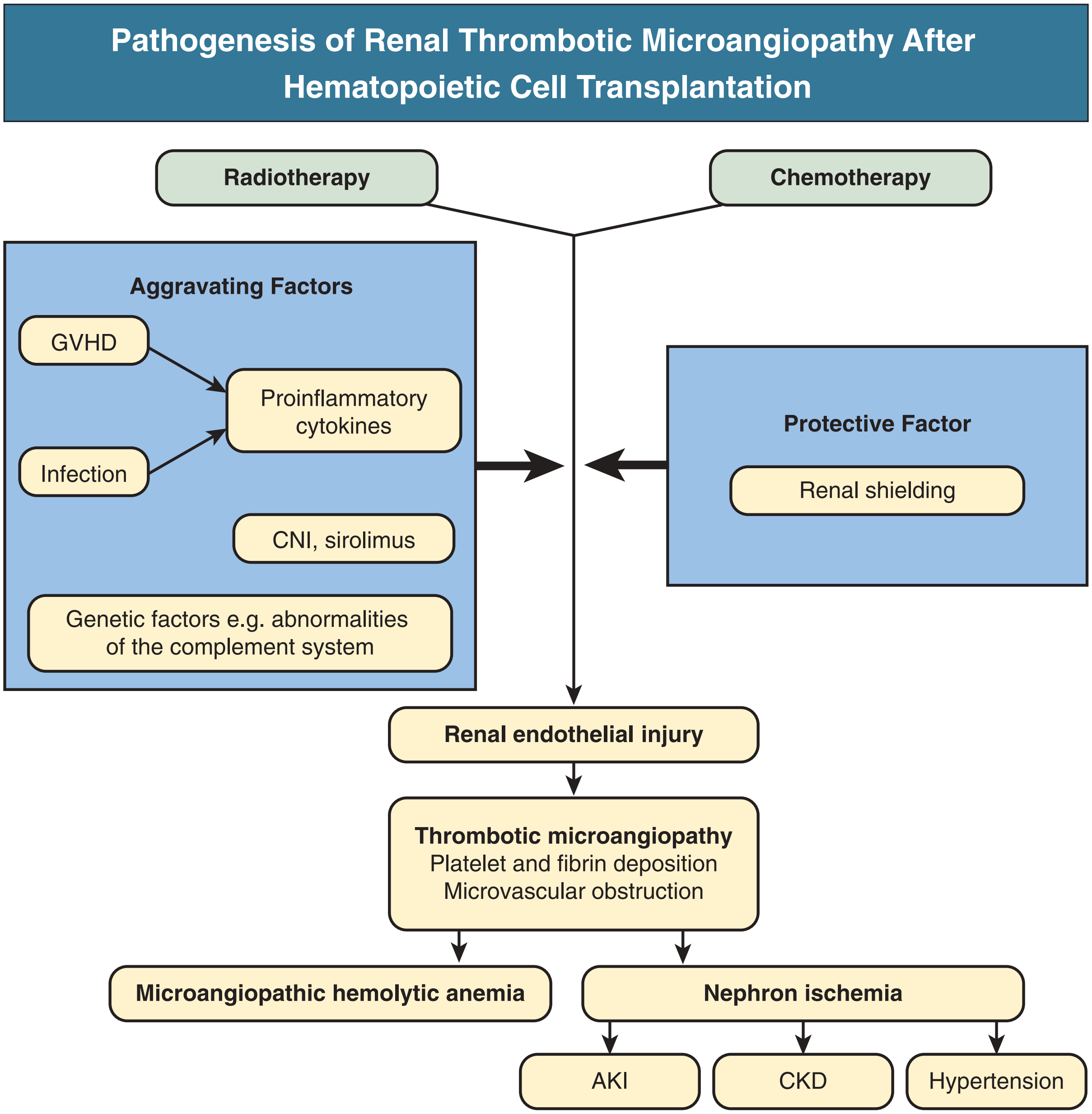
Pathogenesis of Renal Thrombotic Microangiopathy After Hematopoietic Cell Transplantation
Radiotherapy
Chemotherapy
Aggravating Factors
GVHD
Proinflammatory cytokines
Infection
CNI, sirolimus
Genetic factors e.g. abnormalities of the complement system
Protective Factor
Renal shielding
Renal endothelial injury
Thrombotic microangiopathy
Platelet and fibrin deposition
Microvascular obstruction
Microangiopathic hemolytic anemia
Nephron ischemia
AKI
CKD
Hypertension

Fig. 111.5 **Putative pathogenesis of renal thrombotic microangiopathy after hematopoietic stem cell transplantation.** *AKI,* Acute kidney injury; *CKD,* chronic kidney disease; *CNI,* calcineurin inhibitor; *GVHD,* graft-versus-host disease. (Modified from reference 38.)

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SELF-ASSESSMENT QUESTIONS

1. A 28-year-old woman is referred to the renal clinic with serum creatinine 2.3 mg/dl (200 µmol/l). Six years ago she underwent lung transplantation because of respiratory failure associated with cystic fibrosis. The lung transplant is working well. However, her serum creatinine has increased slowly over the last 5 years from 1.1 mg/dl (97 µmol/l). Her medications are cyclosporine, azathioprine, prednisolone, simvastatin, and pancreas enzyme supplements. The main findings on examination are finger clubbing and blood pressure (BP) 148/84 mm Hg. The urine dipstick shows trace protein only. Which of the following is true?
   A. The underlying cause of her chronic kidney disease (CKD) is most likely cyclosporine toxicity.
   B. An urgent renal biopsy is indicated.
   C. Switching azathioprine to sirolimus is indicated.
   D. If her CKD progresses, kidney transplant is contraindicated because of underlying cystic fibrosis.
   E. Diltiazem should be added to control the hypertension.
2. A 30-year-old man is referred to the renal clinic because of rising serum creatinine and worsening hypertension. Eight months ago he underwent an allogeneic stem cell transplant for acute myeloid leukemia (AML). His conditioning regimen included total body irradiation and cyclophosphamide. His early post-transplant course was relatively uncomplicated. However, he remained on cyclosporine because of graft-versus-host disease (GVHD) of the skin. Recent cyclosporine trough concentrations have been 60 to 90 ng/ml. His medications are low doses of cyclosporine, prednisolone, valacyclovir, and sulfamethoxazole-trimethoprim. The main findings on examination are BP 166/98 mm Hg (148/86 mm Hg, 3 weeks ago), mild GVHD of the skin, and mild leg edema. The urine dipstick shows 3+ blood and 3+ protein. Other test results are as follows: white blood cells (WBCs) 4.2 × 10^9/l, hematocrit (Hct) 26.0 (32, 3 weeks ago), platelets 82 × 10^9/l (130, 3 weeks ago), creatinine 2.3 mg/dl (200 µmol/l) (1.2 mg/dl [105 µmol/l], 3 weeks ago), albumin 3.2 g/dl, and 24-hour urine protein 3.2 g. The prothrombin time and activated partial thromboplastin time are normal. Which of the following is true?
   A. The main cause of the renal disease is probably cyclosporine toxicity.
   B. The patient has nephritic syndrome, most likely caused by membranous nephropathy.
   C. The plasma lactate dehydrogenase (LDH), serum haptoglobin, and blood film should be checked urgently.
   D. The main cause of the renal disease is recurrence of AML, with infiltration of the kidneys.
   E. Computed tomography with intravenous contrast should be performed urgently to exclude obstruction of the urinary tract.
3. A 30-year-old man is referred urgently to the renal clinic because of an increase in creatinine from baseline 2.0 mg/dl (176 µmol/l) to 2.9 mg/dl (255 µmol/l). One week ago he was diagnosed with community-acquired pneumonia and treated with antibiotics. His breathlessness and cough have improved, but he reports mild headache and pain in the right big toe. Ten years ago he underwent a heart transplant for severe heart failure caused by idiopathic dilated cardiomyopathy. The heart transplant is apparently working well. His medications are cyclosporine, azathioprine, prednisolone, ramipril, atorvastatin, and (in the last week) cefuroxime plus clarithromycin. Examination shows fine hand tremor, pulse 90/min and regular, BP 142/84 mm Hg, oxygen saturation 98% on room air, normal breath sounds with no added sounds, and no leg edema. The right big toe is inflamed, consistent with acute gout. The urine dipstick shows trace protein only. Tests show serum creatinine 2.9 mg/dl (255 µmol/l), potassium 5.9 mmol/L, WBCs 4.9 × 10^9/l (with normal differential), Hct 30, platelets 189 × 10^9/l. Which of the following is true?
   A. The most likely cause of the acute renal dysfunction is allergic interstitial nephritis resulting from cefuroxime.
   B. The main underlying cause of the CKD is cardiac failure (of the transplanted organ).
   C. If the patient's CKD progresses to GFR below 15 ml/min, the treatment of choice would be peritoneal dialysis.
   D. Allopurinol should be added to treat the gout.
   E. The most likely cause of the acute renal dysfunction is acute cyclosporine nephrotoxicity caused by impairment of cyclosporine metabolism by clarithromycin.
4. A 44-year-old woman is admitted to the intensive care unit with severe, decompensated liver disease. The underlying cause is cirrhosis from hepatitis C (HCV) infection. Over 1 week she becomes oliguric; serum creatinine increases from 1.0 (88 µmol/l) to 2.5 mg/dl (221 µmol/l). The urine dipstick shows trace blood and trace protein only. The fractional urine excretion of sodium is 0.2%. Low-dose noradrenaline is started, causing the mean arterial pressure to increase to 65 mm Hg and the urine output to increase to 800 ml/24 h. A decision is made to list her for an emergency liver transplant. Which of the following is true?
   A. The baseline serum creatinine of 1.0 mg/dl likely reflects normal renal function.
   B. The clinical picture is consistent with hepatorenal syndrome.
   C. The acute renal dysfunction is a result of HCV-related glomerulonephritis.
   D. At this time, a simultaneous liver-kidney rather than a liver-alone transplant should be performed.
   E. After successful liver transplantation, her risk for developing stage 4 or 5 CKD over the long term is negligible.
5. A 39-year-old woman is referred for opinion regarding kidney transplantation. She has a background of complex congenital cyanotic heart disease and has undergone several procedures for this. However, her cardiac function is worsening and she is therefore being considered for cardiac transplantation. Her serum creatinine has steadily increased over the last 3 years. Medications are furosemide, digoxin, bisoprolol, omeprazole. She reports poor appetite and breathlessness on minimal exertion. On examination she is thin, pulse is 114 beats/min and regular, BP 152/92 mm Hg, and respiratory rate 22/min at rest. The fingertips are cyanosed. The jugular venous pressure is increased. There are reduced breath sounds in the left lung base. The liver edge is palpable; the femoral pulses are strong with no bruits. There is trace leg edema. Tests show urine dipstick 3+ protein and trace blood, plasma creatinine 4.0 mg/dl, potassium 5.1 mmol/l, albumin 3.1 g/dl, and 24-hour urine protein 4.2 g. Which of the following is true?
   A. The renal dysfunction is mainly a result of the severe heart failure and thus should improve significantly after successful cardiac transplantation.
   B. Because of the risk that cyclosporine or tacrolimus will worsen renal function after cardiac transplantation, you should advise the cardiologists to avoid using these drugs after transplantation.
   C. Simultaneous heart-kidney transplant is a relatively common procedure and should be considered here.
   D. Simultaneous heart-kidney transplant is an uncommon procedure but should be considered here.
   E. You should recommend that a kidney transplant be performed first and only later consider cardiac transplantation.

112

Palliative Nephrology

Edwina A. Brown, Fliss E. Murtagh

Palliative care is defined by the World Health Organization as "An approach that improves the health-related quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual."[1] The term *supportive care* is usually preferred by patients and families and is the term used by the Kidney Disease: Improving Global Outcomes (KDIGO) summary document on supportive care in kidney disease[2] and likewise in this chapter. As shown in Fig. 112.1, supportive care should begin at the time of diagnosis of advanced kidney disease. Fig. 112.2 shows how the different components can be used at different times.

PROGNOSIS

Informing patients accurately about prognosis is key to individualizing dialysis and associated supportive care. Patients with advanced kidney disease often have other comorbidities and complications of treatment; these and increasing age are causes of a high burden of morbidity affecting quality of life and shortening length of life. Physicians, however, often are not good at estimating prognosis with quotes in recent literature such as *"if you're on dialysis you could last 10, 15, 20 years (male 76 years old)"* or *"you will probably have 6 years on dialysis (male 82 years old)"*.[3] Patients often want to have conversations about life expectancy,[4] and failure to do so can result in high expectations and increased desire for aggressive treatment.[5] Being aware of prognosis is a key part of shared decision making.[6] At the individual level, the surprise question "Would you be surprised if the patient died in the next 6 or 12 months?" has been shown to enhance prognostic prediction,[7] although it has the limitation of being subjective and depending on clinician perception.

Prognostic tools have therefore been developed to enable clinicians to estimate the prognosis of patients. Factors that can be used to develop tools are summarized in Box 112.1; more detailed information can be found in an overview by Couchoud et al.[6]

Prognostic tools, however, have limitations because they provide an estimate of average survival for a population of similar risk but not for the individual. Before using a particular tool, it is important to know whether the patient concerned is similar to those used for the development of the tool in terms of age, ethnicity, renal replacement therapy (RRT), clinical data available, etc. The tool that is most readily accessible is the ARO score, which is based on simple clinical and laboratory data for prevalent European patients on hemodialysis[7]; it can be easily calculated on the ARO Risk Score website.[8] For patients not yet on dialysis, a risk score for mortality in the first 90 days of dialysis has been developed for older patients from the French Renal Epidemiology and Information Network (REIN) registry.[9] In routine clinical practice these tools can inform discussions with patients and families.

The prognostic tools discussed herein are all specific for kidney disease and mostly for patients on dialysis. Clinical tools useful as prognostic indicators in the general population are also applicable in the presence of kidney disease. The concept of frailty is rapidly becoming one of the useful prognostic indicators for hospitalization, complications of procedures, and mortality in the general population.[10] Clinically, frailty manifests as a composite of poor physical function, exhaustion, low physical activity, and weight loss and is associated with an increased risk for falls, cognitive impairment, hospitalization, and death. It is more common in the CKD population and not surprisingly is a strong predictor of mortality.[11] There are various methods of assessing frailty, but the easiest to use clinically is the Canadian Frailty Scale (Table 112.1), which has been shown to correlate with more complex assessment methods and predicts hospitalization and mortality.[12] Using this scale, the Frail Elderly Patient Outcomes on Dialysis (FEPOD) study has shown that it is frailty, not dialysis modality (assisted peritoneal dialysis [PD] and hemodialysis [HD]), that is associated with symptom score, physical functioning, and measures of quality of life.[13] Determining a frailty score routinely in older patients approaching or on dialysis enhances prognostication both of survival and quality of life. Frailty therefore is another factor that should inform discussions with patients and families.

COMMUNICATION AND SHARED DECISION MAKING

Good communication is key to enabling people to optimize quality of life and achieve their goals at all stages of a long-term condition. Conversations must include awareness of prognosis and wishes for end of life planning. These latter conversations are commonly referred to as advance care planning, but ideally they are easier for all concerned if conversations about prognosis and realistic outcomes of potential treatments and their limitations are conducted as part of routine care at all stages of advanced kidney disease. Treatment decisions should be made

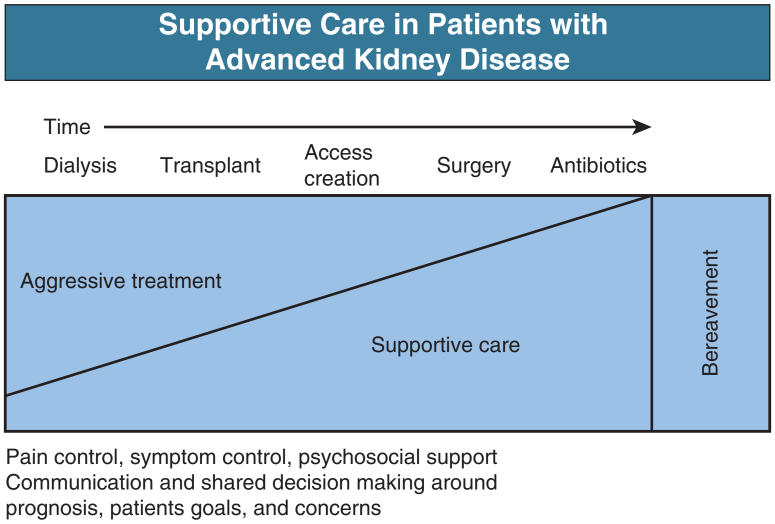

Supportive Care in Patients with Advanced Kidney Disease
Time
Dialysis
Transplant
Access creation
Surgery
Antibiotics
Aggressive treatment
Supportive care
Bereavement
Pain control, symptom control, psychosocial support
Communication and shared decision making around prognosis, patients goals, and concerns

Fig. 112.1 Schematic diagram of how supportive care fits into patient pathway with advanced kidney disease.

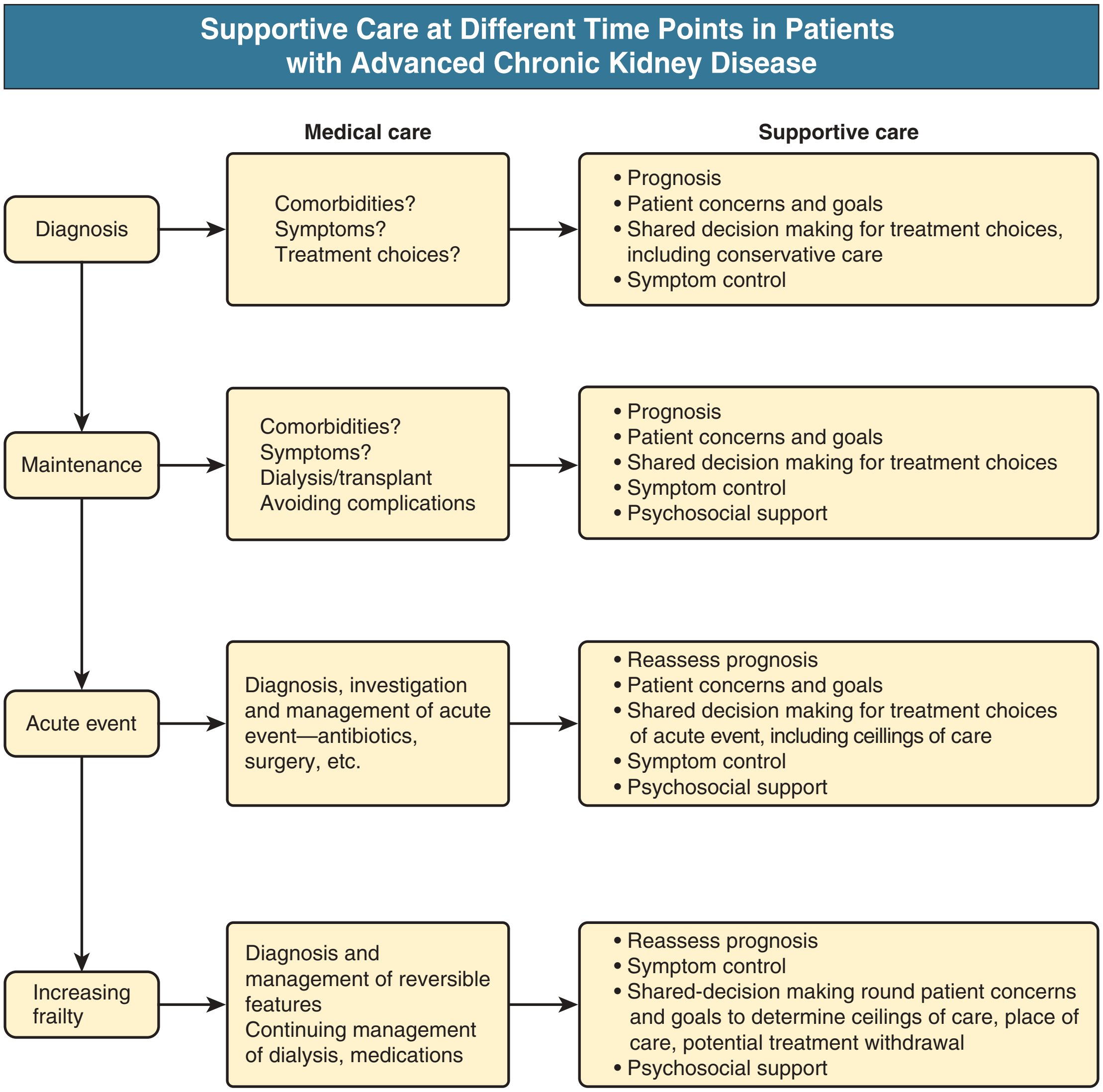

Supportive Care at Different Time Points in Patients with Advanced Chronic Kidney Disease
Medical care
Supportive care
Diagnosis
Comorbidities? Symptoms? Treatment choices?
• Prognosis
• Patient concerns and goals
• Shared decision making for treatment choices, including conservative care
• Symptom control
Maintenance
Comorbidities? Symptoms? Dialysis/transplant Avoiding complications
• Prognosis
• Patient concerns and goals
• Shared decision making for treatment choices
• Symptom control
• Psychosocial support
Acute event
Diagnosis, investigation and management of acute event—antibiotics, surgery, etc.
• Reassess prognosis
• Patient concerns and goals
• Shared decision making for treatment choices of acute event, including ceillings of care
• Symptom control
• Psychosocial support
Increasing frailty
Diagnosis and management of reversible features
Continuing management of dialysis, medications
• Reassess prognosis
• Symptom control
• Shared-decision making round patient concerns and goals to determine ceilings of care, place of care, potential treatment withdrawal
• Psychosocial support

Fig. 112.2 Use of supportive care at different time points in life with advanced kidney disease.

BOX 112.1 Factors Used to Develop Prognostic Tools

Clinical Data

- Age
- Assistance with activities of daily living
- Gender
- Congestive heart failure
- Peripheral vascular disease
- Dysrhythmia
- Active malignancy
- Mobility
- Diabetes
- Body mass index
- Behavioural disorders
- Frequency of hospitalization

Dialysis-Related

- Use of central vein dialysis catheter
- Early nephrology referral

Laboratory Values

- Plasma albumin
- Plasma creatinine
- C-reactive protein

TABLE 112.1 Clinical Frailty Scale

Score	Definition
1	*Very fit:* Robust, active, energetic, well-motivated and fit
2	*Well:* No active disease, but less fit than people in category 1
3	*Well, with treated comorbid disease:* Disease symptoms are well controlled compared with category 4
4	*Apparently vulnerable:* Although not frankly dependent, commonly complain of being "slowed up"
5	*Mildly frail:* With limited dependence on others for instrumental activities of daily living
6	*Moderately frail:* Help is needed with both instrumental and noninstrumental activities of daily living
7	*Severely frail:* Completely dependent on others for the activities of daily living or terminally ill

From reference 10.

BOX 112.2 Time Points for Advance Care Planning Discussions

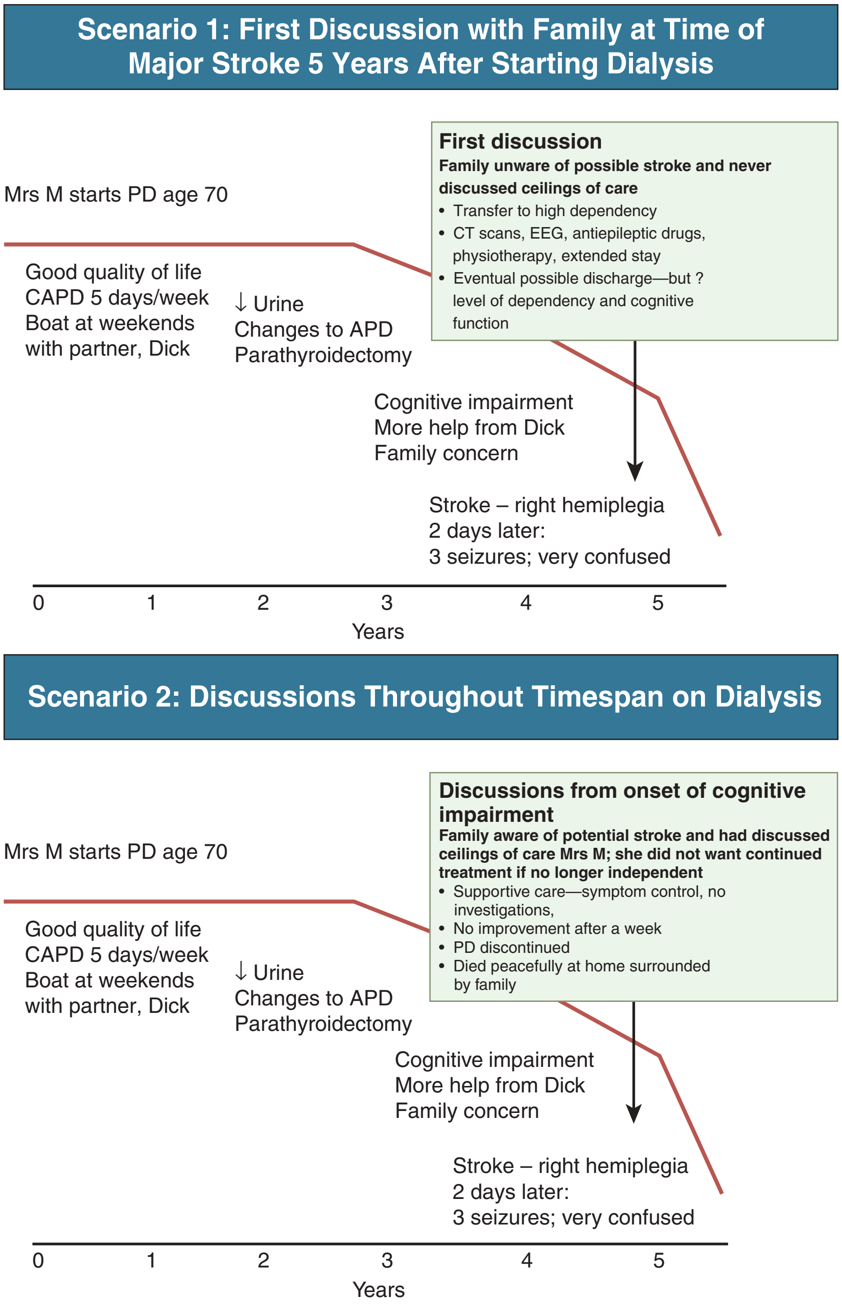
- As part of renal replacement therapy planning, particularly if transplant ineligibility or conservative care is discussed.
- Starting or within first few months of starting dialysis.
- Failing transplant and patient does not want dialysis or is anticipated to have poor outcomes on dialysis.
- Failing peritoneal dialysis (PD) and patient does not want hemodialysis (HD) or is anticipated to have poor outcomes on HD and transplantation not feasible.
- Recurrent vascular access problems in HD patient who does not want or cannot transfer to PD, and transplantation not feasible.
- Patient wants to withdraw from dialysis.
- After intercurrent event that results in worsening of prognosis, such as stroke, fall and bone fracture, worsening cognitive function, new malignancy.
- Development of intercurrent event needing major surgical intervention, such as coronary artery bypass surgery or major abdominal surgery.
- Increasing frailty and/or cognitive decline.
- Answer of "no" to surprise question: "Would you be surprised if patient died in the next 12 months?"

BOX 112.3 Questions and Statements to Use in Advance Care Planning

- How is your health now compared with a few months ago?
- Would you be surprised if I told you that things are not going well?
- It is always hard to predict the future, but it would not be a surprise if some major acute event occurred or your health deteriorated significantly in the next few months (or other applicable time scale). We should therefore discuss what your wishes would be should this occur . . . .
- It is a good idea to talk about what we can do and how to get help if you get more unwell . . . .
- Different people make decisions in different ways. Do you make decisions on your own, do you involve your family, or does someone from your family make important decisions for you?
- Do you have a faith or spiritual beliefs that help you in difficult times?
- Have you ever thought how much treatment you would want if you are very ill, unable to communicate to make your own decisions, and unlikely to leave hospital and be independent?
- You know you have a choice about where you would like your end of life care to take place. Would you like to talk through the options?
- Some people decide to stop dialysis when their health has deteriorated and they feel that dialysis has become a burden and is no longer of benefit. We do not need to mention that any further now, but it is something you may want to discuss later.

with and not *for* the patient, in other words using shared decision making. This is a process in which patients, when faced with an important choice about their health care, can review all the treatment options available to them and participate actively with their health care professional in making that decision,[14] thereby enabling patient autonomy to be respected.[15] Shared decision making is embedded in the U.S. Renal Physicians Association guidelines on dialysis initiation and withdrawal,[16] which state that "they reflect the ethical principle of respect for autonomy because clinicians, family members, and others have an ethical duty to accept the decisions regarding medically indicated treatment made by competent patients and, in the absence of competence, to formulate decisions that would respect patients' wishes, or if wishes are unknown, advance the best interest of their patients." To enable patients and families to make these decisions, they need to be given evidence-based information about what is happening regarding disease process, what is likely to happen regarding prognosis, what the treatment options are available, and what are the realistic outcomes from these treatments. Health care professionals, on their part, should seek to understand the patient's concerns and lifestyle priorities and then use these to guide the patient through decision making about wishes regarding specific treatments, ceilings/limits of care if they are no longer able to make decisions, place of care at end of life, etc. A summary of when such conversations could and should take place are shown in Box 112.2.

There are challenges to having advance care planning discussions—time needed, cultural and linguistic challenges,[17] and overcoming inhibitions of health care professionals to have difficult conversations, particularly when the prognostic future is uncertain.[18] Some useful questions to overcome these challenges are shown in Box 112.3.


Scenario 1: First Discussion with Family at Time of Major Stroke 5 Years After Starting Dialysis

First discussion
Family unaware of possible stroke and never discussed ceilings of care
• Transfer to high dependency
• CT scans, EEG, antiepileptic drugs, physiotherapy, extended stay
• Eventual possible discharge—but ? level of dependency and cognitive function
Mrs M starts PD age 70
Good quality of life
CAPD 5 days/week
Boat at weekends with partner, Dick
↓ Urine
Changes to APD
Parathyroidectomy
Cognitive impairment
More help from Dick
Family concern
Stroke – right hemiplegia
2 days later:
3 seizures; very confused
0
1
2
3
4
5
Years

Scenario 2: Discussions Throughout Timespan on Dialysis

Discussions from onset of cognitive impairment
Family aware of potential stroke and had discussed ceilings of care Mrs M; she did not want continued treatment if no longer independent
• Supportive care—symptom control, no investigations,
• No improvement after a week
• PD discontinued
• Died peacefully at home surrounded by family
Mrs M starts PD age 70
Good quality of life
CAPD 5 days/week
Boat at weekends with partner, Dick
↓ Urine
Changes to APD
Parathyroidectomy
Cognitive impairment
More help from Dick
Family concern
Stroke – right hemiplegia
2 days later:
3 seizures; very confused
0
1
2
3
4
5
Years

Fig. 112.3 How communication and advance care planning can influence patient outcomes. **Scenario 1:** First discussion with family at time of major stroke 5 years after starting dialysis. **Scenario 2:** Discussions throughout time span on dialysis. *APD,* Ambulatory peritoneal dialysis; *CAPD,* continuous ambulatory peritoneal dialysis; *CT,* computed tomography; *EEG,* electroencephalogram; *PD,* peritoneal dialysis.

Conversations about prognosis and advance care planning should be embedded in nephrologic practice. The timing and frequency of discussions can have a huge influence on patient outcomes. Fig. 112.3 gives the example of a woman who has had a major stroke 5 years after starting dialysis at the age of 70 and who has had progressive cognitive impairment in the last 2 years. In the absence of any previous discussions, the family would be unaware of the high probability of stroke and in all likelihood, would not have had discussions about extent of treatment in such an event; there would then be a high probability of them expecting intensive investigations and management. In reality, for this particular patient, there had been a number of discussions after the onset of cognitive impairment and the patient had made it clear that she did not want continuing active management if she was not going to be independent; this made the final decision making by the family very much easier. This has been confirmed by randomized controlled studies in elderly and dialysis populations showing better quality of life at end of life and improved certainty about decision making by close family members.[19,20]

CONSERVATIVE CARE

Conservative (nondialytic) kidney care has been defined (Box 112.4), using the term *comprehensive conservative care* and encompassing all the components required for effective comprehensive care.

BOX 112.4 Definition of Comprehensive Conservative Care

Comprehensive conservative care is planned holistic patient-centered care for patients with stage 5 (glomerular filtration rate category 5) chronic kidney disease that includes:

- Interventions to delay progression of kidney disease and minimize risk for adverse events or complications
- Shared decision making
- Active symptom management
- Detailed communication, including advance care planning
- Psychological support
- Social and family support
- Cultural and spiritual domains of care

Comprehensive conservative care does not include dialysis.

From reference 2.

BOX 112.5 Distinct Conservative Care Populations

Comprehensive conservative care: Conservative care that is chosen or medically advised.

Choice-restricted conservative care: Conservative care for patients in whom resource constraints prevent or limit access to renal replacement therapy; therefore a choice for conservative care cannot be recognized.

Unrecognized stage 5 chronic kidney disease: Chronic kidney disease is present but has not been recognized or diagnosed; therefore a choice for conservative care cannot be recognized.

From reference 2.

It has also been proposed that globally there are three distinct groups within the conservative care population (Box 112.5); this reflects limited availability of RRT, the consequent (lack of) options for choice in low-income and middle-income countries, and constraints on diagnosis of stage 5 chronic kidney disease in resource-poor settings.

Rates of conservative management vary considerably among and within countries, and it is likely that individual nephrology practice is at least a factor in this variation.[21] It is important therefore to consider all available evidence on survival of those managed conservatively and to contrast this to evidence on survival with dialysis. However, this is challenging, because those who are more fit usually opt for dialysis, and others are advised to follow conservative nondialytic management because of comorbidity or other factors that adversely influence survival. This selection bias makes it hard to meaningfully compare survival between those with dialysis and those managed conservatively. The summary of the evidence by O'Connor and Kumar[22] provides a good overview of current evidence, although further comparative studies[23-27] have since been published. This collected evidence shows that there is a substantial survival advantage with dialysis; however, for older people with end-stage renal disease (ESRD) (older than 75 to 80 years) with comorbidity, much of this survival advantage is lost. When time in hospital and receiving dialysis is also taken into account, there is little or no survival advantage to be gained from dialysis for these older patients with comorbidities. However, there are two notes of caution in interpreting and applying this evidence; first it must be recognized that the evidence from those receiving conservative care remains very limited, and second the conservative care population is heterogeneous. This makes it much harder to relate to individual circumstances, yet decisions for conservative care always need to be individually tailored.

BOX 112.6 Situations Where Dialysis Withdrawal is Appropriate

- Patients with decision-making capacity, who being fully informed and making voluntary choices, refuse dialysis or request that dialysis be discontinued
- Patients who no longer possess decision-making capacity
  - who have previously indicated refusal of dialysis
  - whose legal agents/surrogates request that it be discontinued
- Patients with irreversible, profound neurological impairment such that they lack signs of thought, sensation, purposeful behaviour and awareness of self and environment

From the Kidney Disease I Improving Global Outcomes (KDIGO) Controversies Conference on Supportive Care in Chronic Kidney Disease (2)

It is important to also consider symptoms, quality of life, illness experience, and survival. There is robust evidence that patients rarely prioritize survival above all else; quality of life is equally important and often takes precedence.[28] The systematic review cited previously[29] shows that patients managed conservatively (as do those receiving dialysis) report significant symptom burden, with an average of 9 to 17 symptoms. Quality of life is generally similar between patients on dialysis and patients receiving conservative, although there may be some decrease in life satisfaction in relation to dialysis adjustment.[30] Of note, with good renal supportive care many of the conservatively managed patients have stable or improved symptoms and quality of life.[31]

DIALYSIS WITHDRAWAL

As already demonstrated in the case discussed in Fig. 112.3, patients may decide to stop dialysis. The median time to death after stopping dialysis is 8 to 9 days[32] but can be considerably longer if there is significant residual renal function. There is information for patients and carers about stopping dialysis on both U.K. and U.S. patient support websites.[33,34] The situations in which dialysis withdrawal is appropriate are shown in Box 112.6.

Studies suggest that the rate of dialysis withdrawal has increased over the years, but this needs to be interpreted with caution because there is no well-accepted definition of dialysis withdrawal.[35] A recent report published from the Scottish Renal Registry[36] has defined death resulting from withdrawal as patients refusing further treatment, therapy ceased for other reasons, and dialysis withdrawn for medical reasons. In this study, dialysis withdrawal was the primary cause of death in 19% of all deaths (a rate of 41 in 1000 patient-years) over a 7-year period; in a further 17% of patients, withdrawal from dialysis was considered to have contributed to death, but not to be the main cause. Using this definition, deaths attributed to dialysis withdrawal accounted for around a third of deaths; this did not change over the 7 years of the study, but did vary significantly across the different renal centers with dialysis withdrawal accounting for 3.3% to 55.8% of all deaths per center.[36] This variation also has been found on a larger scale between different European countries, with higher reports of dialysis withdrawal if respondents in the survey worked in a public center, if stopping life-supporting treatments was perceived as allowed, if withdrawal decisions were considered shared between patients and doctors, and if palliative care was reimbursed by payers.[37] The patient factors associated with dialysis withdrawal vary in individual studies, but many of the following have been consistently identified: older age, female sex, White race, higher comorbidity burden (particularly cerebrovascular disease), being on HD, early initiation of dialysis, and late referral to nephrologist.[36,38,39]

Withdrawal from dialysis is ethically and clinically acceptable only after a process of shared decision making with the patient (and close persons if the patient is no longer able to make decisions). These discussions need to be attuned to the culture (ethnic and religious) of the individual.[17] It is also incumbent on all providers caring for a patient who is contemplating stopping dialysis to address potentially remedial factors contributing to the decision, such as depression or other symptoms, such as pain, as well as potentially reversible social factors.[2] **It is essential to ensure access to appropriate supportive and/or hospice care as an integral part of care after any decision to withdraw dialysis.**[2] Details of this are discussed in the following section.

SYMPTOM CONTROL AND MANAGEMENT OF LAST DAYS

Symptoms are as common in those managed conservatively as among those on dialysis, with 3 in 4 reporting weakness and pruritus; 1 in 3 reporting drowsiness, breathlessness, and edema; and more than 1 in 2 patients with ESRD reporting pain.[40] These symptoms are not mild; a high proportion (over two thirds) of those with pain, for instance, have moderate or severe pain, often related to comorbid conditions rather than to renal disease. In addition, symptoms often accumulate, with an average of 12 symptoms experienced by each patient that impair quality of life and need optimal management.

Evidence on management of symptoms is often extrapolated from other populations or based on best understanding of the pharmacodynamics and pharmacokinetics in severe renal impairment. This evidence is limited but is well summarized in a recent series of articles.[41]

In the last days of life, additional symptoms may arise from uremia (nausea, vomiting, drowsiness, myoclonus, pruritus), fluid overload (breathlessness and edema), and immobility and poor tissue perfusion (pain, muscle soreness, pressure sores). It is best practice to prescribe "as required" doses of an analgesic, an antiemetic, a sedative, and an antisecretory agent for all patients with ESRD as they enter the last few days of life, to anticipate any distressing symptoms and ensure they can be rapidly addressed.

As end of life approaches, both patient and family often need much more information and explanation than is provided by health professionals. Encouragement to ask questions, straightforward but sensitively judged responses, and frequent opportunities for professionals to check on concerns and anxieties, can go a long way to provide support to the patient and family at a difficult and challenging time.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following factors have been shown to be associated with a poor survival prognosis in an 80-year-old man who has been on dialysis for 2 years?
   - **A.** Being on peritoneal dialysis
   - **B.** Peripheral vascular disease
   - **C.** Use of central venous catheter
   - **D.** Requiring assistance to get dressed
   - **E.** Low plasma albumin
2. Advance care planning should include which of the following?
   - **A.** Legal process resulting in advance decision
   - **B.** Informing patient that he or she will not be resuscitated
   - **C.** Discussion about prognosis
   - **D.** Identification of patient concerns
   - **E.** Opportunity for patient to record future wishes
3. Which of the following statements can be made about dialysis withdrawal?
   - **A.** Approximately 20% of deaths of dialysis patients are stated to be due to dialysis withdrawal.
   - **B.** Death invariably occurs within 3 days of stopping dialysis.
   - **C.** Dialysis withdrawal can be viewed as euthanasia.
   - **D.** Shortness of breath is the main symptom after withdrawing dialysis.
   - **E.** Dialysis can be stopped in patients lacking decision-making capacity who have made a previous decision to this effect.
4. The following statements can be made about conservative care:
   - **A.** Survival rates of multimorbid patients older than 80 years are similar on dialysis and conservative care.
   - **B.** Survival of functionally independent patients 70 to 75 years old are the same on dialysis and conservative care.
   - **C.** Patients choosing conservative care should be persuaded to start dialysis if they deteriorate acutely.
   - **D.** Anemia management with erythropoietin is appropriate for patients choosing conservative care.
   - **E.** Conservative care is not “rationing” because patients choose not to have dialysis themselves.

ANSWERS

CHAPTER 1

1. A. Are unable to replicate
2. E. Serves as the effector structure of mesangial cell contraction
3. A. 30 nm
4. D. Contain nitric oxide synthase

CHAPTER 2

1.
    - A. Albumin has an effective radius of 3.6 nm and is small enough to be filtered.
    - B. The filtration barrier is negatively charged, which restricts filtration of negatively charge proteins.
    - C. Net ultrafiltration pressure is determined by the balance of hydrostatic and oncotic pressure across the capillary.
    - **D. Correct. Dilation of the afferent arteriole alone will increase hydrostatic pressure within the glomerular capillary network and therefore increase filtration.**
    - E. Mesangial cells are contractile and can influence the net filtration area.
2.
    - **A. Correct. The proximal tubule normally reclaims almost all of the filtered glucose via SGLT2. Impairment of this pathway can explain glycosuria in Fanconi syndrome.**
    - B. Impaired fluid reabsorption in the proximal tubule can explain polyuria. However, the proximal tubule is "leaky" and cannot sustain a large osmotic gradient, so this statement is incorrect. It reabsorbs large amounts of water because of a high hydraulic permeability.
    - C. Approximately 65% of the filtered calcium is reabsorbed in the proximal tubule and injury to this segment can cause hypercalciuria. This answer is incorrect because calcium reabsorption mostly occurs through the paracellular pathway and not via a calcium pump in the apical membrane.
    - D. The proximal tubule reabsorbs phosphate via a dedicated cotransport protein that uses the electrochemical gradient for sodium. Impairment of this process, as can occur in the Fanconi syndrome, causes hyperphosphaturia.
    - E. This is incorrect. The proximal tubule is a leaky epithelium.
3.
    - A. Vasopressin-stimulated sodium and urea transport in the thick limb of Henle and will increase the gradient.
    - **B. Correct. Increased blood flow through the medullary vasa recta causes "washout" of osmolytes from the interstitial fluid, diminishing the gradient.**
    - C. Activation of this system increases the medullary gradient.
    - D. Activation of this system increases the medullary gradient.
    - E. Urea contributes significantly to the gradient.

CHAPTER 3

1. D.
   Larger than average body size based on height and weight.
2. F
   Chronic kidney disease is defined as markers of kidney damage or decreased GFR for ≥3 months, so ascertainment of kidney damage and confirmation of decreased GFR could be used to confirm the diagnosis.
3. B.
   ACE inhibitors cause a reversible decline in GFR in patients with chronic kidney disease.

CHAPTER 4

1. B. Is not adequate for the evaluation of the renal patient
   This is because reagent strip detects only albumin, has a low sensitivity (does not detect urine albumin ≤0.25-0.30 g/l), supplies only semiquantitative results, and there is no standardization between manufacturers.
2. A. Is the correct approach for urine sediment examination
   This is correct because phase contrast plus polarized light allows the best identification of morphologic details, especially of cells and casts, and allows the best identification of lipids and crystals when they come with unusual morphology.
3. D. Are not adequate for the evaluation of the renal patient
   This is correct because automated urine sediment analyzers do not identify clinically relevant epithelial cells (renal tubular cells, transitional cells either deep or superficial, decoy cells); underestimate casts, of which they can recognize only hyaline and “nonhyaline” or “pathologic” subtypes; identify only a few types of crystals; do not identify lipids.

CHAPTER 5

1. C. Hypoechoic
2. A. CO2 angiography
3. D. Diffusion-weighted MRI
4. D. History of cerebral aneurysm clip
5. A. Noncontrast CT scan

CHAPTER 6

1.
   - **A. Correct. Half-life of naproxen is up to 16 hours; therefore after 24 hours platelet function would still be deranged.**
   - B. This level of BP is not a contraindication.
   - C. This may indicate the presence of urinary infection, but in the absence urinary symptoms it is not a contraindication to biopsy.
   - D. With appropriate ultrasound imaging it should be possible to perform a biopsy of the kidney away from the cysts.
   - E. Although this may make visualization of the kidneys difficult, high BMI is not a contraindication to renal biopsy.

2.
   - A. This is likely related to pre-eclampsia, and a biopsy should not be required for diagnosis.
   - B. Investigation for this can be delayed until after the pregnancy is complete, assuming renal function is stable.
   - C. This will require imaging of the renal tract, but a renal biopsy is unlikely to be useful during pregnancy.
   - D. This is likely related to pre-eclampsia, and a biopsy should not be required to diagnose this.
   - **E. Correct. This may indicate the presence of a renal disease that may require specific treatment during pregnancy, and therefore knowledge of the underlying pathologic process is important.**

3.
   - A. This is possible, but B is a better answer because the bleeding diathesis is correctable.
   - **B. Correct. This will provide functioning platelets to circumvent the clopidogrel-mediated platelet dysfunction.**
   - C. This will not reverse clopidogrel-induced platelet dysfunction.
   - D. A delay of at least 7 days is required for the correction of the effects of aspirin and clopidogrel on platelets.
   - E. This will not reverse clopidogrel-induced platelet dysfunction.

4.
   - A. This supports a diagnosis of diabetic nephropathy, and the diagnosis usually can be comfortably made with clinical criteria alone.
   - B. This supports a diagnosis of diabetic nephropathy, and the diagnosis can usually be comfortably made with clinical criteria alone.
   - C. This would be expected with diabetic nephropathy.
   - **D. Correct. The proteinuria of diabetic nephropathy is progressive over months to years. A negative urinalysis 4 months earlier suggests the presence of an alternative diagnosis to diabetic nephropathy.**
   - E. This provides no additional information in terms of clarifying the cause of proteinuria.

CHAPTER 7

1. B. Underfilling of the arterial circulation resulting from splanchnic venous dilation causing neurally and hormonally mediated renal sodium retention

   This patient presents with extracellular fluid expansion secondary to chronic liver disease/cirrhosis, as suggested by consistent history of alcohol dependence and physical examination findings. In cirrhosis, nitric oxide and carbon monoxide overproduction leads to splanchnic and peripheral arteriolar vasodilation. In advanced stages of cirrhosis, this causes underfilling of the systemic arterial vascular space. Baroreceptor-mediated activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system stimulation, and nonosmotic release of antidiuretic hormone (ADH) occur to restore the normal blood volume homeostasis. This results in renal sodium and water retention and constitutes the major mechanism for sustained ascites formation.

2. D. Administer intravenous mannitol to increase osmotic pressure within the tubule and thus sodium and water reabsorption

   Therapy for extracellular fluid volume excess in patients with cirrhosis attempts to achieve negative sodium balance by dietary sodium restriction and diuretics. Other measures can be used when the patient has inadequate or no response to diuretics or when rapid decompression of the abdomen is desired. Large-volume paracentesis with albumin infusion can thus be used. Intravenous mannitol has augmented natriuresis in diuretic-resistant patients with cirrhosis but is not typically recommended.

3. C. Treat for presumptive bacterial peritonitis

   The clinical scenario is consistent with presumptive spontaneous bacteria peritonitis (SBP). Although the patient remains hypotensive, there is clear evidence that her venous volume is now replete; in this case a pressor might be a reasonable choice. Randomized trials have reported adverse outcomes of patients in the intensive care unit treated with HES compared with lactated Ringer solution. The creatinine rise indicates acute kidney injury, and the urine sodium concentration suggests that she may have developed acute tubular necrosis. There is no clear indication for dialysis, despite the rise in creatinine.

CHAPTER 8

1. D. Increased solute load and measurement of electrolyte-free water clearance

   A calculation would reveal that this patient is excreting electrolyte-free water despite the urine osmolality being much greater than serum osmolality. In such a patient setting, the failure to replace electrolyte-free water losses results in increased serum sodium concentration. The hyperosmolality of the urine is primarily caused by the extremely high excretion of urea in this patient receiving high-protein enteral feedings.

2. B. Patient probably has idiopathic SIADH

   The data described fulfil the criteria for the syndrome of inappropriate antidiuretic hormone secretion (SIADH). This patient not taking a thiazide diuretic does not protect her from developing SIADH, which can occur in elderly individuals occasionally without an obvious underlying cause. The high urinary osmolality speaks against poor solute intake. There is no known change in vasopressin metabolism in elderly patients.

3. B. 0.5 ml of 5% dextrose in water per milliliter of urine

   This patient also is excreting electrolyte-free water, most likely because of the loop diuretic. The regimen would match water losses, and the serum sodium would remain unchanged. Because the patient is also hypervolemic, a negative sodium balance is desirable and would be undermined by the other three regimens, all of which contain sodium.

CHAPTER 9

1. **D. Hypomagnesemia often leads to renal K^+ wasting and hypokalemia. Correction of the hypomagnesemia, whether by discontinuation of causative medications or by magnesium supplementation, corrects the renal K^+ wasting and allows successful correction of the hypokalemia.**
2. A. Terazosin
   Blockade of α_1-adrenoreceptor can stimulate cellular K^+ uptake. This class of medication does not lead to hyperkalemia.
3. Hypokalemia is associated with which of the following conditions?
   E. All are correct.

CHAPTER 10

1. C. Correct. Malignant neoplasias
   - A. Secondary hyperparathyroidism is associated with normal or low plasma calcium level.
   - B. Cholecalciferol or ergocalciferol therapy rarely induce hypercalcemia, except when very high doses are administered.
   - D. Familial hypocalciuric hypercalcemia is a rare disease.
   - E. Hypomagnesemia induces hypoparathyroidism and/or peripheral resistance to PTH and thus hypocalcemia.
2. D. Vitamin D overload; E. Treatment by calcium-based phosphate binders
   - A. Primary hypoparathyroidism is a common cause of hypocalcemia.
   - B. Secondary hyperparathyroidism occurs when plasma calcium and/or 1,25(OH)$_2$-vitamin D levels decrease.
   - C. Hyperphosphatemia
   - **D. Correct. This treatment may be a cause of hypercalcemia, not hypocalcemia.**
   - **E. Correct. This treatment may be a cause of hypercalcemia, not hypocalcemia.**
3. B. Adrenocorticotropin hormone
   - A. Parathyroid hormone decreases phosphate reabsorption by the proximal tubule.
   - **B. ACTH**
   - C. FGF-23 decreases phosphate reabsorption by the proximal tubule.
   - D. Klotho is a factor required for the proper response of the proximal tubule to FGF-23.
   - E. Growth hormone increases phosphate reabsorption by the proximal tubule.
4. E. Worsening of secondary hyperparathyroidism
   - A. It may be associated with, but not clearly causally linked to, untreated hyperparathyroidism in patients with CKD.
   - B. It may be associated with, but not clearly causally linked to, untreated hyperparathyroidism in patients with CKD.
   - C. It may be associated with, but not clearly causally linked to, untreated hyperparathyroidism in patients with CKD.
   - D. It may be associated with, but not clearly causally linked to, untreated hyperparathyroidism in patients with CKD.
   - **E. Correct. Worsening of secondary hyperparathyroidism is causally linked to untreated hyperparathyroidism in patients with CKD.**
5. A. Anemia

CHAPTER 11

1. B. Increases proximal tubular ammonia production

In normal individuals, the net effect of K^+ deficiency is typically a minor change in acid-base balance. Chronic K^+ deficiency increases the proximal tubule apical membrane Na^+-H^+ antiporter and basolateral membrane Na^+-HCO_3^--CO_3^{2-} cotransporter activities. Chronic K^+ deficiency also increases proximal tubular ammonia production and increases collecting duct H^+ secretion. As counterbalance to these effects, K^+ deficiency decreases aldosterone secretion, which can inhibit distal acidification. Thus, in normal individuals, the net effect of K^+ deficiency is typically a minor change in acid-base balance.

2. D. Nonthyroid glycoproteins Rhbg and Rhcg are involved in collecting duct ammonia secretion.

The nonerythroid glycoproteins Rhbg and Rhcg are likely involved in collecting duct ammonia secretion. Most of the ammonia (NH_3) that leaves the proximal tubule is transported out of the loop of Henle, predominantly in the thick ascending limb (TAL). Lumen-positive voltage provides a driving force for passive paracellular ammonium (NH_4^+) transport out of the TAL. NH_4^+ can be transported out of the lumen by the furosemide-sensitive Na^+-K^+-2Cl transporter. NH_4^+ also can leave the lumen across the apical membrane K^+ channel of the TAL cell. Ammonia is secreted by the collecting duct.

3. D. Daily volatile acid production is approximately 1 mmol H^+.

In general, animal foods are high in proteins and organophosphates, thereby providing a net acid diet. Lysine and arginine yield acid on metabolism. Sulfur-containing amino acids are metabolized to H_2SO_4. Under normal circumstances, daily net nonvolatile acid production is approximately 1 mmol H^+/kg.

CHAPTER 12

1. B. Correct. Serum HCO3⁻ concentration will increase after oral bicarbonate administration but then decrease to 18 mmol/l after therapy is discontinued.
   - A. Choice A is incorrect because distal, not proximal, RTA is associated with nephrocalcinosis.
   - **B. The patient presents with hypokalemia and normal gap acidosis in association with glycosuria and normal plasma glucose concentration. These findings suggest Fanconi syndrome and type 2 or proximal renal tubular acidosis (RTA). The large amount of proteinuria but only a trace positive dipstick suggests excretion of a cationic protein caused by multiple myeloma. With proximal RTA, administration of bicarbonate will only transiently increase serum [HCO_3^-], and once discontinued, plasma [HCO_3^-] will fall to a lower T_{max}, usually 16 to 18 mmol/l.**
   - C. A side effect of bicarbonate therapy is a worsening of hypokalemia due to increased renal K^+ wasting as distal Na^+ delivery is increased.
   - D. The urine will acidify in proximal RTA once the serum bicarbonate falls to the lower T_{max} after discontinuation of oral bicarbonate therapy.
   - E. The urine anion gap is not negative in proximal RTA because proximal tubular dysfunction also impairs renal ammonia genesis.
2. C. Correct. Serum uric acid levels are likely to be low in this patient.
   - A. The child may present with an anion gap metabolic acidosis alone, particularly soon after ingestion.
   - B. Hypokalemia is the result of increased renal potassium excretion. Renal K^+ wasting is the result of increased distal delivery of Na^+ in combination with increased circulating aldosterone (secondary to volume depletion).
   - **C. With high-dose aspirin therapy or in the patient with aspirin overdose, the renal excretion of uric acid is increased and hypouricemia may be present. In this setting, the hepatic glucuronidation of salicylic acid is saturated, and large quantities of free salicylate are filtered into the tubule. Free salicylate interferes in the reabsorption of uric acid by the proximal tubule, accounting for the uricosuric effect. Aspirin overdose is associated with a variety of acid-base and electrolyte disturbances. Salicylates have a direct stimulatory effect on the respiratory center, such that respiratory alkalosis is a prominent feature in the overdose setting. An anion gap metabolic acidosis is also present primarily as a result of increased production and accumulation of ketoacids and lactic acid. Salicylic acid accumulation accounts for only a minor component of the increase in anion gap.**
   - D. Urinary Na^+ excretion is increased because of urinary excretion of Na^+-salicylate
   - E. Lactic acid production is increased because of the uncoupling effect of aspirin on oxidative phosphorylation in the mitochondria. Adult patients with aspirin overdose usually present with a mixture of respiratory alkalosis and anion gap metabolic acidosis.
3. A. Correct. Propylene glycol toxicity
   - **A. The development of the anion gap metabolic acidosis in association with an increased osmolar gap is best explained by propylene glycol toxicity. Propylene glycol is used as a diluent to enhance the solubility of various drugs, including lorazepam. With high doses infused for prolonged periods, propylene glycol can accumulate in the plasma and lead to an osmolar gap. Lactic acid is a by-product of metabolism, thus explaining the development of lactic acidosis. Case reports suggest prolonged propylene glycol exposure can also cause acute renal failure.**
   - B. The serum glucose concentration of 120 mg/dl excludes the diagnosis of diabetic ketoacidosis.
   - C. Lactic acidosis is likely present but only as part of the toxicity of propylene glycol toxicity. Lactic acidosis is not characteristically accompanied by an osmolar gap.
   - D. The mild worsening of renal failure is not of sufficient magnitude to explain the development of an anion gap acidosis.
   - E. Isopropyl alcohol leads to an increased osmolar gap as a result of the accumulation of acetone. The metabolism of this alcohol does not consume HCO_3^- and is not associated with the development of metabolic acidosis.

CHAPTER 13

1. A.

While metabolic alkalosis is caused by a variety of factors, including chloride depletion, potassium depletion or increased secretion of mineralocorticoids, the end result is *always* impaired renal excretion of excess bicarbonate.

2. D.

The most important next step is the history and physical examination. Any laboratory data obtained should be interpreted in relation to history and physical. If the patient has a clear history of nausea and vomiting, for example, no further laboratory tests are needed for management. Although blood gases may be helpful in some instances, history and physical examination will provide the indication for such measurements. Urine chloride and aldosterone levels are not helpful in the most common causes of metabolic alkalosis.

3. B.

A central abnormality in the pathophysiology of metabolic alkalosis is continued stimulation of ENaC. For excess bicarbonate to be excreted, this transporter must be downregulated. The other transporters are often activated or suppressed in various causes of metabolic alkalosis, but not uniformly in all causes.

4. D.

The history and physical examination findings in this woman are suggestive of pseudohyperaldosteronism, so one should go right to measurements of serum aldosterone and renin. Serum aldosterone and renin levels should both be vanishingly low in Liddle syndrome or in the syndrome of apparent mineralocorticoid excess. Serum aldosterone will be elevated, with a very low renin level in primary hyperaldosteronism or in glucocorticoid remedial aldosteronism. Urine chloride is only helpful if one is suspecting surreptitious vomiting, and such a patient would not have hypertension or a body mass index of 26. There is no indication for computed tomography or measurement of blood gases in this patient.

CHAPTER 14

1. E.

Acute adaptation to respiratory acid-base disorders (respiratory acidosis and respiratory alkalosis) originates exclusively from titration of the body's nonbicarbonate buffers. It remains unaltered in patients with end-stage renal disease. By contrast, chronic adaptation to respiratory acid-base disorders entails changes in renal acidification mechanisms. Therefore chronic adaptation is essentially absent in patients with end-stage renal disease. Consequently, these patients experience greater deviations in blood pH than normal subjects in response to chronic respiratory acidosis and chronic respiratory alkalosis.

2. B.

There is acidemia and hypercapnia, signifying the presence of respiratory acidosis (i.e., a primary increase in Pa_{CO_2}, the respiratory component of the Henderson equation). The Pa_{CO_2} is elevated by 22 mm Hg above the average normal value of 40 mm Hg. In response to sustained hypercapnia, upregulation of renal acidification mechanisms generates new HCO_3^- for the body fluids, resulting in an average increase in serum $[HCO_3^-]$ of about 0.35 mEq/l for each millimeter of mercury chronic increment in Pa_{CO_2}. This process requires 3 to 5 days to reach completion. Therefore serum $[HCO_3^-]$ would be expected to increase by 7.7 mmol/l ($22 \times 0.35 = 7.7$) above the average normal value of 24 mmol/l, that is, to the level of 31.7 mmol/l, a value that is in close agreement with the observed value of 31 mEq/l. There is appropriate hypochloremia and the serum anion gap is normal at 9 mmol/l. The data are consistent with chronic respiratory acidosis. Acute respiratory acidosis is excluded, because the serum $[HCO_3^-]$ is higher than that obtained in response to acute adaptation (on average, serum $[HCO_3^-]$ increases by about 0.1 mEq/l for each millimeter of mercury acute increment in Pa_{CO_2}). There is no support for metabolic acidosis, as a single or mixed disorder, because serum $[HCO_3^-]$ is increased and appropriate for the level of chronic hypercapnia.

3. E.

A clue to the coexistence of a mixed acid-base disorder is the normal blood pH despite substantial deviation in both Pa_{CO_2} and serum $[HCO_3^-]$ from normal values. The treatment with diuretics and a low-sodium diet resulted in the superimposition of metabolic alkalosis on the background of a continuing chronic respiratory acidosis. For a sustained level of Pa_{CO_2} that is higher than the average normal level of 40 mm Hg by 24 mm Hg, serum $[HCO_3^-]$ would be expected to increase by 8.4 mmol/l ($24 \times 0.35 = 8.4$) above the average normal value of 24 mmol/l, that is, to the level of 32.4 mEq/l. Note that serum $[HCO_3^-]$ is substantially higher than the level signifying the coexistence of an element of metabolic alkalosis. This is not an uncommon occurrence in patients with CO_2 retention treated for circulatory congestion with diuretics and a low-sodium diet. The resulting rise in blood pH can further damp the ventilatory drive and worsen CO_2 retention and hypoxemia. The acid-base data are not consistent with the simple disorders listed, metabolic alkalosis, acute respiratory acidosis, or chronic respiratory acidosis. In addition, they are not consistent with chronic respiratory acidosis and metabolic acidosis, because the serum $[HCO_3^-]$ is higher, not lower, than anticipated for the prevailing level of sustained hypercapnia.

CHAPTER 15

1.
   - A. Tubular proteinuria is low-molecular-weight proteinuria (including smaller proteins such as α_1-microglobulin), whereas immunoglobulins are not usually present in significant amounts.
   - B. The metabolic response to heavy proteinuria is variable, and sometimes a normal serum albumin is maintained, probably as a result of both increased albumin synthesis and reduced catabolism.
   - C. In orthostatic proteinuria, there is *less* proteinuria when lying down; the early morning urine has no increase in protein.
   - **D. Correct. Light chain excretion should be suspected when the urine dipstick is negative for albumin when other tests show heavy proteinuria.**
   - E. Functional proteinuria occurs with fever, exercise, heart failure, and hyperadrenergic states.
2.
   - A. True (Reference: Kidney International 2013; 3[Suppl 1]:1-150).
   - B. The major mechanism by which ACE inhibitors and ARBs reduce proteinuria is hemodynamic, reducing glomerular efferent arteriolar tone. However, they also may directly reduce glomerular capillary wall permeability.
   - C. Risk for hyperkalemia when using the combination of ACE inhibitor and ARB increases with falling glomerular filtration rate (GFR). Addition of a loop diuretic will usually reduce serum potassium.
   - **D. Correct. Statin or a statin-ezetimibe combination is recommended in adults younger than 50 years with CKD only if there is established cardiovascular disease or diabetes.**
   - E. Dietary protein recommendations must account for urine protein loss to minimize the risk for malnutrition.
3.
   - A. Diuretic resistance is common in nephrotic syndrome with normal GFR; reduced protein binding limits drug access to the site of action in the tubule, increased protein binding once the drug has reached the urine reduces efficacy; and intestinal edema may reduce drug absorption.
   - B. Dietary protein recommendations should take account of urinary losses, but very high protein intakes (e.g., 2 to 3 g/kg/d), even if achievable, may worsen proteinuria.
   - **C. Correct. It also should be considered when the serum albumin is 2 to 2.5 g/dl if there are additional risk factors for thromboembolism, such as immobilization in hospital or a prior history of thromboembolism.**
   - D. Microscopy and culture of ascetic fluid is required only when there is any evidence of systemic infection; but routine screening for infection is not useful.
   - E. Nephrotic children are more prone than adults to hypovolemia. Care is needed to avoid too rapid diuresis, which may provoke shock.

CHAPTER 16

1.
   - A. 70% of White and 50% of Asian patients with MN exhibit these autoantibodies.
   - B. 10% or less of patients with MN exhibit these autoantibodies.
   - C. Occur in neonatal MN.
   - **D. Correct. Has been related to atypical hemolytic uremic syndrome.**
   - E. May induce MN.

2.
   - A. Classic pathway complement activation is typical of this condition.
   - B. Classic pathway complement activation is typical of this condition.
   - C. Classic pathway complement activation is typical of this condition.
   - **D. Correct. Despite autoantibody deposition in glomeruli and lung alveoli there is usually no systemic complement consumption.**
   - E. Classic pathway complement activation is typical of this condition.

3.
   - **C. Correct. Podocyte, in particular slit diaphragm, injury typically leads to severe, often nephrotic proteinuria.**

4.
   - A. FSGS mostly results from focal podocyte damage.
   - B. FSGS is a nonspecific term to describe a glomerular scar and should not be confused with the clinical entity FSGS.
   - **C. Correct. Some clinical FSGS cases seem to originate from as-yet unknown circulating factors, which can give rise to rapid post-transplant recurrence of the disease.**
   - D. So far there is little evidence to implicate autoimmunity in the majority of FSGS cases.
   - E. Although some FSGS may relate to mutations of podocyte proteins, most cases originate from other types of podocyte injury.

CHAPTER 17

1. D.

   MCD may be precipitated by upper respiratory tract infections, allergens, certain drugs (nonsteroidal antiinflammatory drugs [NSAIDS] and interferon-α alfa), and certain tumors, classically Hodgkin lymphoma.
2. D.

   A number of factors have been associated with MCD, including angiopoietin-like-4, CD80/B7.1, IL-13, and hemopexin. None of the other factors have been linked with MCD. (See text.)
3. C.

   Treatment of MCD requires 4 to 6 weeks of high-dose steroids given daily followed by a taper. Alternate-day steroids are commonly used during the taper to minimize side effects. Most patients will undergo a remission with treatment. Spontaneous remissions are rare. Frequent relapsers can be treated with an 8- to 12-week course of cyclophosphamide.

CHAPTER 18

1. D. Amlodipine
2. B. Glomerulomegaly and perihilar segmental sclerosis and hyalinosis
3. C. Remission of proteinuria is a strong predictor of a favorable outcome.

CHAPTER 19

1. C. Autosomal dominant
2. C. *CTN4*
3. A. Glomerular epithelial
4. B. 30%
5. B. Coenzyme Q_{10}

CHAPTER 21

1. A.

The IF finding of strongly positive IgG and C3 with a kappa light chain restriction is compatible with the diagnosis of an MPGN secondary to a monoclonal gammopathy. The results of serum or urine protein electrophoresis are not provided. However, these studies are negative in a large number of patients. A MPGN due to infection (option B) is usually associated with strong IgM on IF. MPGN secondary to alternative pathway of complement (option C) is characterized by predominant C3 staining with little or no immunoglobulin deposition. The biopsy shows a MPGN type I based on the old EM classification, but the case cannot be considered idiopathic given the IF findings.

2. D.

Focal segmental glomerulosclerosis (option A), minimal change disease (option B), and membranous nephropathy (option C) are all causes of nephrotic syndrome, defined as proteinuria greater than 3.5 g/24 h and serum albumin less than 3.5 g/dl, which is not present in this patient. The nephritic sediment and low C4 in a patient with HCV infection indicates cryoglobulinemic glomerulonephritis. The presence of circulating cryoglobulins is further supported by a positive rheumatoid factor.

3. A.

Henoch-Schönlein purpura nephritis (option B) and anti-GBM disease (option C) are not associated with hypocomplementemia. Poststreptococcal glomerulonephritis (option D) is typically associated with low serum complement C3. Mixed cryoglobulinemia is typically associated with activation of the classic complement pathway, manifested by low levels of complement C4.

4. D.

Although the skin rash on the lower extremities and nephritic syndrome suggest a diagnosis of Henoch-Schönlein purpura and IgA nephropathy (option A), the low C4 complement level is not compatible with this diagnosis. Linear staining for IgG (option B) is seen in anti-GBM disease, but anti-GBM serologic result is negative. An association between C3 glomerulonephritis and autoimmune diseases has been described, but patients usually exhibit positive ANA and/or anti-DS-DNA antibodies. Although acute or chronic tubulointerstitial nephritis is the most common lesion in patients with Sjögren syndrome, MPGN and mesangioproliferative glomerulonephritis can be seen later in the disease course. IF usually shows dominance of IgM.

CHAPTER 23

1.
   - A. Fish oil is recommended, although the evidence is rather weak.
   - B. There is inconsistent evidence from observational studies of a benefit for tonsillectomy.
   - C. This treatment approach exceeds the dosage used in previous trials, and prednisolone is recommended only after 6 months of optimal supportive therapy, including blood pressure control with renin-angiotensin system blockade.
   - **D. Correct. Small randomized trials have not shown consistent evidence of benefit for this agent.**
   - E. A randomized trial showed no additional benefit when azathioprine was used in addition to corticosteroids.
2.
   - **D. Correct. Cellular crescents were not associated with clinical outcome in the original Oxford Classification, although only a small number of cases had crescents in the original analysis**
3.
   - A. IgAN is more common in Asia than Europe.
   - B. The diagnosis of IgAN requires a renal biopsy. Glycosylation of serum IgA is abnormal in the majority but not all cases of IgAN.
   - D. More commonly, AKI with macrohematuria is due to acute tubular injury secondary to blockage by erythrocytes.
   - E. There is no evidence that different maintenance immunosuppressive regimens influence the recurrence rate of IgAN.
4.
   - A. Although most common in childhood, IgAV can occur at any age.
   - **B. Correct. The same alteration in IgA glycosylation is described in IgAV and IgAN.**
   - C. There is no evidence that delay reduces recurrence risk.
   - D. A French controlled trial of cyclophosphamide in adults with IgAV failed to detect benefit compared with steroids alone (reference 50).
   - E. Randomized trials showed no benefit of corticosteroids in reducing nephritis risk.

CHAPTER 24

1. B.

   It is not uncommon for low levels of autoantibodies to persist some months after successful treatment of the acute illness, so we would not consider reinstituting plasma exchange or prolonging exposure to cyclophosphamide. In our experience, any persisting low-level autoantibodies disappear over subsequent months even when immunosuppression is withdrawn, so this is our preferred approach. However, one could justify continuing immunosuppression until autoantibodies become undetectable (or 1 year at most) to potentially bring forward the time when transplantation could be considered, in which case MMF would probably be preferred over continuing cyclophosphamide.
2. C.

   Recovery of renal function is very unlikely if all glomeruli are severely affected with crescents. In such cases there is no renal benefit from immunosuppression, so potentially toxic treatment is only justified if there is lung hemorrhage. In this case we would recommend supportive treatment and close monitoring anticipating spontaneous reestablishment of self-tolerance and disappearance of autoantibodies, followed by preparation for renal transplantation.
3. B.

   Goodpasture generally has such an acute and dramatic manifestation, with renal failure, haematuria, and oliguria with normal sized kidneys, that it does not generally get labeled “unknown cause.” And recurrence of Goodpasture’s after transplantation is now practically unheard of. Therefore this would be unlikely here. Alport syndrome, however, may progress without any particular symptoms and be labeled as unknown cause. New anti-GBM disease post-transplant is therefore more likely to be the very rare condition of Alport anti-GBM disease.

   In this case, subsequent analysis at a reference laboratory demonstrated there were abundant serum antibodies to alpha-5 collagen IV at the time the standard anti-GBM assay was negative.

CHAPTER 25

1.
   - A. GN occurs only in small-vessel vasculitis.
   - **B. Correct. GN occurs only in small-vessel vasculitis.**
   - C. GN occurs only in small-vessel vasculitis because it is a manifestation of capillary inflammation.
   - D. GN occurs only in small-vessel vasculitis.

2.
   - A. One third to one fourth of patients with anti-GBM also have ANCA.
   - B. ANCA disease may recur even if the anti-GBM disease enters remission.
   - **C. Correct. ANCA occurs with anti-GBM, and the ANCA disease may recur even if the anti-GBM disease enters remission.**
   - D. The disease is more like anti-GBM disease.

3.
   - A. GN does not occur in PAN. GN is a marker of small-vessel vasculitis, and PAN is a medium-vessel vasculitis.
   - B. Pulmonary hemorrhage does not occur in PAN. Pulmonary capillaritis is a marker of small-vessel vasculitis, and PAN is a medium-vessel vasculitis
   - C. Polymyalgia rheumatic is associated with giant cell arteritis and not PAN.
   - **D. Correct. There is an association between hepatitis B infection and PAN.**

4.
   - A. The gradual narrowing of arteries by chronic inflammation does not cause acute ischemia with infarction, unlike PAN, which can cause infarction because of acute inflammatory narrowing and thrombosis.
   - B. The gradual narrowing of arteries by chronic inflammation does not cause acute renal failure.
   - C. GN is not a feature of Takayasu arteritis.
   - **D. Correct. Narrowing of main renal arteries by the arteritis causes renovascular hypertension.**

5.
   - A. Clinical trials have shown no difference in adverse events.
   - **B. Correct. Clinical trials have shown noninferiority between induction therapy with rituximab compared with cyclophosphamide.**
   - C. Clinical trials have shown noninferiority between induction therapy with rituximab compared with cyclophosphamide.
   - D. Rituximab has been approved by the FDA for induction therapy.

CHAPTER 26

1. C. Mycophenolate mofetil (MMF) or cyclophosphamide is an appropriate choice. Ovarian protection or cryopreservation of eggs should be considered if cyclophosphamide is to be used.
2. C. Reduce the MMF to 1000 mg bid and plan to continue for 3 years unless otherwise indicated.
3. A. Corticosteroids
4. B. Intravenous rituximab

CHAPTER 27

1. E. Best evaluated by assessment of brain natriuretic peptide (BNP) in patients with glomerular filtration rate (GFR) <30 ml/min/1.73 m^2
2. C. Frequently responsible for nondiabetic glomerulosclerosis
3. E. Electron microscopy
4. A. Renal failure

CHAPTER 28

1. C. Lecithin–cholesterol acyltransferase deficiency
2. B. Bezafibrate
3. C. Idiopathic (primary) membranous nephropathy
4. D. Antiphospholipid antibody test

CHAPTER 29

1. A. Thrombocytopenia, nonimmune hemolytic anemia, with or without neurologic and/or renal dysfunction
2. B. Shiga toxin *E. coli*–associated hemolytic uremic syndrome
3. C. *CFH* mutations
4. B. Eculizumab
5. C. TTP with anti-ADAMTS13 antibodies

CHAPTER 30

1. B.
   Glomerulosclerosis, tubular atrophy, and tubulointerstitial lesions are typical pathologic findings in diabetic nephropathy.
2. E.
   Type of diabetes.
3. D.
   Acanthocytes in urine sediment.
4. B.
   Inflammasome activation in the diabetic kidney.

CHAPTER 32

1. C. Rheumatoid arthritis
2. C. Gliclazide
3. D. Anemia in diabetic patients can occur even with normal renal function.
4. E. Formation of renal calculi

CHAPTER 33

1.
   A. Atrial natriuretic peptides can work quickly, but generally have only small effects on blood pressure in normal humans.
   B. Endothelin has variable effects on blood pressure in normal humans, but most effects occur over hours to days.
   C. Although the kallikrein-kinin system can act relatively quickly, it is thought to contribute only in minor ways to regulation of blood pressure in normal humans.
   D. Modulation of the renin-angiotensin-aldosterone system generally takes hours to days to affect blood pressure in normal humans.
   E. Correct. Catecholamines are heavily involved in modulation of blood pressure during hypovolemia and/or hemorrhage, especially in normal human subjects. (See Fig. 33.3.)
2.
   A. None of his three blood pressures fall into the <120/<80 mm Hg range.
   B. Correct. HEDIS 2016 and its several predecessors have used the lowest systolic and lowest diastolic blood pressures, even if measured separately, as the blood pressure for this visit. As a result, his blood pressure for this visit would be 138/88 mm Hg, which is in the prehypertensive range, according to JNC 7. (See references 24 and 47.)
   C. In many clinical trials, the average of the last two of three readings is used as the blood pressure for a visit, which would be 140/91 mm Hg in this case. This would be in the stage 1 hypertensive range, according to JNC 7. But HEDIS 2016 changed its methodology recently, so that the lowest systolic blood pressure need not be recorded simultaneously with the lowest diastolic blood pressure. (See references 24 and 47.) Note also that JNC 8 suggested a systolic treatment target of less than 150 mm Hg for individuals older than 60 years, although this is quite controversial.
   D. None of his three blood pressures fall into the >160/>100 mm Hg range.
   E. This diagnosis is appropriate for systolic blood pressure ≥140 mm Hg and diastolic blood pressure <90 mm Hg. In the calculation using either option B or C, both of these conditions are not met (either 138/88 or 140/91 mm Hg).
3.
   A. This is most appropriate for a healthy person with blood pressures in the <130/<85 mm Hg range, according to JNC 7. But there is the unresolved issue of CKD, which needs to be confirmed or rejected, and which might (according to the “suggestion” of KDIGO) prompt drug therapy if the albumin excretion rate was much higher.
   B. This is most appropriate for a healthy person with prehypertension, according to JNC 7. But there is the unresolved issue of CKD, which needs to be confirmed or rejected, and which might prompt more intensive treatment than just lifestyle modifications.
   C. Correct. The diagnosis of CKD hinges on a 3-month history of abnormal renal function, which has not yet been established. Repeat testing to confirm the diminished GFR is necessary; a repeat blood pressure measurement is unlikely to cause drug therapy to be initiated, given that KDIGO and JNC 8 now recommend a blood pressure of <140/90 for patients with CKD, although KDIGO “suggests” <130/80 mm Hg for those with abnormal albumin excretion rates.
   D. This is the JNC 7 recommendation for healthy people with initial blood pressures in the stage 1 hypertension range. It might be appropriate here, but there is the unresolved issue of CKD that also needs to be addressed. Rechecking renal function in 2 more months might be appropriate, but it would not fulfill the diagnostic criteria for CKD.
   E. The U.S. Food and Drug Administration does not recognize albuminuria as an indication for antihypertensive drug therapy, and his blood pressures do not meet current diagnostic criteria for hypertension. Angiotensin-receptor blockers have prevented the progression of prehypertension to hypertension, but are not currently indicated or recommended for this use. Many nephrologists would argue that even a little albuminuria is prognostically bad, but there are few, if any, outcomes data to demonstrate that giving an antiproteinuric drug improves the time to death, dialysis, or renal transplantation.
4.
   A. This is probably higher than the prevalence of pseudohypertension, which is said to be associated with a positive Osler maneuver. No such finding is described in the vignette; she is likely too young to have developed this condition.
   B. This is the expected prevalence of secondary hypertension in the hypertensive population. Although it is possible that she has secondary hypertension, there are no clinical clues, and the description is more likely that of masked hypertension.
   C. Correct. This is the expected prevalence of masked hypertension, which fits the description in her case. It is likely that an ambulatory blood pressure monitor or home blood pressure monitoring will demonstrate elevated blood pressures, which might prompt treatment. Some have speculated that masked hypertension can occur in people with child care responsibilities, if they arrange for a babysitter during office visits.
   D. This is the expected prevalence of white coat hypertension, which does not fit her case history, in that she has target organ damage and normal office blood pressures, the opposite of what would be expected with white coat hypertension.
   E. This is the expected, age-adjusted, prevalence of hypertension in the United States over the last 15+ years. Yet her in-office blood pressures do not meet diagnostic criteria for this diagnosis; it is likely that because NHANES also uses an automated sphygmomanometer, she would not be identified as hypertensive in national surveys.
5.
   A. Renal biopsy is more often used to determine the cause of glomerulonephritis or nephrotic syndrome and is seldom useful in the diagnosis of hypertension.
   B. Although iothalamate clearance is more accurate than calculations of estimated GFR, it is expensive; exposes staff, patient, and the environment to radioactivity; and was abandoned by the National Institutes of Health after the vanguard phase of the African American Study of Kidney diseases and hypertension (AASK). The CKD-Epi equation is more accurate (especially for those with an estimated GFR >60 ml/min/1.73 m^2) than the updated MDRD equation, which is widely used by most U.S. laboratories.
   C. A search for a secondary cause of hypertension is typically undertaken only when there is strong suspicion on clinical grounds or when the blood pressure is resistant to treatment. Screening all hypertensives for secondary hypertension is unlikely to be cost-effective.
   D. The most likely diagnosis for him is white coat hypertension, which typically does not respond with a lowered office blood pressure after institution of antihypertensive drug therapy. It might be worth a try, but it is unlikely to improve his office blood pressures much and puts him at risk for hypotension outside the office.

E. **Correct. The most likely diagnosis for him is white coat hypertension, but some people with this diagnosis progress to sustained hypertension, which can be detected by home blood pressure monitoring. He should be counseled about therapeutic lifestyle changes as appropriate (e.g., DASH diet, dietary salt restriction, weight reduction, tobacco avoidance, reduction of alcohol). If and when sustained hypertension is diagnosed, he would be a good candidate for drug therapy.**

CHAPTER 34

1. B.
   Salt sensitivity increases with age.
2. E.
   The presence of transmural necrosis should prompt consideration of vasculitis, not primary hypertension
3. E.
   Although coffee is not a risk factor, caffeine tablets, or high caffeine content such as in “power drinks” may be potential risk factors for hypertension.

CHAPTER 35

1. C.
   Although stress reduction techniques may be beneficial for other reasons, they are not recommended by ASH/ISH for the management of hypertension.
2. B. 1 mm Hg.
3. D. People younger than 40 years
4. A. Has little or no effect on BP.

CHAPTER 36

1. C.

A common side effect of dihydropyridine (DHP) CCBs is dose-dependent peripheral edema, which is not caused by fluid retention but by transudation of fluid from the vascular compartments into the dependent tissues as a result of precapillary arteriolar dilation. There is evidence that this edema also may be reduced by coadministration of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) because of their effects on venous capacitance. (de la Sierra A. Mitigation of calcium channel-related oedema in hypertension by antagonists of the renin–angiotensin system. *J Hum Hyptens.* 2009;23[8]:503-511.)

2. C.

Early studies focused primarily on diastolic BP as the treatment target, but systolic BP is more difficult to control and more closely linked to cardiovascular (CV) outcomes and should now be the primary but not the sole focus of treatment. (See references 4 to 6.)

3. B.

Data from the ONTARGET and ALTITUDE trials demonstrated that dual RAS blockade in high-risk patients with an ACE inhibitor plus ARB combination in ONTARGET,[28] or an ACE inhibitor or ARB plus a direct renin inhibitor (DRI) in ALTITUDE,[29] was no more effective than renin-angiotensin-aldosterone (RAAS blocker monotherapy at preventing major CV events in a high-risk population, including those with diabetes. The risk for adverse events, especially renal impairment, was greater with dual RAAS blockade in both studies.

4. E.

Most patients with drug-resistant hypertension are likely to be retaining sodium and will respond to further diuretic therapy. The PATHWAY-2 study demonstrated that low-dose spironolactone 25 to 50 mg/day, when added to A+C+D, was more effective at lowering BP than placebo, a β-blocker (bisoprolol), or α-blocker (modified-release doxazosin). (See reference 19.)

5. C.

ARBs likely have a renoprotective effect similar to those of ACE inhibitors in nondiabetic CKD, but supportive data are limited. (Asselbergs FW, Diercks GFH, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation.* 2004;110(18):2809-2816; Esnault VLM, Brown EA, Apetrei E, et al. The effects of amlodipine and enalapril on renal function in adults with hypertension and nondiabetic nephropathies: a 3-year, randomized, multicenter, double-blind, placebo-controlled study. *Clin Ther.* 2008;30:482-498; Marin R, Ruilope LM, Aljama P, et al. A random comparison of fosinopril and nifedipine GITS in patients with primary renal disease. *J Hypertens.* 2001;19:1871-1876.

CHAPTER 37

1. D.

   The patient has hypertensive urgency, not a hypertensive emergency. In the absence of target organ damage, the patient can be treated less aggressively. The key is rapid follow-up (within a week).

2. C.

   While the INTERACT2 trial does suggest that reduction of BP to levels of 140/90 in subjects with hemorrhagic stroke, nitroprusside is not a desired antihypertensive agent as it obliterates cerebral autoregulation, and nicardipine is a superior agent. Reducing BP to 160/90 remains the standard target for these patients.

3. B.

   For subjects with aortic dissection, reducing the BP to 100 mm Hg systolic is the goal. Labetalol is an effective antihypertensive agent for this purpose.

CHAPTER 38

1.
   A. Mutations affecting the aldosterone synthase gene *(CYP11B2)* are present in FH-I. They are not a common cause, however, of APA.
   B. Mutations in the mineralocorticoid gene are not a common cause of APA.
   C. Mutations in the AT1 receptor are not a common cause of APA. Some evidence suggests, however, that activating autoantibodies directed against the AT1 receptor may be pathogenic in primary aldosteronism from bilateral adrenal hyperplasia.
   D. Correct. Mutations in the *KCNJ5* gene are present in approximately 40% of APA.
   E. Mutations in ENaC occur in Liddle syndrome, but not in APA.
2.
   A. Eplerenone appears to have less effect to decrease blood pressure (BP) in patients with primary aldosteronism.
   B. The rate of side effects and drug discontinuation appears to be similar between spironolactone and eplerenone.
   C. Correct. Spironolactone appears to decrease BP significantly more, by about twofold, than does eplerenone in patients with primary aldosteronism.
   D. The rate of side effects and drug discontinuation appears to be similar between spironolactone and eplerenone.
3.
   A. Most patients with primary aldosteronism do not have hypokalemia.
   B. Cannot differentiate between primary aldosteronism and secondary hyperaldosteronism and has significantly less sensitivity to identify primary aldosteronism.
   C. Although a suppressed plasma renin activity is a hallmark of primary aldosteronism, by itself it cannot identify primary aldosteronism.
   D. Correct. This is the preferred first-line test for primary aldosteronism.
   E. Cannot identify primary aldosteronism from other causes of hypertension.

CHAPTER 39

1. D.

   Typical signs and symptoms are frequently absent or subtle in any form of endocrine hypertension. Hypertension frequently remains present and requires ongoing pharmacotherapy even when the underlying condition has been appropriately managed. Overall, most cases of endocrine hypertension have no clear familial origin. Resistance to multiple combinations of multiple antihypertensive drugs is indeed a frequent alert to the possible presence of endocrine hypertension.
2. B.

   Organ imaging is not indicated until urinary free cortisol, overnight low-dose dexamethasone suppression test results, and/or late night salivary cortisol levels are found to be abnormal, consistent with Cushing syndrome. High-dose dexamethasone suppression testing is used later in the workup when plasma ACTH is elevated, if it is necessary to distinguish between pituitary and ectopic sources of ACTH. Bilateral inferior petrosal sinus sampling is used when preliminary biochemical tests and imaging yield equivocal results and it is necessary to prove the pituitary or nonpituitary location of excess ACTH release.
3. B.

   The majority (over two thirds) of incidentalomas are not hormonally active. In large carefully characterized series, up to 4% of incidentalomas are adrenal carcinomas. Incidentalomas are associated with a somewhat higher prevalence of hypertension than the matched population without incidentaloma.

CHAPTER 40

1.
   A. In this patient the presenting BP is higher than the limit for tPA administration; thus administration of intravenous tPA after acute BP lowering to <185/110 mm Hg is appropriate.
   B. Correct. After intravenous tPA administration, the American Heart Association/American Stroke Association guidelines recommend maintenance of BP <180/105 mm Hg. Therefore a diastolic BP of 110 mm Hg should be lowered to a target value of <105 mm Hg. In this case the patient presented with signs consistent with an acute ischemic stroke, and given that the CT scan shows no hemorrhage, acute cerebral ischemia is the most likely diagnosis. In that setting the correct first-line therapy in the absence of contraindications is intravenous tPA.
   C. In this patient intravenous labetalol or nicardipine would be the drug of choice. Sublingual nifedipine is proscribed because nifedipine can lead to a substantial reduction in BP.
   D. In the setting of acute ischemic stroke there are no evidence-based data to support use of vasopressors to augment BP, especially in this case in which BP is elevated and above the recommended threshold for post tPA BP management.
2.
   A. Because the patient reportedly had the first presentation 2 days previously, it is unlikely that any further clinically significant expansion will occur.
   B. Lowering BP has not been conclusively proven to decrease the incidence of hematoma expansion.
   C. Because the patient is fully conscious with a relatively small hematoma, lack of decline after 2 days from the onset of symptoms and no associated hydrocephalus, there is no clinical evidence for increased intracranial pressure (ICP) and no indication for ICP monitoring.
   D. Some studies had suggested that there may be perihematomal ischemia around an ICH, but this theory has been largely discredited by more recent studies.
   E. Correct. This patient presents with an ICH without intraventricular extension or hydrocephalus and no impairment of consciousness. In this case, clinically significant hematoma expansion is expected in about 40% of the patients. Additionally, hematoma expansion in hypertensive ICH is rare after the first 36 hours.
3. E.
   All of the mentioned are features of carotid hyperperfusion syndrome.

CHAPTER 41

1. C.
   This patient has coarctation. She has key clinical signs, including hypertension, heart murmur best heard over the posterior thorax and radio-femoral pulse delay. One must also consider Takayasu arteritis, but the symmetry in pulses and bruits make this diagnosis less likely. Similarly, the other choices would also be on the differential, but the key finding of radio-femoral delay makes coarctation the correct answer.
2. B.
   This patient has atherosclerotic RA stenosis on the right side. The present evidence-based consensus recommendations are to optimize medical therapy first, including the use of renin-angiotensin-aldosterone system (RAAS) blockade. Given the risk for renal disease progression and electrolyte abnormalities, once a RAAS blocker is started a patient should be monitored closely. Revascularization is not indicated until medical therapy is optimized.
3. D.
   This patient has acute kidney injury (AKI) with a marked increase in proteinuria. Her $(\dot{V}/\dot{Q})$ scan suggests pulmonary embolism; thus she likely has renal vein thrombosis. A renal ultrasound and renal vein Doppler study will assist with the diagnosis. Given her lupus history the antiphospholipid antibody is necessary to probe the cause of the thrombotic events. Given her presentation and the high probability $(\dot{V}/\dot{Q})$ scan, CTA of the pulmonary arteries is not needed to confirm the diagnosis of pulmonary embolism and would also unnecessarily expose this patient with AKI to intravenous contrast.
4. D.
   This patient has diminished renal function at baseline with a current AKI. The renal dysfunction would make a captopril renogram difficult to interpret. There is also risk to the patient with intravenous contrast exposure (CTA) and gadolinium exposure (MRA). Hence, the best choice is to perform direct angiography and employ carbon dioxide in lieu of radiocontrast.
5. C.
   Given the new-onset atrial fibrillation associated with flank pain, renal infarction via arterial embolism is high on the differential diagnosis. The lack of dysuria and pyuria make a pyelonephritis less likely. The CT with and without contrast along with an LDH evaluation will allow for the effective diagnosis of nephrolithiasis and/or a renal infarction.
6. B.
   This patient has a post–coronary angiography rise in serum creatinine making either contrast or cholesterol emboli the likely diagnoses. The increase in eosinophils and the nature of the rash suggest cholesterol emboli because contrast-mediated renal injury would not manifest with a rash. Although the AKI, rash, and eosinophils could be indicative of acute interstitial nephritis, the proximity to the coronary artery instrumentation and stent placement make cholesterol emboli more likely.

CHAPTER 42

1. B. Hypernatremia
2. D. Trimethoprim
3. E. All of the above
4. A. Proteinuria 2 g/day
5. C. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

CHAPTER 43

1.
   - A. Women with ADPKD with hypertension have a higher risk for preeclampsia and preterm delivery than those without hypertension, and therefore answer A is incorrect.
   - B. Preimplantation genetic testing can be offered, but many women with ADPKD prefer to conceive spontaneously.
   - **C. Correct. Aspirin should be offered to all women with chronic hypertension to reduce the risk for preeclampsia.**
   - D. Amlodipine has not been demonstrated to be teratogenic, but more experience of safety is with nifedipine, which could be offered as an alternative agent but requires twice or three times daily dosing. BP control before pregnancy should be optimized.

2.
   - A. Conception after transplantation is recommended to be delayed until at least 12 months post-transplantation to ensure graft stability. The optimal time to conceive remains unclear; however, in view of increased maternal age and graft stability in this case, it would not be unreasonable to switch MMF to azathioprine at 12 months, ensure graft stability, and then for the woman to attempt to conceive.
   - B. Breastfeeding should be encouraged in women with renal transplants, particularly those with preterm deliveries with greatest infant benefit. Standard immunosuppression during pregnancy, that is, prednisolone, azathioprine, and tacrolimus, can be continued safely with lactation, and only minimal quantities of each drug have been identified in breast milk.
   - C. There are no data regarding breastfeeding with MMF, and therefore it is not currently recommended. Azathioprine should be substituted for MMF. High-dose prednisolone may be associated with gestational diabetes, maternal infection, osteoporosis, and preterm delivery and therefore should be avoided.
   - **D. Correct. Women with lupus nephritis may continue to have anti-Ro or La antibody that is transferred by the placenta and may lead to neonatal lupus syndromes, including fetal heart block. Fetal cardiac monitoring from 16 to 18 weeks of gestation is recommended in those with positive antibody.**

3.
   - **A. Correct. At this early gestation, attempts should be made to prolong pregnancy to optimize neonatal outcomes.**
   - B. Fetal assessment will determine timing of delivery. If maternal compromise persists despite BP control, delivery may be needed, but a balance between maternal and fetal benefit needs to be considered by obstetricians, nephrologists, and neonatologists. This presentation also could be consistent with progression of underlying renal disease, and placental and fetal ultrasound will help determine whether preeclampsia is evolving.
   - C. Intravenous magnesium should be used only if there is evidence of neurologic involvement such as brisk reflexes, scotoma, or HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) but not routinely in a woman with suspected preeclampsia.
   - D. Labetalol may be used to treat hypertension, but there is no evidence of benefit of aspirin to treat gestational hypertension and its associated complications.

CHAPTER 44

1. E.

   These have all been shown to contribute to the rate of progression of the renal cystic disease in ADPKD.

2. C.

   The risk for rupture of an intracranial aneurysm depends on their size and location. Aneurysms in the posterior circulation of the circle of Willis have an increased risk for rupture compared with those in the anterior circulation. Although some authors argue that all patients with ADPKD should undergo presymptomatic screening for intracranial aneurysms, there is no evidence to support the efficacy or cost-effectiveness of this strategy. Most intracranial aneurysms do not rupture. Screening for intracranial aneurysms by magnetic resonance angiography does not require administration of gadolinium.

3. A.

   Hypocitraturia is a common metabolic abnormality in patients with ADPKD even before there is a decline in renal function. Hypercalciuria, hyperuricosuria, and hyperoxaluria do not occur more frequently in these patients. Renal tubular acidosis is rarely associated to ADPKD.

4. D.

   The HALT PKD study showed that ACE inhibitor monotherapy is very effective to control BP in the majority of patients with ADPKD; however, superiority to β-blockers has not been proven in head-to-head studies. Rigorous BP control was found to be superior to standard control in young patients with ADPKD with a GFR >60 ml/min/1.73 m^2 in the HALT PKD Study A clinical trial, but rigorous BP control was not used in Study B with more advanced ADPKD.

CHAPTER 45

1. E.
ARPKD has a diverse set of extrarenal complications that primarily involve the liver, less commonly impact growth, and very rarely involve intracranial aneurysms.
2. B.
The term *nephronophthisis* derives from Greek, meaning "progressive loss of nephrons." Nephron loss combined with fibrosis (another hallmark of NPHP) leads to small kidneys.
3. C.
Angiomyolipomas are a major clinical feature of TSC and the most common renal lesion in patients with TSC patients.
4. D.
VHL-associated disease clusters into two complexes based on the nature of the germ-line mutation.
5. A.
MSK is generally considered to be a sporadic disorder, but familial clustering with autosomal dominant inheritance and evidence for genetic alteration in the RET-GDNF axis suggest a genetic basis for MSK in at least a subset of patients.

CHAPTER 46

1.
   B. His mother has Alport syndrome.
2.
   E. All of the above.
3.
   C. Hearing loss in Alport syndrome initially targets high frequencies above the range of conversational speech.

CHAPTER 47

1. C. Gitelman syndrome
2. E. All are correct
3. B. Enhanced Na^+ transport through the epithelial Na^+ channel ENaC in the collecting duct
4. C. 5% Dextrose in water

CHAPTER 48

1. B. Cystinosis
2. A. Arginine, lysine, ornithine
3. B. Medications
4. E. SLGT2
5. D. ClC-5

CHAPTER 49

1. A.

   Although hyperfiltration was thought to develop in older children and teenagers, recent studies such as the Baby HUG study (see references 24 to 26) have shown that it occurs from infancy, as young as 9 months old. The glomerular filtration rate (GFR) will typically peak in early adulthood and then starts to decline from the third to fourth decade of life. (See Fig. 49.7.)

2.

   A. The prevalence is the same in both patient groups as the majority of hemoglobin in both groups is HbS, leading to an increased risk for SCN.

   B. α-Thalassemia protects against albuminuria as it reduces the hemolysis rate. Increased hemolysis has been shown to be associated with increased risk for developing albuminuria. (See references 17 and 28.)

   C. Patients with HbSS disease are more at risk for developing albuminuria and SCN than patients with HbSC disease.

   D. High levels of hemolysis are associated with increased risk for albuminuria. (See reference 28.)

3.

   A. These agents should be used in patients with SCD and proteinuria, but serum potassium should be monitored. Studies in patients with nondiabetic proteinuric renal disease have demonstrated that inhibition of the renin-angiotensin system slow progression of CKD. Although patients with SCD are at increased risk for developing hyperkalemia, these drugs can be used safely if the potassium is monitored.

   B. Only one small trial in SCN has been carried out and was negative.

   C. Inhibitors of the renin-angiotensin-aldosterone system (RAAS) can cause acute kidney injury during periods of dehydration and illness, so they should always be stopped in patients who are acutely unwell.

   D. Nocturnal administration can avoid postural hypotension and improve the symptoms of nocturia in some patients. There are no specific advantages to taking the medication in the morning.

CHAPTER 50

1. A.

   Unilateral renal agenesis occurs in approximately 1 in 500 to 1 in 1000 births. Bilateral renal agenesis occurs in approximately 1 in 10,000 births. Unilateral renal agenesis is often inherited in an autosomal dominant manner, and therefore ultrasound screening of first-degree relatives is recommended. It can occur as part of numerous syndromes, including Kallman syndrome, branchio-oto-renal syndrome, and Fraser syndrome.

2. C.

   Patients with prune-belly syndrome present with a characteristic clinical triad:

   1. An abnormal urinary tract, including a grossly dilated bladder with bilateral hydroureteronephrosis and often evidence of vesicoureteral reflux
   2. Abdominal muscle aplasia or hypoplasia
   3. Bilateral cryptorchidism in males

   The disorder can be seen rarely in females. Although males exhibit azoospermia, successful paternity has been reported using intracytoplasmic sperm injection.

3. B.

   Ureterosigmoidostomy can cause a hyperchloremic, hypokalemic acidosis. Large quantities of ammonium ions are produced by the action of the fecal bacteria on urinary ammonia. Ureterosigmoidostomies are associated with an increased risk for developing colon cancer usually after a period of 20 to 30 years.

4. E.

   Posterior urethral valves are obstructing membranous folds found in the male posterior urethra and do not occur in females. Most cases are now detected on antenatal ultrasound, but many patients present as infants with failure to thrive, urinary tract infection (UTI), or difficulties voiding. Urinary drainage is achieved through primary valve ablation during cystoscopy or vesicostomy. Urofacial syndrome is a rare autosomal recessive disorder that can manifest with UTI and features of a neuropathic bladder with a dilated upper urinary tract; however, patients display a characteristic facial grimace when smiling.

5. B.

   Asymptomatic UTIs often do not require treatment (except during pregnancy). For patients with urinary diversions, it is important to obtain a catheter specimen of urine because urine taken from a bag is invariably infected. Struvite or calcium phosphate stones are most common in the context of infected urine.

CHAPTER 51

1. B. Ciprofloxacin
2. D. Periodic screening and treatment of asymptomatic bacteriuria
3. B. Nitrofurantoin
4. C. Pregnant women and patients undergoing urologic instrumentation

CHAPTER 52

1. C.

   Immune reconstitution inflammatory syndrome (IRIS) is a pathogen-specific inflammatory response in HIV-infected patients that may be triggered after initiation, re-initiation, or change to more active antiretroviral therapy. It is a paradoxical phenomenon of apparent clinical and radiologic worsening occurring in HIV-infected patients who had TB, inactive cytomegalovirus retinitis, or quiescent cryptococcal infection. It is usually accompanied by an increase in CD4 cell count and/or a rapid decrease in viral load. It may occur in patients with HIV when treatment with antivirals is started together with specific chemotherapy. Higher incidence of IRIS has been observed if the load of organisms is higher.

2. D.

   In the usual doses, ethambutol is a bacteriostatic drug. It is bactericidal only if very high doses are used.

3.
   - A. Painless macroscopic hematuria occurs in immunoglobulin A nephropathy, other glomerular diseases, and urinary TB. In other conditions, such as stone, tumor, trauma, and acute urinary tract infection, it is painful.
   - B. Acid sterile pyuria is unique to tuberculosis. The combination of persistent increase in urinary white cells, negative conventional cultures, and acidic pH of urine.
   - C. Sterility (in women) and epididymorchitis is a common genital involvement in females and males, respectively.
   - D. Characteristic lack of constitutional symptoms in urinary TB. Most symptoms are related to drug treatment.
   - **E. Icterus is not a manifestation of TB. If it occurs, it is due to drug therapy.**

4.
   - A. No dose change. The main route of excretion is by the biliary route.
   - **B. Dose to be modified. For streptomycin, increase dosing interval (over 45 years, 50% dose) and monitor for ototoxicity. For ethambutol, increase dosing interval and monitor visual acuity, field, and color vision.**
   - C. Pyrazinamide should be avoided in liver disease. Use carefully for short term in renal failure.
   - D. No dose change. The main route of excretion by the biliary route.

5. B.

CHAPTER 53

1. C.

   C. *albicans* is the species isolated most commonly in both urinary tract infections (UTIs) and candidemia.
2. E.

   Pyuria is not a helpful sign for the diagnosis of a *Candida* UTI when a catheter is present or when there is a concomitant bacterial infection. If there is no catheter and no bacteriuria, pyuria is sometimes useful as a marker for UTI with *Candida* species.
3. B.

   Flucytosine is excreted in the urine, and serum levels rise when creatinine clearance is diminished. Toxic effects on bone marrow and liver and are directly related to serum levels greater than 100 μg/ml. The other drugs are metabolized in the liver or elsewhere in the body and do not accumulate with kidney failure.
4. B.

   Shown by placebo-controlled clinical trial (see reference 14).

CHAPTER 54

1. B. Schistosoma-associated *Salmonella* bacteremia
2. D. Infiltrative bladder cancer
3. D. Concomitant virus-induced cryoglobulinemia

CHAPTER 55

1. A.

   Infection-related GN in developed countries is more often seen in adults with comorbidities, often infected with *Staphylococcus*. It often is IgA-dominant, and this is now more common than post-streptococcal GN in these areas. (See reference 2.)

2. A.

   Complement levels related to the alternative complement pathway are decreased, whereas those such as C4 and C1q associated with other complement pathways typically are not reduced. (See reference 6.)

3. A.

   Infective endocarditis–related GN often may manifest as crescentic GN, but not always, with immune complex deposition. (See reference 28.)

4. B.

   A meta-analysis of 12 clinical trials with 317 patients found that combined antiviral and immunosuppressive therapy can improve proteinuria in HBV-associated GN without altering HBV replication or damaging liver or renal function. (See reference 43.)

CHAPTER 56

1. A.
   APOL1 renal risk variants are associated with FSGS variants but not with immune complex kidney disease.
2. C.
   Tenofovir disoproxil fumarate causes proximal tubular dysfunction (Fanconi syndrome); tenofovir alafenamide is much less likely to do so because of reduced uptake from plasma into tubular cells via the organic ion transporters. The other medications do not cause this syndrome.
3. D.
   Chronic tubular injury resulting from tenofovir or other tubular toxins manifests as tubular atrophy and interstitial nephritis, but the characteristic finding of tenofovir is enlarged and abnormal mitochondria in proximal tubular epithelial cells. Tenofovir is a nucleoside analogue that inhibits DNA synthesis. The mitochondrial toxicity is unique to the kidney perhaps because of accumulation and phosphorylation.

CHAPTER 57

1.

- **A. Antibiotic therapy is important to reduce struvite stone growth and for stone prevention. Bacteria will remain in the stone interstices and stones will continue to grow unless chronic antibiotic suppression is maintained or the calculi are completely eradicated. Thus a short course of antibiotics is not sufficient.**
- B. Struvite stones are composed of magnesium ammonium phosphate and calcium carbonate apatite. They form when urease production by certain bacteria that breaks down urea to ammonium and a carboxyl group.
- C. Insoluble urinary phosphate forms a solid phase with magnesium, calcium, and ammonium.
- D. With alkaline urine, urinary phosphate becomes insoluble and forms a solid phase with magnesium, calcium, and ammonium.
- E. Bacteria will remain in the stone interstices after a short course of antibiotics until calculi are completely eradicated by surgical interventions.

2.

- A. Dietary salt restriction is associated with decreased urine calcium excretion.
- B. Animal protein ingestion increases the frequency of renal stone formation by a number of mechanisms, including generation of sulfate ions, which render urinary calcium ion less soluble, and metabolic acidosis, which can cause calcium release from bone and a consequent increase in the filtered load of calcium.
- **C. Several studies have demonstrated that there is a decrease in stone incidence when people consume adequate dietary calcium. This beneficial effect has been attributed to intestinal binding of ingested oxalate by dietary calcium.**
- D. Most calcium stones are composed of calcium oxalate, either alone or in combination with calcium phosphate or uric acid. Thus dietary oxalate should be restricted.

3.

- A. Uric acid stones are radiolucent and therefore poorly visible on plain radiographs.
- **B. Uric acid stones often occur in patients with insulin resistance. The rising incidence of obesity and insulin resistance in the United States has led to a parallel increase in uric acid stones.**
- C. Allopurinol should be prescribed if uric acid excretion remains high despite dietary intervention, to keep urinary uric acid excretion below 750 mg/day. This patient already had uric acid excretion below 750 mg/day.
- D. Low urine pH is the principal metabolic disorder found in patients with uric acid stones. Potassium citrate can raise urine pH and prevent stone formation.
- E. An increase in urine volume for more than 2 to 2.5 liters daily has been proven to reduce the incidence of stones. This patient's urine volume was only 1.5 liter per day and thus inadequate.

CHAPTER 58

1.

A. Hydronephrosis describes dilation of the upper urinary tract and can occur in the absence of functional obstruction.

B. Urinary tract obstruction may affect neonates, children, and adults of both genders, and the underlying causes and outcomes are therefore highly diverse, with most patients not developing ESRD.

C. Urinary tract obstruction may be associated with oliguria or even anuria if the obstruction is bilateral and complete. However, it is important to note that patients with a partial obstruction may report polyuria and nocturia as a result of an impaired ability of the kidney to concentrate the urine.

D. Urine dipstick analysis is highly variable in patients with urinary tract obstruction, and there are no "typical" findings. Microscopic hematuria may be evident in patients with renal calculi or tumors, but urinalysis is often negative for blood and protein.

E. Urinary tract obstruction results in urinary stasis and is a risk factor for infection, with infections often being more difficult to eradicate if obstruction is ongoing.

2.

A. Recent work suggests the opposite, with the development of marked diuresis (>7 liters per 24 hours) being associated with a very good outcome with preservation of renal function.

B. Examples include adynamic segments of the ureter that result in pelviureteral junction obstruction, and diseases such as multiple sclerosis or diabetes may be complicated by a hypertonic or atonic bladder, respectively.

C. Many inflammatory, degenerative, or neoplastic conditions may affect the retroperitoneum and involve the ureters, thereby causing urinary tract obstruction.

D. The obstructed kidney develops chronic inflammation that is associated with progressive scarring. Long-term obstruction leads to profound parenchymal damage and cortical thinning.

E. Patients with IgA nephropathy may develop severe macroscopic hematuria. The red cells are of glomerular origin and may thus obstruct the nephron lumen and cause significant intrarenal urinary tract obstruction that is associated with acute renal dysfunction.

3.

A. Various aspects of tubular function may be abnormal, including urinary acidification, potassium handling, and urinary concentration.

B. The blood flow of the obstructed kidney is also reduced, with renal vasoconstriction associated with increased intrarenal levels of angiotensin II and thromboxane A_2.

C. Renal tract ultrasound remains the first-line investigation for the majority of patients with suspected urinary tract obstruction because it does provide very useful information despite being operator dependent. Non–contrast-enhanced spiral CT scanning is useful for the primary assessment of patients with acute flank pain but, unlike ultrasound, does expose the patient to radiation.

D. A diuresis renogram is used to assess whether a dilated system is actually obstructed. The absence of functional obstruction is indicated by the rapid washout of the isotope after diuretic administration.

E. Although unusual, urinary tract obstruction may occur in the absence of hydronephrosis, as in transplanted kidneys that are encased in dense fibrous tissue. In addition, retroperitoneal fibrosis or infiltrating tumors may surround the ureters and prevent dilation but still obstruct native kidneys.

CHAPTER 59

1. C.
   Standard practice is to manage distal nonobstructing calculi conservatively for a period of 2 to 4 weeks, with a trial of medical expulsive therapy, given the high spontaneous passage rate.
2. D.
   Any patient with unexplained visible hematuria should undergo full urologic workup with flexible cystoscopy, renal function tests, and CT urogram, although local resources often dictate other imaging strategies such as intravenous urography (IVU) and ultrasound as first-line interventions. Anticoagulation should not be considered an explanation for hematuria because underlying malignancy is common.
3. C.
   Partial nephrectomy has emerged as a favorable procedure when compared with radical nephrectomy because concerns over reduced oncologic clearance have been unfounded. If technically possible, this should be performed laparoscopically. Although cryosurgery and radiofrequency ablation are promising alternatives to partial nephrectomy, they should be considered experimental at present.

CHAPTER 60

1. A.

   Both NSAIDs and PPIs are among the classes of drugs most commonly responsible for AIN.

2.
   - A. This diagnostic procedure does not have a poor negative predictive value.
   - B. This diagnostic procedure does not have a poor negative predictive value.
   - C. Some drugs other than NSAIDs can induce AIN associated with heavy proteinuria, including ampicillin, rifampin, lithium, interferon, phenytoin, pamidronate, and D-penicillamine.
   - **D. Correct. The course of drug-induced AIN is not always benign, and it leads to chronic kidney disease in at least 40% of the cases.**

3. D.

   The course of drug-induced AIN is not always benign, and it leads to chronic kidney disease in at least 40% of the cases.

CHAPTER 61

1. E.
   All of the above.
2. B.
   Voiding cystourethrogram.
3. E.
   All of the above.

CHAPTER 62

1.
   - A. Calcific deposits in the interstitium are characteristic of hypercalcemic nephropathy.
   - B. This patient has anorexia nervosa and associated hypokalemic nephropathy.
   - C. Noncaseating granuloma is the classic finding of sarcoidosis but is relatively nonspecific.
   - D. Infiltration of IgG4-positive mononuclear cells is the central feature of IgG4-related tubulointerstitial nephritis.
   - E. Acellular interstitial nephritis with intranuclear inclusion bodies in the proximal tubules is observed in chronic lead nephropathy.
2.
   - A. Uroepithelial carcinoma often develops in patients with analgesic nephropathy.
   - B. Inflammatory bowel disease can be associated with chronic tubulointerstitial nephritis, but that is a distinct clinicopathologic entity.
   - C. Cerebral aneurysm is observed in patients with autosomal dominant polycystic kidney disease.
   - E. Angiokeratoma is characteristic in patients with Fabry disease.
3. A.

   This is a case of chronic lithium nephropathy with nephrogenic diabetes insipidus. MRI without the use of gadolinium or ultrasound is useful in the detection of the microcysts in the kidney. Blood oxygen level–dependent MRI (BOLD-MRI) is used to evaluate oxygenation of various organs, including the kidney, but its clinical use is still preliminary.

CHAPTER 63

1. B.
   All of the above.
2. A.
   All of the above.
3. B.
   All of the above.
4. E.
   All of the above.

CHAPTER 64

1.
   - A. Calcium is associated with prerenal kidney impairment.
   - B. Uric acid is not a common cause of renal injury in myeloma.
   - **C. Correct. Myeloma cast nephropathy is due to an excess of filtered light chains exceeding the capacity of the proximal tubule and causing distal cast formation.**
   - D. Immunoglobulins are not filtered and may cause other forms of mesangial or glomerular injury.
   - E. β_2-Microglobulin is a marker of cell turnover and injury but is not nephrotoxic.
2.
   - A. Amyloidosis usually manifests with nephrotic syndrome.
   - B. LCDD usually manifests with nephritic syndrome, and less than 20% have myeloma.
   - **C. Correct. Cast nephropathy secondary to proximal tubular injury and distal tubular cast obstruction is the most common histologic pattern of injury in 30% to 50% of all biopsy samples.**
   - D. Urate nephropathy is a very rare complication of myeloma.
   - E. Tubular crystals are a very rare form of light chain disease often manifesting with Fanconi syndrome.
3. E.

   The proteasome inhibitor bortezomib is the most effective chemotherapy for the rapid targeting of plasma cells to reduce the light chain load.
4. D.

   The serum free light chain ratio by nephelometric assay is the most sensitive and specific test for the rapid diagnosis of myeloma in patients with acute kidney injury. The others provide additional information but are less sensitive, slower to perform, and not diagnostic. A renal biopsy is diagnostic but may not be needed in the presence of a highly abnormal free light chain ratio.

CHAPTER 65

1. D.

In a Danish population-based study of 1.2 million cancer patients, the incidence of AKI defined by the RIFLE criteria was highest in patients with renal cell cancer (44%), multiple myeloma (33%), liver cancer (32%), and leukemia (28%). Compared with patients without cancer, critically ill patients with cancer have a higher incidence of AKI requiring RRT. In a prospective survey of 3558 patients admitted to a comprehensive cancer center, AKI occurred in 45% of patients during the first 2 days and in 55% thereafter. The study also found significant correlation with diabetes mellitus, hyponatremia, and exposure to intravenous contrast, chemotherapy, and antibiotics and was associated with poorer clinical outcomes. The presence of cancer alone should not preclude patients from being considered for dialysis. Critically ill cancer patients with advanced renal failure would benefit of dialysis for at least 48 hours so a proper evaluation can be made for the role of continuing dialysis.

2. A.

Many malignancies enhance tumor survival by overexpressing ligands that bind these inhibitory T cell receptors, such as programmed death-1 protein (PD-1) and cytotoxic T lymphocyte–associated antigen-4 (CTLA-4). This leads to a decrease of infiltrating activated T cells within the tumor microenvironment and inhibits antitumor T cell responses. Ipilimumab is a fully human, immunoglobulin G1 (IgG1) monoclonal antibody that blocks CTLA-4, and pembrolizumab is a monoclonal antibody that antagonizes the PD-1 receptor. Biopsy-proven acute interstitial nephritis (sometimes with granulomas) has been shown to be the most common pathologic finding in AKI caused by ipilimumab and pembrolizumab. Glucocorticoids have been shown to be an effective treatment with reversal of kidney injury in most cases.

3. C.

This case fits the proposed laboratory and clinical criteria for tumor lysis syndrome. With the hyperkalemia, hyperphosphatemia, hyperuricemia, AKI, oliguria, and large tumor burden, RRT would be the most effective modality for treatment. Rapid release and accumulation of potassium and phosphate will develop in the setting of chemotherapy initiation, which can be life threatening. Use of urinary alkalinization and IVFs in a patient with oliguria may lead to more volume overload. Also, urinary alkalinization may cause calcium-phosphate deposition within the tubules (acute nephrocalcinosis). Treatment of the acute hyperkalemia with insulin and glucose will transiently shift the potassium into cells, but will be insufficient. The patient has mild hydronephrosis that may be contributing to AKI; however, initiation of chemotherapy will shrink the tumor mass and resolve the hydronephrosis.

4. B.

The patient presents with euvolemic hyponatremia, which is likely the syndrome of inappropriate antidiuretic hormone secondary to his malignancy. A retrospective analysis of 3357 patients with cancers noted that hyponatremia (serum sodium <135 mEq/l) developed in 47% of admissions. Hyponatremia in these cancer patients increased hospital length of stay and 90-day mortality, in a graded, inverse fashion compared with their degree of hyponatremia. In another publication, 46% of 3446 cancer patients with at least one serum sodium manifested hyponatremia.

CHAPTER 66

1. A.

   Acute tubular injury occurs in tubular regions secondary to an imbalance between blood supply and metabolic work. The proximal tubule (especially the S3 segment) and loop of Henle both lie within the outer medulla where blood supply is limited and both have high metabolic requirements secondary to sodium reabsorption at these sites (Na-K-ATPase).
2. D.

   Reduction in left ventricular function triggers the release of potent vasoconstrictors (sympathetic nervous system, angiotensin II, antidiuretic hormone, endothelin) that can cause AKI by impairing renal perfusion. NSAIDs inhibit the production of protective prostaglandins impairing compensatory afferent arteriole vasodilation in this setting. Note that NSAIDs may cause acute interstitial nephritis (sometimes associated with heavy proteinuria), acute papillary necrosis, and, rarely, AKI associated with minimal change disease.
3.
   - A. Cisplatin inhibits mitochondrial adenosine triphosphate generation.
   - B. Methotrexate may form intratubular crystals that block tubular flow and cause an interstitial nephritis.
   - C. Gentamicin accumulates in proximal tubular cells and interferes with cellular energetics and induces oxidative stress.
   - D. Amphotericin punches holes in cell membranes.
   - E. Tacrolimus causes renal vasoconstriction leading to renal ischemia in addition to direct tubular toxicity.
4. Contributing factors include renal vasoconstriction, obstruction from tubular cell casts, and enhanced tubuloglomerular feedback as a result of increased delivery of chloride to the macula densa.

CHAPTER 68

1.
   A. Presence of anion gap acidosis with high serum phosphate level, hyperkalemia, and urinalysis positive for blood yet no red blood cells on urine microscopy is consistent with rhabdomyolysis.[46] Note that his serum creatinine level is higher than expected for his degree of acute kidney injury (AKI) given increased release of creatinine from injured muscle.
   B. Although it is conceivable that his aortic dissection could have expanded to involve both kidney arteries. In the setting of a normal blood lactate level, bilateral renal artery occlusion would not explain his anion gap acidosis, urinalysis findings, or rapid rise in serum phosphate level.
   C. Kidney biopsy is reserved for cases in which the diagnosis remains uncertain. The cause of AKI is consistent with rhabdomyolysis in this case.
   D. The clinical picture does not fit for a small-vessel vasculitis, which characteristically has both blood and protein on urinalysis and red blood cells with red blood cell casts on urine microscopy.
   E. Urine indices may be helpful in distinguishing between prerenal AKI and acute tubular necrosis (ATN); however, neither of these causes would explain the acid-base values, electrolyte disorder, or urinalysis.
2.
   A. In the setting of antidiuresis and the presence of antidiuretic hormone, urine osmolality can approach 1200 mOsm/kg.
   B. Fractional excretion of urea less than 35% is associated with renal sodium conservation in prerenal settings.
   C. With healthy kidneys, serum creatinine levels are less than 1.7 mg/dl. Therefore the levels of BUN to serum creatinine exceed 20:1, which is consistent with prerenal conditions.
   D. In a state of volume contraction, spot urine sodium levels would be expected to be less than 20 mEq/l.
   E. E is incorrect.
3.
   A. Although a kidney ultrasound can be diagnostic of urinary obstruction, it is not the best option in this case because it cannot provide therapeutic relief of the obstruction.
   D. A postvoid bladder catheterization can both diagnose and treat opioid-induced urinary retention or prostate-related obstruction.

CHAPTER 69

1. D.
   Thyroid disorders are not associated with the risk of AKI.
2. C.
   The incidence of AKI in hospitalized patients has increased by approximately 13% per year over the last three decades.
3. D.
   All of the above appear to be consequences of AKI.
4. B.
   The incidence of stage 4 CKD or greater in AKI survivors is approximately 120 per 100,000 person-years.

CHAPTER 70

1. C.
   Randomized controlled trials have shown that starches increase the risk for dialysis.
2. E.
   Metformin should be stopped to prevent lactic acidosis associated with metformin accumulation and the other drugs to prevent acute kidney injury (AKI).
3. A.
   Urine output should be maintained around 300 ml/h until CK levels are lower than 5000 U/L.
4. B
   Correct.

CHAPTER 71

1.
   A. The use of intermittent acute renal replacement therapy (ARRT) as initial modality results in the same outcomes as the use of continuous renal replacement therapy (CRRT) as initial modality, as long as one switches in a timely manner as best practice and clinical indications dictate. Patients who are hemodynamically unstable, including those with cardiogenic shock, appear to have better organ recovery if they are treated with CRRT or prolonged intermittent renal replacement therapy (PIRRT).
   B. This is still an experimental approach, and to date definitive evidence is missing or negative. Importantly, high-volume CVVH removes beneficial substances (e.g., antibiotics, amino acids, etc.) and is therefore not harmless; however, the risks versus benefits of this promising therapy are still unknown
   C. High-quality evidence shows that thrice-weekly treatment is adequate as a default prescription for those receiving intermittent RRT modalities. Of course, an individual's clinical situation might mandate more intensive treatment for any given case, but this does not mean that more intensive treatment is better for all cases.
   D. Correct. Delivering adequate dialysis is a core quality indicator for RRT programs and mandates routine and regular measurement of delivered dose; underdelivery is the rule, rather than the exception.

2.
   A. Catheter choice should be based on their operating characteristics, to suit the requirements of the patient, the therapy, and the moment. None are inherently "better" than the others.
   B. Evidence-based guidelines and cumulative clinical experience both favor the use of arteriovenous access for intermittent HD.
   C. Correct. Recent advances in catheter design include the use of symmetric (nonstepped) bias-cut spiraled ports on their tips. Unlike catheters with stepped tips, this design results in minimal or acceptable access recirculation in both normal and reversed configuration.
   D. Left-sided internal jugular and subclavian catheters provide flows that are more erratic and up to 100 ml/min lower than elsewhere. Femoral and right-sided internal jugular or subclavian catheters provide the best *Qb*. Overall, data support a recommendation for right-sided internal jugular catheters with bias-cut spiraled ports as the first choice for intermittent HD and PIRRT, with femoral and left-sided internal jugular catheters as the second and third choices, respectively.

3.
   A. Low rates of infection require both adherence to specific clinical guidelines and grounding of activities within a formal quality improvement framework. There is strong evidence that standardizing catheter insertion techniques to best practice results in a near-zero catheter-related infection rate. The relevant interventional bundles are contained in position statements of the Institute for Healthcare Improvement (IHI) and the Centers for Disease Control and Prevention (CDC) Healthcare Infection Control Practices Advisory Committee (HICPAC). The core elements appropriate for dialysis catheters are listed in Box 71.3.
   B. Topical antibiotic ointments are not recommended because of their potential to promote fungal infections and antimicrobial resistance.
   C. Antibiotic- or antiseptic-impregnated lines are recommended by the CDC for patients whose catheters are expected to remain in place for longer than 5 days, and those at high risk for infection (e.g., extensive burn injury, neutropenia, etc.).
   D. There is ongoing controversy around the risk for infection with different insertion sites, but on balance the internal jugular site is preferred, especially in those with a larger body mass index. However, it is likely that the way the catheter is handled is more important at preventing

CHAPTER 72

1. C.
   A and B.
2. D.
   No established therapy for these patients has been shown to improve outcome.
3. D.
   Hemoconcentration is an indicator of plasma refill during ultrafiltration.
4. C.
   Replace ACE-inhibitor with sacubitril/valsartan.

CHAPTER 73

1.

A. Correct. Patients with HRS have vasodilation of the splanchnic circulation as a result of the activation of the vasodilator systems at this level

B. Correct. In patients with HRS the heart cannot increase its output to compensate for a decrease in cardiac preload (secondary to the accentuation of splanchnic arterial vasodilation)

C. Correct. Systemic inflammation represents an important pathogenic factor for HRS

D. HRS is a functional renal disorder. The presence of significant glomerular and/or tubular disease excludes the diagnosis

2.

B. HRS is a functional renal disorder with a diagnosis that is based on clinical criteria. Moreover, renal biopsy is risky in patients with liver disease with severe coagulopathy.

C. Activation of the vasoconstrictor systems (the renin-angiotensin-aldosterone system, the sympathetic nervous system, and vasopressin) is a key factor in the pathogenesis of HRS. Plasma renin activity/concentration is markedly increased in the majority of patients. However, its measurement is complicated and not useful in the clinical setting.

D. Correct. The diagnosis of HRS is mainly one of exclusion and should be suspected in any patient with subacute or chronic liver disease with advanced liver failure and portal hypertension who develops progressive renal impairment.

3.

A. HRS should be suspected in any patient with subacute or chronic liver disease with advanced liver failure and portal hypertension.

B. Correct. In the splanchnic circulation, there is marked arteriolar vasodilation resulting in reduction of systemic vascular resistance and arterial hypotension.

C. Activation of the vasoconstrictor systems (the renin-angiotensin-aldosterone system, the sympathetic nervous system, and vasopressin) is a key factor in the pathogenesis of HRS.

D. Correct. HRS occurs in patients with advanced liver failure. The presence of ascites is mandatory.

E. Infection is the most frequent trigger event of HRS.

4.

A. Among the vasoconstrictor therapies, intravenous terlipressin, combined with daily albumin infusion, is the preferred therapy.

B. TIPS could be an alternative treatment of type 1 HRS in patients without response to terlipressin/norepinephrine plus albumin.

C. Dialysis is not tolerated in patients with HRS (already hypotensive) and does not improve survival. It should be reserved for critically ill cirrhotic patients with severe uremia and volume overload.

D. Some studies suggest that albumin dialysis may have beneficial effects in patients with type 1 HRS.

E. In patients with HRS, the administration of midodrine, octreotide and albumin is much less effective in improving renal function than the combination of terlipressin plus albumin.

5.

A. Primary prophylaxis of SBP with norfloxacin prevents SBP delays the development of HRS, and improves short-term survival in cirrhotic patients with advanced cirrhosis.

B. Albumin infusion prevents HRS in patients with SBP.

C. Two randomized controlled trials have failed to show that albumin administration improves survival in infections other than spontaneous bacterial peritonitis (SBP).

D. No study supports this contention.

CHAPTER 74

1. C.

   See the equation on page 872: Fraction of normal dose = 1 – 0.8(1-0.25) = 0.4

   Therefore the dose should be reduced to 40% of the original dose.
2.
   A. High-flux membranes have larger pore sizes and therefore increase removal.
   B. Low protein binding allows a greater portion of unbound drug to be available for clearance.
   C. A low volume of distribution indicates a larger portion of the drug dose that is in the plasma available for removal by dialysis.
   D. Correct. Large molecular sizes prevent drug removal because the drug cannot pass through the membrane pores
3.
   A. Correct. Renally cleared, although it has a wide therapeutic index and limited toxicity, so dose reduction usually is not clinically required for standard courses of oral doses.
   B. Extensively renally cleared with significant toxicity requiring significant dose reduction.
   C. Extensively renally cleared with significant toxicity and narrow therapeutic index requiring significant dose reduction.
   D. Extensively renally cleared with significant potential toxicity requiring dose reduction.
   E. Extensively renally cleared with significant potential toxicity requiring significant dose reduction.
4.
   A. Clarithromycin is a potent CYP3A4 and P-glycoprotein (P-gp) inhibitor significantly increasing sirolimus exposure.
   B. Phenytoin is a potent enzyme-inducing agent that significantly increases the metabolism of coadministered hepatically cleared drugs such as prednisolone.
   C. Fluconazole is a weak inhibitor of CYP3A4 and P-gp and may increase tacrolimus exposure, especially during prolonged combination use.
   D. Correct. Roxithromycin is a weak inhibitor of CYP3A4 and P-gp and rarely causes clinically significant increases in drug exposure, especially during typical 5-day courses of therapy.
   E. Verapamil is a strong inhibitor of CYP3A4 and P-gp and significantly increases everolimus exposure.

CHAPTER 75

1.
   - **A. Correct. Extensively renally cleared. Accumulation in renal impairment increases the risk for bleeding.**
   - **B. Correct. Extensively renally cleared. Accumulation in renal impairment increases the risk for central nervous system (CNS) adverse effects.**
   - C. Significantly renally cleared, although accumulation is not clinically significant and dose reduction is usually not required.
   - D. Extensively hepatically cleared. Dosing is based on clinical response.
   - **E. Correct. Extensively renally cleared. Accumulation in renal impairment increases the risk of CNS adverse effects.**

2.
   - A. Weak CYP3A4 inhibitor. CNI concentration may increase. Base subsequent dose modification on measured CNI concentration changes.
   - **B. Correct. Strong CYP3A4 inhibitor. CNI concentration expected to increase. Avoid combination or significantly reduce CNI dose if combination is essential.**
   - C. Renally cleared and does not affect CYP3A4. No interaction expected.
   - D. Renally cleared and does not affect CYP3A4. No interaction expected.

3.
   - A. Hepatically cleared without active or toxic metabolites
   - **B. Correct. Metabolized to oxypurinol, which can accumulate in renal impairment**
   - C. Renally cleared without active or toxic metabolites
   - D. Hepatically cleared without active or toxic metabolites
   - **E. Correct. Metabolized to toxic metabolite meperidine, which is renally cleared**

4.
   - A. **Correct. Small molecule that is renally cleared and significantly removed by dialysis**
   - B. Large volume of distribution so minimal amounts removed by dialysis
   - **C. Correct. Small molecule renally cleared and significantly removed by dialysis**
   - D. Significantly protein bound so minimal removal by dialysis
   - **E. Correct. Small molecule renally cleared and significantly removed by dialysis.**

CHAPTER 76

1. B.
   Aristolochic acid nephropathy.
2. C.
   Chronic tubulointerstitial nephritis (Balkan endemic nephropathy).
3. A.
   Cystine crystal.
4. A.
   Acute rejection.

CHAPTER 77

1. A.

   The KDIGO guideline on the classification of CKD recommends using a CGA staging system, including cause of disease, GFR, and level of albuminuria.
2. C.

   The presence of albuminuria has been linked to the development of albuminuria in many studies (see references 1 to 3). Work by the CKD Prognosis Consortium found that low GFR remains a significant risk factor for morbidity (including end-stage renal disease [ESRD]) and mortality in older adults[4] and that there was little difference in the risk associated with albuminuria between men and women.[5] Assays for proteinuria are less accurate than those for albuminuria.
3. B.

   APOL1 risk alleles are almost solely present in persons of African descent. However, lower socioeconomic status and poor access to medical care is a big determinant of racial disparities in ESRD as well as other health outcomes.
4. C.

   Rates of new dialysis patients rise progressively with age, at least until approximately 75 to 80 years of age. They are highest in some Southeast Asian countries and the United States, among males, and among people with lower socioeconomic status.
5. D.

   Among patients with CKD, vascular mortality rates are higher than in the general population; if rates of these were lower, a greater number of people would survive to reach ESRD. Issues of competing in other senses of the word are not relevant. Propensity score matching is a technique for dealing with potential confounders, not competing risks.

CHAPTER 78

1. B.

   Podocytes are damaged by excessive protein load after size selectivity is lost. Protein uptake by podocytes may occur through binding to megalin, a receptor for albumin and immunoglobulin light chains that is endocytosed after ligand binding, as shown in cultured murine podocytes. Excessive protein uptake by podocytes also induces transforming growth factor-β (TGF-β) production, which contributes to cell apoptosis, an additional cause of podocyte loss in proteinuric glomerulopathies.
2. A.

   Loss of podocytes secondary to protein-induced cell injury may lead to reduced production of vascular endothelial growth factor (VEGF), a molecule constitutively expressed and secreted by podocytes, influencing the formation of glomerular endothelial fenestrae and eventually promoting endothelial cell apoptosis.
3. B.

   Exposure of rat proximal tubular cells to excess autologous albumin, as in the case of proteinuric nephropathies, results in the formation of the N-terminal 24-residue fragment of albumin (ALB_{1-24}). This peptide is taken up by dendritic cells, where it is further processed by proteasomes into antigen peptides. These peptides were shown to have the binding motif for MHC class I and to be capable of activating $CD8^+$ T cells.
4. C.

   The progressive enlargement of cysts in the renal tubules in autosomal dominant polycystic kidney disease is largely attributable to the proliferation of mural epithelial cells and transport of fluid into cavities generated by accelerated epithelial cell growth.

CHAPTER 79

1. E.
   SPRINT found no benefit of the Intensive intervention with regard to protecting kidney function in the CKD cohort.
2. E.
   ACE inhibitor and ARB therapy are generally comparable. However, the evidence strongly favors ACE inhibitor with regard to reducing mortality. For this reason, ACE inhibitor should be the initial choice for renin-angiotensin system (RAS) blocker therapy.
3. E.
   In comparing proteinuria magnitude between large populations (e.g., epidemiology studies), spot uPCR is acceptable because the marked variability of spot uPCR likely is random. So this variability is offset when the spot uPCR values are averaged and then compared between the study populations. However, in individual patient management, reliance on spot uPCR results can lead to errors in management because its large inherent variability.

CHAPTER 80

1. D.
   Cardiovascular disease.
2. C.
   The Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) formula.
3. B.
   Weight.
4. B.
   Nocturia.
5. D.
   Creatinine 13.5 mg/dl.

CHAPTER 81

1. D.
   Hyperhomocysteinemia.
2. E.
   The calcific aortic stenosis progression rate is only slightly higher in dialysis patients compared to the general population.
3. C.
   Stroke.
4. C.
   Carvedilol.

CHAPTER 82

1. E.
   The RBC life span is usually normal.
2. D.
   The defined upper dose limit of epoetin is 60,000 IU/wk because it is known that cardiovascular toxicity occurs above this dose level.
3. A.
   Patients receiving darbepoetin alfa were randomized to either a target hemoglobin (Hb) of 13 or a target Hb of 9 g/dl.
4. D.
   Intravenous iron may improve the anemia of chronic kidney disease in up to 30% of patients not receiving ESA therapy who have a low ferritin level.

CHAPTER 83

1.

A. Up to 40% of patients with bacteremia do not develop fever in CKD. This is a direct consequence of the CKD-related immune deficit and makes fever a very unreliable sign for any kind of infection.

B. Patients with CKD often have volume overload that impairs the reliability of radiologic chest findings.

C. The Mendel-Mantoux skin test for tuberculosis is negative in the majority of CKD patients who had contact with *Mycoplasma tuberculosis*. This test should be replaced by interferon-γ release assays that have a much better sensitivity in this patient group.

D. Correct. Blood culture can and should be used frequently in CKD patients with suspected bacteremia; CKD does not influence the sensitivity

E. C-reactive protein is elevated permanently or intermittently in the majority of CKD patients in the absence of infection.

2.

A. Correct. Nearly 80% of dialysis patients who have acute HBV infection develop chronic infection. This is a much higher percentage than that found in the general population infected with the virus (~10%).

B. Acute infections with HBV often go unnoticed in patients with CKD because the typical symptoms are missing as a result of immune deficit. In particular, jaundice is very infrequent.

C. Vaccination efficacy is impaired by immune deficiency of CKD. Therefore patients should always receive double-dose injections and many need extended vaccination schedules.

D. HCV infection is a more chronic disease with few clinical symptoms in all patients. The immune deficit of CKD does not relevantly alter the clinical course of the infection.

E. Standard hygienic precautions are of utmost importance for the prevention of nosocomial hepatitis virus infection. The strong decrease in new infections of HBV may be facilitated by vaccination; however, the successful containment of HCV risk in dialysis depends solely on hygiene, indicating the importance of these measures.

3.

A. The plasma levels of several coagulation factors may be affected by uremia. However, those changes do not generally induce prolonged prothrombin time.

B. In the same vein, changes in plasma levels of several coagulation factors by uremia do generally not prolong partial thromboplastin time.

C Some minor changes in platelet counts may occur in CKD because consumption of platelets may override their bone marrow production. However, severe thrombocytopenia does not generally occur. Very low platelet counts should raise the awareness for other, specific underlying hematologic diseases

D. Anemia may contribute to hemorrhagic diathesis. However, anemia in CKD will usually manifest as hypochromic or normochromic anemia, because of iron deficiency and/or low erythropoietin levels.

E. Correct. None of These

4.

A. Desmopressin acts by releasing large factor VIII:von Willebrand factor multimers from endothelial cells into the plasma, and potentially by increasing the membrane glycoprotein expression of platelets.

B. Estrogens may act on coagulation by limiting the production of L-arginine, which is a precursor of nitric oxide. Thus estrogens may lower elevated nitric oxide (NO) production in CKD patients and subsequently reduce NO-induced guanylyl cyclase stimulation and cyclic guanosine monophosphate (cGMP) synthesis, which will finally increase TXA and adenosine diphosphate availability. Estrogens may additionally lower hemorrhagic diathesis by affecting production of coagulation factors and of their inhibitors.

C. TXA is an antifibrinolytic agent, which may be considered for life-threatening bleeding events in CKD patients.

D. The effects of cryoprecipitates are supposed to be mediated by factor VIII:von Willebrand factor multimers, fibrinogen, and other factors that enhance platelet aggregation.

E. Correct. Clopidogrel is an antiplatelet agent, which may be considered in primary and secondary prevention of cardiovascular disease. As a side effect, it may induce more bleeding events

CHAPTER 84

1. C.

   Although the PTH value of this woman is in the desired range, her phosphate levels are too high. In particular in this situation, additional calcium loading should be avoided.
2. E.

   The very low PTH of this dialysis patient is almost diagnostic of low turnover bone disease. The key measure to improve bone turnover is avoidance of calcium loading.
3. E.

   Calcimimetics are not licensed for use in patients with stage 4 CKD stage. There is concern that in this situation calcimimetics lead to increases in serum phosphate.

CHAPTER 85

1. A.
   Use of gabapentin for neuropathic pain.
2. F.
   A, B, and C are correct.
3. C.
   Iron overload and deposition in the basal ganglia.

CHAPTER 86

1. B.

Low predialysis urea and electrolytes along with low cholesterol may indicate a reduced protein and calorie intake and warrant further dietary investigation. The breathlessness also may indicate that although the target weight has been stable for months, dry weight has been lost over previous weeks (or months) and has been replaced by fluid, so reassessment of target weight is needed. It is a common mistake to see low blood urea nitrogen and electrolytes in a dialysis patient and reduce the amount of dialysis given. This can cause appetite to reduce further, exacerbating the problem. Serum albumin, with its relatively long half-life, does not always drop with a poor dietary intake and therefore is not a good marker of nutritional status on its own. Although one might consider starting a diuretic in a patient with some urine output, there is no indication to restrict fluids in this patient.

2. C.

The patient is very enthusiastic about exercise and was found to be taking protein supplements. Protein intake works out to be 1.5 g/kg of body weight. If protein intake is high, a reduction toward 1 g/kg may reduce symptoms and also lesson the phosphate and potassium intake and the acid load. Although the BMI is 27, if the patient is exercising extensively, this higher BMI may reflect a higher muscle mass; a lower calorie intake is not necessarily indicated. In fact, if protein intake is being reduced, it will be important to ensure that advice is given to maintain calorie intake for weight maintenance. Sodium intake is high, and because the blood pressure is elevated, it would be very beneficial to advise on ways to reduce sodium in the diet. Potassium is at the top of the reference range, but reducing protein intake often leads to a reduction in the potassium intake, and the correction of acidosis with bicarbonate is likely to also have a beneficial effect on potassium.

3. D.

The symptoms suggest reduced gastric emptying, possibly because of a combination of diabetic autonomic neuropathy and renal failure. Reducing dialysis volumes would be wrong because having clearances above the minimum target does not exclude inadequate dialysis as a cause of his symptoms (and 2-liter exchanges are not particularly large for this patient). It may even be appropriate, if other measures do not help, to increase the dialysis prescription in case there is a contribution of uremia to his symptoms. Attempting a weight-reduction diet would be inappropriate in this patient, who is already losing weight and raising concerns about his nutrition. Initial forms of nutritional supplementation would be by oral means (dietary advice and supplements if needed) rather than amino acid dialysate as first-line treatment.

CHAPTER 87

1. E.
   All of the above.
2. E.
   In all patients.
3. E.
   Is not limited to any subgroup of patients with uremic pruritus
4. D.
   Warfarin and coumarins.
5. E.
   Is related to exposure to iodine radiocontrast agents.

CHAPTER 88

1.

A. Kidneys of patients with ADPKD have typically many more than four or five cysts and are most often drastically enlarged compared with normal kidneys with simple cysts.

B. Correct. ACKD is a common finding in patients with ESRD ranging from about 20% at the begin of RRT to nearly 100% after more than 10 years. Hematuria may be one of the typical complications of renal cysts.

C. We recommend that asymptomatic dialysis patients younger than 60 years with a high life expectancy should be screened for ACKD and RRC. However, the cumulative incidence of RCC in ACKD is probably less than 1%.

D. Cystic disease of organs other than the kidneys is not a typical feature of ACKD.

E. Exposure to benzidine and 2-naphthylamine is a risk factor for the development of transitional cell cancer (TCC) of the bladder. A connection to ACKD has not been established.

2.

A. Some of the increased risk for malignancy is directly related to the underlying renal disease. For example, patients with analgesic nephropathy or Chinese herbs/aristolochic acid nephropathy are at high risk for development of TCC of the upper urinary tract. In addition, the immunosuppression that may have been administered to patients with immune-mediated renal disease, such as cyclophosphamide therapy, may predispose to bladder and ureteral cancer.

B. Registries from the United States, Europe, and Australia have shown an increased risk for cancer of the kidneys and bladder, cervix, and thyroid and other endocrine organs, as well as multiple myeloma in patients with ESRD, compared with the general population.

C. Cyclophosphamide is carcinogenic and may increase the risk for developing lymphomas, leukemia, skin cancer, TCC of the bladder, or other malignancies.

D. Plants containing aristolochic acids have a long history for medicinal purposes and are commonly used in Chinese herbs. Compounds of this family have been shown to be carcinogenic, mutagenic, and nephrotoxic. They are associated with kidney disease and urothelial cancers.

E. **Correct. Large registries have not shown an increased risk for cancer of the intestinal tract in dialysis patients compared with that in the general population.**

3.

A. ACKD is a common finding in patients with ESRD ranging from about 20% of patients being affected at the beginning of RRT to nearly 100% after more than 10 years of RRT.

B. Up to 25% of kidneys with ACKD harbor tumors, most of which are papillary adenomas and only about one third are carcinomas.

C. ACKD does usually not cause any symptoms. If symptomatic, it can manifest with hematuria or symptoms of cyst infection.

D. Correct. ACKD is a risk factor of RRC, but only less than 1% of affected patients develop RCCs so that nephrectomy is not indicated. We suggest, however, that asymptomatic patients with high life expectancy should be screened by ultrasound on a yearly basis to detect suspicious masses.

E. Contrast-enhanced CT and MRI are the most sensitive diagnostic procedures to detect renal masses. Especially for small kidney tumors they are superior to ultrasound.

CHAPTER 89

1. A.

This patient has the typical findings of a hypersensitivity reaction to a nonsteroidal antiinflammatory drug (NSAID).[1] Clinically, this syndrome manifests with the abrupt onset of nephrotic syndrome and an acute deterioration of renal function. The pathologic findings are usually a combination of MCD and interstitial nephritis (with a T cell infiltrate and minimal eosinophil accumulation).[1] Spontaneous recovery on discontinuance of the drug is the rule, but corticosteroid therapy may hasten recovery in severe renal failure and perhaps prevent long-term sequelae.[2]

1. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: Physiologic foundations and clinical implications. *Am J Med.* 1999;105:13S-24S.
2. Inoue M, Akimoto T, Saito O, et al. Successful relatively low-dose corticosteroid therapy for diclofenac-induced acute interstitial nephritis with severe renal failure. *Clin Exp Nephrol.* 2008;12:296-299.

2. B.

Recent data have demonstrated that elderly nursing home patients who start HD seldom achieve significant functional benefit and many continue to deteriorate or even deteriorate at a faster rate than before starting dialysis.[1] Home HD and assisted PD are options but likely will not result in any significant benefit for this patient other than allowing her to remain in her care setting. The first 3 months after dialysis is begun is a very vulnerable period, and if there is no benefit seen within this time frame, it is unlikely that the patient will see any significant functional improvement from dialysis moving forward.[2]

1. Kurella M, Covinsky K, Collins A, Chertow G. Octogenarians and nonagenarians starting dialysis in the United States. *Ann Intern Med.* 2007;146:177-183.
2. Jassal S, Watson D. Dialysis in late life: Benefit or burden. *Clin J Am Soc Nephrol.* 2009;4:2008-2012.

3. B.

Although older than 75 years, this man does not have any additional risk factors precluding transplantation. His outcome with a kidney transplant would likely be superior to that on dialysis even at this age. After transplantation, his highest risk for death would be within the first 3 to 4 months. He would benefit the most if he received a kidney transplant preemptively or within 6 months of starting dialysis. Even if he is not able to undergo surgery within this time, the longer he waits while undergoing dialysis, the poorer his overall and graft survival. Although true regardless of age, living donation is particularly attractive for this patient because of the likelihood that the time on dialysis will be shorter and the improved outcomes associated with shorter organ cold ischemia time. The results of the old-for-old program in Europe suggest that the use of donors with less-than-perfect organs is acceptable; therefore there is no contraindication to older patients going on the extended-criteria donor wait list.[1]

1. Frei U, Noeldeke J, Machold-Fabrizii V, et al. Prospective age-matching in elderly kidney transplant recipients: A 5-year analysis of the Eurotransplant Senior Program. *Am J Transplant.* 2008;8:50-57.

CHAPTER 90

1. B.

In patients who are suitable for kidney transplantation, outcomes with a kidney transplant are superior to any dialysis modality. Preemptive transplantation gives superior outcomes to transplantation after dialysis has been started. A living donor kidney gives superior outcomes to a deceased donor kidney.

2. D.

The IDEAL study[16] showed no improvement in outcomes with early initiation of dialysis, but health care costs were increased.[17]

3. C.

There is no single threshold of eGFR when dialysis should be started. Answers B and D can be managed without dialysis.

4. D.

Physical and psychological preparation for dialysis or transplantation takes many months. The appropriate trigger for transferring a patient to multidisciplinary renal care is therefore the time before RRT is expected to be needed, rather than an arbitrary level of kidney function.

5. A.

If a patient expresses a clear wish not to have dialysis, the physician is obliged to respect this because to treat patients against their will constitutes an assault.

6. C.

In the presence of a good performance status and little or no comorbidity, age alone does not indicate a poor prognosis on dialysis.

CHAPTER 91

1. C.

The primary patency of AVF is 60% to 70% at 1-year follow-up. AVGs have a primary patency of 25% because of a higher number of thromboses resulting from stenoses in the AVG conduit. To get higher patencies, AVGs need multiple interventions. This is not the case in AVFs.

2. B.

A flow of 800 ml/min is just enough to keep an access open. Further flow reduction by banding or RUDI has the risk for fistula thrombosis. Therefore the first treatment option is to enhance flow to the forearm and hand by bypass surgery (DRIL procedure).

3. D.

Multiple studies clearly indicate tunneled central venous catheter over nontunneled central venous catheter because of the higher risk for infection. Other items outlined in the answers are similar between tunneled and nontunneled catheters.

4. A.

The thrombosis rate of autogenous AVF is lower compared with AVG because of a lower incidence of stenosis formation resulting in flow decline. In addition, AVFs can experience lower flows because of the presence of endothelium in the access conduit. These cells prevent thrombosis. Only with very low flows (<400 ml/min) the risk for thrombosis increases, while, for instance, in AVGs this risk is already present with higher flow rates (usually ~600 ml/min).

5. B.

Recent studies show high recurrence rates for primary percutaneous transluminal angioplasty without stenting of central vein occlusions. Primary stent placement results in better primary patencies.

CHAPTER 92

1. B.
   False
2. C.
   Less than 30% residual stenosis and resolution of physical indicators of stenosis.
3. D.
   A and B.
4.
   A. An ultrasound of the kidneys should be performed in all patients with chronic renal failure to rule out obstructive uropathy and polycystic kidney disease and to exclude advanced, irreversible disease (small kidneys with thin cortex) for which a biopsy will not be useful.
   B. In many patients with acute renal failure, the cause is apparent from the clinical picture (i.e., sepsis) and imaging is useful only when the cause is not apparent, the clinical picture suggests urinary obstruction, and it is not clear how much of the renal failure is acute or chronic.
   C. Correct. Ultrasound is the modality of choice for diagnosing bladder outlet obstruction, with a negative study essentially ruling this out.
   D. Normal ureters are too small to be detected by sonography. Even when dilated, they are often not apparent because of overlying bowel gas.
5. E.

CHAPTER 93

1. A.

   Endotoxin molecular weight is too high (~100,000) and thus cannot pass through dialysis membranes.

2. C.

   The bacterial microflora in the gut metabolizes some amino acids and other precursors into uremic toxins, for example, tryptophan into indoles, L-tyrosine into *p*-cresol, and choline into trimethylamine.

3. D.

   A large body of high-quality evidence indicates that a hemodialysate at a temperature below the patient's core temperature results in improved intradialytic hemodynamic stability.

4. A.

   A recent study showed an increased morbidity and mortality in HD patients with prolonged intradialytic hypoxemia.

5. B.

   Water preparation according to national and international guidelines is the foundation of dialysate preparation.Chapter 94

1. C.

   Probably 3 hours of dialysis time because there would not be enough time to remove interdialytic volume without a dangerously high ultrafiltration rate. The other factors may not be optimal but are far less dangerous.

2. A.

   Use of antihypertensive drugs in large trials rarely reduce systolic BPs by more than 10 mm Hg. The other actions are more effective, particularly C and D together.

3. B.

   Application of abdominal pressure would not be useful in these circumstances. Decreasing dialysate temperature will cause arteriolar vasoconstriction, and reducing ultrafiltration will maintain circulating volume. Having a easier (higher) weight target to reach will indirectly result in lower ultrafiltration rates and maintenance of BP.

4. D.

   An increase in dialysate flow rate does not affect the convective volume in online HDF. All the other actions listed here, either individually or in combination with one or more of the other actions, are useful to increase convection volume.

5. C.

   This indicates the importance of apparently even small degrees of residual function. (2.00 is the minimal standard KtV prescribed dose.)

CHAPTER 95

1. C.
   Intravascular volume depletion.
2. D.
   Avoidance of excessive interdialytic weight gains.
3. E.
   Heparin exposure.
4. B.
   Potting compound.
5. E.
   All of the above.

CHAPTER 96

1. B.
   The glucose molecules are smaller than the ICO molecules and therefore are relatively “inefficient” as osmotic agents in small pores, but relatively more efficient across AQP.
2. E.
   None of the catheters above shows significant clinical superiority
3. C.
   Increases in small-solute transport (PET_{creat}) combined with no or only moderate increases in the UF coefficient (L_pS)
4. D.
   They produce higher concentrations of the dialysate effluent marker CA-125.
5. E.
   Icodextrin is polydispersed, but with 30% of the molecules being larger than 3 kDa.
6. A.
   Small pores

CHAPTER 97

1. A and C.
   A is false because although there is some emerging evidence of the superiority of the laparoscopic technique, this is not a substitute for a well-audited and experienced surgical team. C is false because normal pH solutions should be considered if available. Note that E is true but occasionally is due to fluid tracking down the abdominal wall from a deep cuff leakage.
2. B and C.
   B is false because antifungals should be commenced intraperitoneally, but the catheter should be removed and treatment continued systemically. C is false because treatment should await cultures; the indications for immediate treatment are purulent discharge of clinical evidence of infection of the tunnel. Note that D is true for both exit site infections and peritonitis. E is true and remains the most common reason for PD-associated peritonitis death.
3. B and D.
   B is false because the target should take residual renal function into account; an anuric patient obtaining less than 1 liter should have his or her membrane and prescription examined. D is false; CT can be used to confirm that obstructive symptoms are a result of encapsulation but should not be used to screen for EPS in the absence of symptoms. Note that A is true because of both increasing solute transport and loss of osmotic conductance. For E, progressive loss of osmotic conductance is not treatable, and PD should be continued only in patients with otherwise low life expectancy.

CHAPTER 98

1. A.

   Ethylene glycol is metabolized to glycolic acid and oxalate by alcohol dehydrogenase. Its presentation is associated with oxalate crystals in the urine and a raised anion gap acidosis.
2. E.

   Acute kidney injury is not associated with a raised osmolar gap, whereas all of the other conditions are.
3. C.

   All of the other drugs/poisons are effectively removed by intermittent HD.
4. A.

   Hemoperfusion remains the 1st choice treatment for removal of theophyllines.

CHAPTER 99

1.
   - A. Not linked to plasma exchange.
   - B. Plasma exchange can be a treatment for hyperviscosity syndromes: replacement with albumin or fresh-frozen plasma (FFP) does not alter normal plasma viscosity.
   - **C. Correct. This is a very common complication, especially when using FFP replacement that contains citrate.**
   - D. Can be associated with the need for central venous access to undertake plasma exchange but uncommon
   - E. Thrombocytopenia can occur
2.
   - **A. Correct. Should be started immediately while awaiting complement studies and possible use of eculizumab**
   - B. Probably no role for plasma exchange
   - C. Evidence for any benefit of plasma exchange increasingly absent: critical therapy is early start of chemotherapy probably including bortezomib to rapidly deplete light chains
   - D. No role for plasma exchange
   - E. No good evidence for benefit of plasma exchange in lupus nephritis, and patients should start urgent therapy with cyclophosphamide, mycophenolate, or rituximab
3.
   - **A. Correct. Good evidence for benefit of plasma exchange**
   - B. CD4 staining alone is not sufficient to diagnose antibody-mediated rejection
   - C. No good evidence for benefit; initially drug should be stopped
   - D. No role for plasma exchange
   - E. No role for plasma exchange

CHAPTER 100

1. B.

   HLA genes are inherited in a mendelian codominant fashion, meaning that a copy of each HLA gene (i.e., one haplotype) is inherited from each parent and expressed as antigens. It can thus be predicted that siblings from the same set of parents will have a 25% chance of having zero mismatches, 50% chance of one haplotype mismatch, and 25% chance of two haplotype mismatches. In kidney transplantation, efforts are made to match HLA-A, -B, and -DR genes and proteins.

2. D.

   Both cellular and antibody types of rejection can be early or late, fulminant or indolent, and isolated or concomitant and can share pathologic features on biopsy. Tubulitis is a characteristic feature of acute cellular-mediated rejection.

3. E.

   Patients normally have no preexisting immunoreactivity to alloantigen, unless they have been exposed to alloantigen through pregnancy, blood transfusion, or prior transplantation. However, microbial antigens that cross-react with alloantigens (molecular or antigenic mimicry) can lead to the generation of alloantigen-specific memory cells through a process termed *heterologous immunity*.

4. C.

   T cells recognize alloantigen as peptides presented by intact MHC molecules on donor (direct pathway) or recipient (indirect pathway) antigen-presenting cells. MHC class II molecules process extracellular proteins for presentation to CD4 T cells. The MHC class I system is designed to sample intracellular, not extracellular, proteins and present them to CD8 T cells.

CHAPTER 101

1. A.

Calcineurin inhibitors (CNIs) are still considered the cornerstone of modern immunosuppression, but CNI nephrotoxicity has limited progress in graft survival for the past two decades. Chronic renal injury is presumably the result of prolonged renal vasoconstriction with ischemia and over time is characterized by afferent arterial hyalinosis and tubulointerstitial fibrosis. Hypertension is common after transplantation but usually can be managed with a combination of antihypertensive agents. TMA is rare but potentially serious adverse advent that may require the reduction or removal of the offending CNI. Alopecia is a common side effect seen with tacrolimus, but hirsutism is associated with cyclosporine.

2. C.

Belatacept is a selective T cell costimulation blocker that binds to CD80 and CD86 on antigen-presenting cells, thereby blocking CD28-mediated costimulation. So far, belatacept appears to be a promising renal-sparing agent. Eculizumab blocks complement C5 cleavage, thus preventing the formation of the C5b-9 membrane attack complex, and it has been used as rescue therapy for refractory acute rejection. Basiliximab is a monoclonal antibody that targets CD25 on the IL-2 receptor, and it is used as induction immunosuppression. Rituximab in a monoclonal antibody that is directed against the CD20 antigen, which blocks B cell proliferation and differentiation, and it has been used in the treatment of antibody-mediated rejection and desensitization protocols.

3. D.

Mycophenolate has a black box warning for its use during pregnancy because an increased risk for first-trimester miscarriages and congenital birth defects. Patients are strongly advised to stop mycophenolate if pregnant or attempting to get pregnant. Both tacrolimus and prednisone are U.S. Food and Drug Administration (FDA) pregnancy class C but have been successfully used throughout pregnancy. Despite being an FDA pregnancy class D agent, azathioprine has been around for 50 years and has been considered acceptable by the transplant community.

4. B.

Basiliximab induces a relatively mild immunosuppression and is used as an induction agent, but not to treat established acute rejection.[9,10] Antithymocyte globulin is a potent polyclonal agent that depletes T and B lymphocytes and has been used as therapy for steroid-resistant acute rejection. Rituximab is a monoclonal antibody that targets B cells and is used as a treatment for acute antibody-mediated rejection. Intravenous immunoglobulins appear to reduce alloantibodies through inhibition of antibody production—though the mode of action is not well understood—and it used as therapy for acute antibody-mediated rejection.

CHAPTER 102

1. A.

   Active sepsis will likely worsen with immunosuppression, and so it is important to have this resolved before transplantation. Responses B to E are no longer seen as contraindications, although special care must be taken to address the specific issue and potentially modify the immunologic, medical, and surgical approach to transplantation.

2. D.

   A normal stress echocardiography result does not necessarily exclude coronary heart disease, however the negative predictive value for myocardial infarction or cardiac death is in excess of 90% in patients with renal failure.

3. D.

   Deceased donors over the age of 60 years without any other medical history of significance meet the definition for expanded-criteria donors. If there is a history of hypertension or death from a cerebrovascular accident, the age for classifying a donor as meeting expanded-criteria can be lower between 50 and 59 years old. Diabetes, smoking, vascular disease, and hepatitis C virus (HCV) are not factors used to classify donors as expanded-criteria. The new KDRI/KDPI system is more detailed and does use donor age, diabetes, hypertension, HCV, and mode of death in the formula when deriving the donor score.

4. B.

   A colonoscopy would usually be considered only in donors with bowel symptoms, iron deficiency, or a family history of colonic cancer. Urine microscopy and imaging are important tests in assessing underlying renal conditions in the donor and defining anatomy before donation. Hepatitis serology is important in assessing the risk for disease transmission. An electrocardiogram will help define the donor's cardiac status and possible risks associated with the surgical procedure and anesthetic.

5. C.

   A positive T cell cytotoxicity–dependent crossmatch is likely to be indicative of a very high level of donor-specific antibodies against class I human leukocyte antigen, making the risk for hyperacute rejection extremely high. Additionally, this test is functional in that it uses T cells from the donor (therefore expressing antigens that also may be present on the allograft) to assess the recipient's immunologic reactivity to the allograft.

CHAPTER 103

1. A and D.
2. A and D.
3. C.
4. C and E.
5. A.

CHAPTER 104

1. D.

The most recent Banff criteria for the diagnosis of antibody-mediated rejection requires 1) evidence of circulating donor-specific antibodies 2) histologic evidence of tissue injury in the form of microvascular inflammation, arteritis, thrombotic microangiopathy, and/or acute tubular injury, and 3) evidence of antibody/endothelial interaction in the form of either peritubular capillary C4d deposition, at least moderate microvascular inflammation, or molecular markers. Option D is the only answer here that includes these criteria.

2. B.

While the utility of induction immunosuppression in patients at low immunologic risk is debatable, acute rejection rates are significantly lower in higher immunologic risk patients treated with lymphocyte depleting agents vs. IL-2 receptor antibodies. Answer A refers to OKT3 which is no longer in production. Answer C is incorrect in that patients treated with IL-2 receptor antibodies are likely at LOWER risk of lymphoproliferative disorders vs. those treated with lymphocyte depleting agents. Finally, anti-CD52 therapy reduces early acute rejection rates, with higher rebound rejection rates after 12 months.

3. B.

The ELITE-SYMPHONY study showed tacrolimus/MMF/prednisone containing regimens to be associated with lower acute rejection rates compared to a sirolimus-containing CNI-free regimen (answer A). Belatacept may prove to improve long term graft outcomes compared to CNI-containing regimens, however is associated with increased rates of acute rejection early after transplant. Early prednisone withdrawal strategies (answer D) are used by approximately 30% of US transplant programs and are associated with an approximately 2-fold increased risk of acute rejection, especially in patients at higher immunologic risk NOT receiving lymphocyte-depleting induction.

4. C.

This patient has banff class II cellular rejection, the appropriate treatment for which includes rATG. Options A and B may be adequate for more mild forms of acute cellular rejection (banff class 1a). Option D describes treatment for antibody-mediated rejection.

CHAPTER 105

1. C.

   There has been no conclusive evidence to suggest that vaccination increases the risk for allograft dysfunction or acute rejection. Intranasal influenza vaccine is a live attenuated influenza vaccine and is contraindicated before and after transplantation. Vaccinations should be administered at least 4 to 6 weeks before transplantation to achieve optimal immune response.
2. D.

   The AST Infectious Diseases Community of Practice guidelines recommend that antiviral therapy be continued until the following criteria are met: (1) Resolution of clinical symptoms, (2) Virologic clearance below a threshold negative value based on laboratory monitoring with CMV QNAT or pp65 antigenemia, and (3) Minimum 2 weeks of antiviral therapy.
3. B.

   The effectiveness of currently available antiviral agents is of uncertain benefit. In nearly all case series reported, adjuvant antiviral agents were initiated in conjunction with immunosuppression reduction. Furthermore, although antiviral therapy may reduce viral load, viral clearance may require continuous immune control. Judicious immunosuppression reduction may allow sufficient reconstitution of BKV-specific T cells to control BKV replication while maintaining adequate immunosuppression to prevent allograft rejection. The routine recommendations of antiviral therapy or immunosuppression class switching in the prevention or treatment of BK virus–related clinical syndromes await results of large prospective randomized trials.

CHAPTER 106

1. B.

   The beneficial effect of ACE inhibitors or antiotensin receptor blockers (ARBs) on patient or graft survival has not been consistently demonstrated. The KDIGO guidelines suggest a blood pressure goal of less than 130/80 mm Hg for kidney transplant recipients irrespective of the level of albuminuria. There has been no conclusive evidence that one class of antihypertensive agent is superior to another in the transplant setting. Hence, treatment should be individualized based on efficacy, tolerability, concomitant comorbidity, and drug-drug interactions with immunosuppressive agents.

2. C.

   To date, there have been no data to support the routine addition of nonstatin drug to statin therapy to further reduce cardiovascular disease events in the general population or in the transplant setting. However, based on the safety and efficacy data of ezetimibe use among chronic kidney disease patients, ezetimibe can be considered as a second-line treatment option for high-risk kidney transplant recipients who are intolerant of statin or are refractory to statin therapy. Mammalian target of rapamycin (mTOR) inhibitor–based immunosuppression is associated with the worst lipid profiles, followed by cyclosporine, and to a lesser extent tacrolimus.

3. B.

   The diabetogenic effect of corticosteroids, calcineurin inhibitors (tacrolimus > cyclosporine), and mTOR inhibitors have been well-described. However, neither azathioprine nor mycophenolic acid derivatives are diabetogenic.

CHAPTER 107

1. D.
   Human leukocyte antigen (HLA) alloantibodies.
2. C.
   Only 1, 2, and 3 are correct.
3. E.
   1, 2, and 4 are correct.

CHAPTER 108

1. A.
   Risk is approximately 5% to 10% within 10 years after transplantation for IgAN, less than 1% for B, C, and D and E does not recur
2. E.
   A histologic diagnosis pre- and post-transplantation is required for the diagnosis of recurrent disease.
3. D.
   Plasma exchange should be commenced once a diagnosis of recurrent FSGS is made, with a plan to complete approximately nine cycles of therapy.

CHAPTER 109

1. B.
   Statistical method of maximizing the information available for analysis of outcome from a group of patients and events.
2. C.
   Acute rejection, graft failure, lost to follow-up, and patient death.
3. C.
   Method of combining the results from all similar trials to gain statistical power.

CHAPTER 110

1. F.

There are several options for insulin-dependent diabetics, depending on cardiac status, surgical candidacy in general, and availability of a living donor kidney transplant.

2. B.

Pancreas transplants require additional amounts of immunosuppression because of an increased risk for rejection. The other statements are all true.

3. E.

Transplantation of an adequate islet cell mass through the portal vein to the liver can establish a normal hemoglobin A_{1c} in patients with lower BMI.

CHAPTER 111

1.
   - A. The slowly falling glomerular filtration rate (GFR), the hypertension and the bland urinalysis are all suggestive of chronic cyclosporine nephrotoxicity.
   - B. A renal biopsy is not considered urgent in the setting of bland urinalysis and a high pretest probability of cyclosporine toxicity, although it may be performed at some point for confirmation and prognostication purposes.
   - C. The combination of sirolimus + cyclosporine *increases* the risk for further renal damage.
   - D. Cystic fibrosis of itself is not a contraindication to renal transplantation.
   - E. Diltiazem will impair the metabolism of both cyclosporine and simvastatin, increasing their blood and tissue concentrations, which will increase the risks for acute kidney injury (AKI) and rhabdomyolysis.

2. C.

The most likely process here given the risk factors (time frame, total body irradiation) and clinical and laboratory features (hypertension, low platelets, rising creatinine with proteinuria and hematuria) is thrombotic microangiopathy. Plasma LDH, serum haptoglobin, and blood film will confirm this suspicion. Membranous nephropathy tends to cause nephrotic (not nephritic) syndrome. Hematologic malignancies can infiltrate the kidneys, leading to AKI, but would not manifest with nephritic syndrome. Ultrasound is the preferred method for identifying obstructive uropathy (especially in the setting of renal dysfunction, in which intravenous contrast could cause further renal injury).

3. E.

Clarithromycin increases cyclosporine levels (by reducing cytochrome P450 [CYP]3A activity, which is involved in cyclosporine metabolism), giving rise to the typical manifestations of acute calcineurin inhibitor toxicity: tremor, AKI, hyperkalemia. Allopurinol and azathioprine should not be coadministered because of the risk for severe pancytopenia. Preemptive kidney transplant would be the best treatment for this patient because he is young, relatively healthy, and likely to withstand the stress of kidney transplant surgery.

4. B.

Here, the baseline serum creatinine of 1.0 mg/dl likely reflects some degree of CKD, given the young age, female gender, and likely low muscle mass in the face of end-stage liver disease. Glomerulonephritis, although not uncommon in hepatitis C infection, tends to have a more subacute presentation and—at least when acute—is characterized by hematuria and proteinuria. Simultaneous liver-kidney transplant is not currently indicated because her acute kidney dysfunction has been ongoing for 1 week only. Given her baseline CKD and current AKI, she has a significant risk for developing severe CKD over the long term.

5. D.

Although severe heart failure is likely contributing to the renal dysfunction, the hemodynamic insults at cardiac transplantation and the post-transplant nephrotoxic medications (without which outcomes are poor) make it more likely that the renal function will further deteriorate. Furthermore, the proteinuria suggests there is also intrinsic kidney disease such as secondary focal segmental glomerulosclerosis (which can occur in cyanotic heart disease). Therefore, although not commonly performed, simultaneous heart-kidney transplant should be considered here. A kidney transplant in isolation (i.e., without an improvement in cardiac status) is not recommended because of her high risk for morbidity and mortality perioperatively.

CHAPTER 112

1. B, D, E.
   Survival on dialysis for elderly patients does not depend on dialysis modality, but is related to frailty and comorbidities
2. C, D, E.
   Advance care planning is an outcome of shared decision making and is not a legal process. It therefore involves sharing information between patient and health care team to arrive at an informed decision made by the patient
3. A and E.
   Dialysis withdrawal is withdrawal of life-sustaining treatment that is no longer effective in sustaining quality of life for the patient. In the absence of renal function, patient survival is around 7 days, depending on comorbidities; survival can be considerably longer if the patient still has some residual renal function.
4. A, D, E.
   The decision for a patient to have conservative care is made after shared decision making. A number of retrospective studies have shown no survival advantage of dialysis compared with conservative care for patients older than 80 years and multimorbid patients older than 75 years. Conservative care is no dialysis but includes optimal management of kidney disease complications, comorbidities, and symptoms.

INDEX

Page numbers followed by "*f*" indicate figures, "*t*" indicate tables, and "*b*" indicate boxes.

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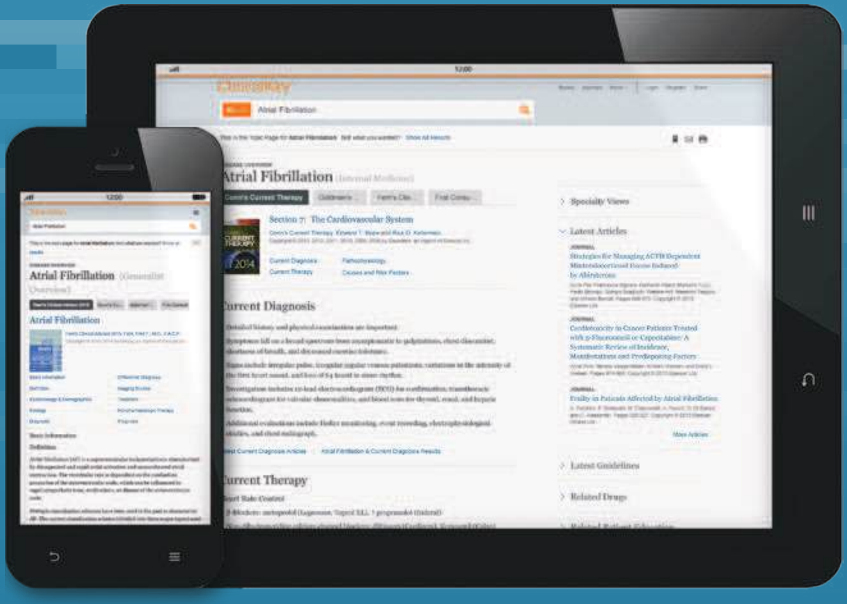

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